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Recent progress in the synthesis of limonoids and limonoid-like natural products

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Limonoid and limonoid-like natural products have demonstrated diverse bioactive properties and attracted considerable synthetic efforts. They provide a good platform to examine the viability of methodologies in the efficient construction of complex skeletons. In this review, we have discussed the recent progress in the syntheses of limonoids and limonoid-like natural products, covering from January 2011 to March 2020. The key transformations are highlighted. Finally, we summarize current "state-of-art" advance on novel synthetic strategy in syntheses of linonoids and limonoid-like molecules. Besides, future outlook are also presented.

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1 Introduction

Limonoids are widely distributed in nature and have diverse biological activities.[1] To date, various limonoids have been identified in nature. Structurally, the typical limonoid skeleton is characterized as 4,4,8-trimethyl-17-furanylsteroid. Besides, intact limonoids are defined as the unaltered bond of the parent nucleus, a pentacyclic carbon skeleton. Degraded limonoids commonly result from the oxidative cleavage of the parent nucleus, featured by fused bicyclic γ- or δ-lactones.[2] Seco-limonoids are the oxidative fragmentation of one or more androstane cores. Finally, highly decorated limonoids are generally acknowledged as a high degree of ring fission and rearrangement of the parent nucleus. Considerable endeavours have been devoted toward the syntheses of limonoids.[2,3] Consequently, a 22-year synthetic campaign from Ley's group led to the historical synthesis of Azadirachtin,[4] with the discovery of new chemistry, thus encouraging more challenging

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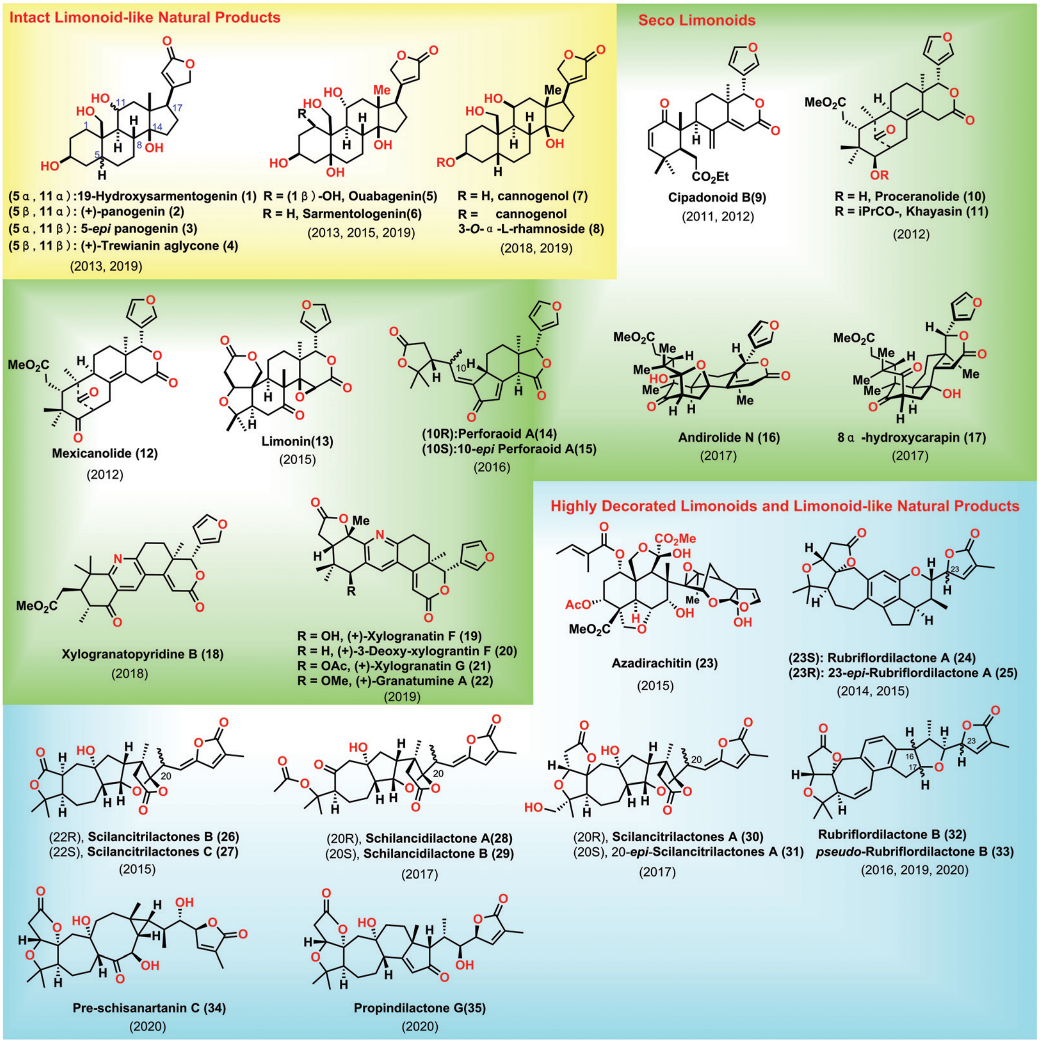


Fig. 1 Selected limonoids and limonoid-like natural products that have been synthesized since 2011.

syntheses from researchers. To maintain the coherence and focus of this review, degraded limonoids and synthetic studies toward limonoids are not highlighted herein.[3] Besides, the successful syntheses of limonoid-like natural products, especially cardenolides and nortriterpenoids, will be included in this review.[5] This review describes the syntheses of limonoids and limonoid-like natural products covering from January 2011 to March 2020 to avoid duplicating the beautiful review released by Heasley in 2011 (Fig. 1).

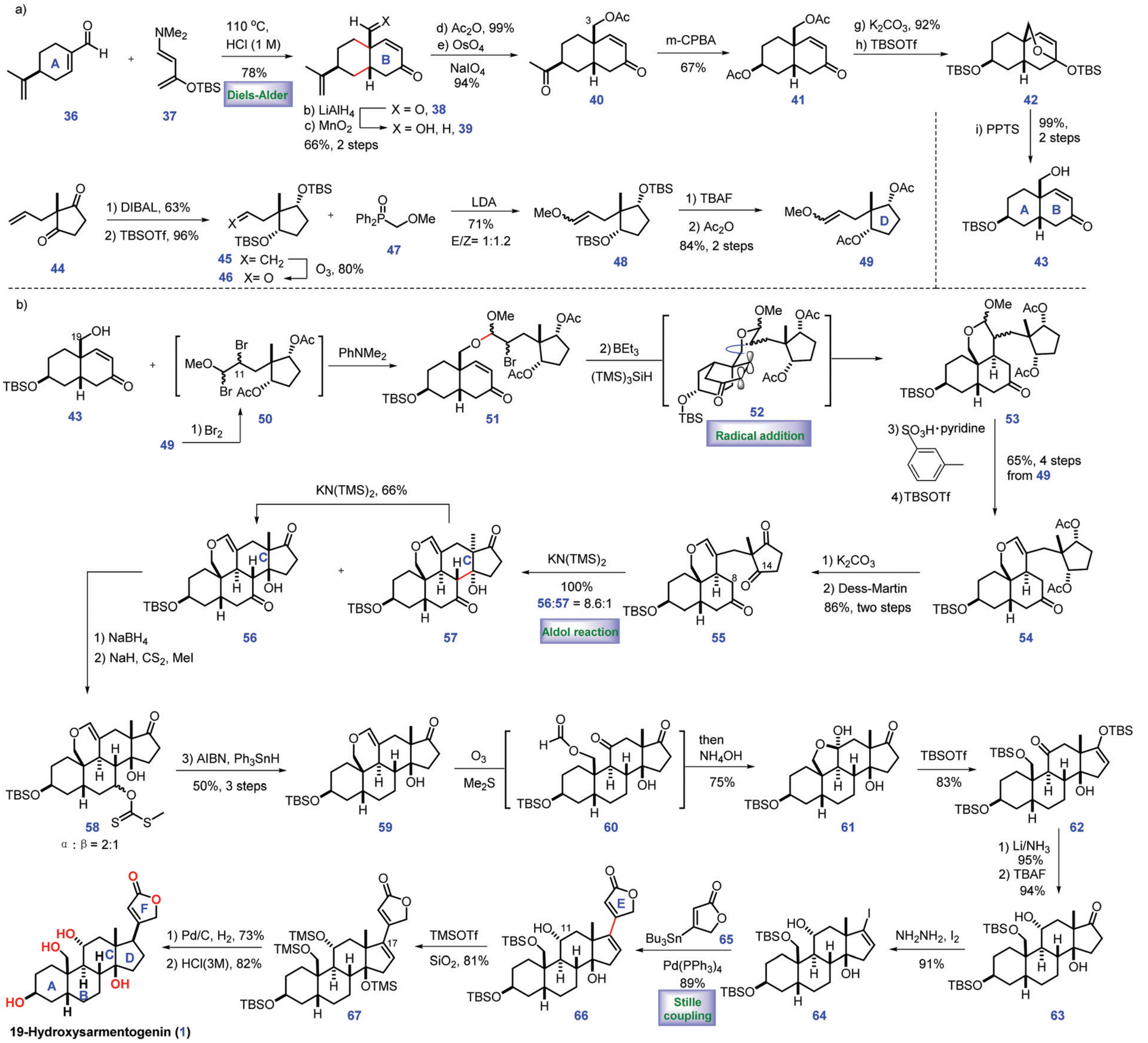
2. Intact limonoid-like natural products

2.1 Inoue's synthesis of 19-hydroxysarmentogenin (2013)

Cardiotonic steroids can be considered as a group of intact limonoid-like natural products,[3] which contain cardenolides and bufadienolides. Their structural variations are attributed to the oxygenation patterns located on C1, C3, C5, C11, C14 and C19 or epoxide. Cardiotonic steroids have demonstrated diverse biological activities.[7]

9-Hydroxysarmentogenin-3β-O-β-6-deoxyguloside (**1**), a cardiotonic steroid, was isolated from *Crossopetalum gaumeri* (Loes.) in the Yucatec Mayan community.[7] It possesses eight continuous stereo-centres, *cis* A/B and C/D ring fusion, a tertiary 14 β-hydroxyl group, and a 17β-unsaturated lactone, posing a considerable challenge for its total synthesis. In 2013, Inoue and co-workers described the total synthesis of 19-hydroxysarmentogenin **1** (Scheme 1).[8]

The pursuit of **1** commenced with the intermolecular Diels–Alder reaction of (*S*)-perillaldehyde **36** with the Rawal diene **37**[9] followed by acidic treatment, resulting in the desired enone **38** with *cis* selectivity at ring fusion (Scheme 1a). The two carbonyl groups in **38** were subsequently reduced, followed by chemo-selective oxidation of the resultant allylic alcohol at C7 to give **39**, which was further acetylated and oxidatively cleaved to generate ketone **40**. Compound **40** was subjected to a Bayer–Villiger reaction, leading to the C3-acetylated **41**. With **41** in hand, the removal of the two acetyl-



Scheme 1 Inoue's synthesis of 19-hydroxysarmentogenin (2013).

ated alcohols followed by treatment with TBSOTf furnished **42**. PPTS mediated the de-protection of the TBS ether at C7, furnishing ketone alcohol **43**. At this stage, their task was to prepare fragment **49**. They attempted to utilize a six-step sequence from the known di-ketone **44** [10] to obtain **49**, which involved the stereo-selective reduction of bis-ketone, alcohol protection, alkene oxidative cleavage, Horner–Wadsworth–Emmons reaction, and conversion of the TBS protecting group into an acetyl group.

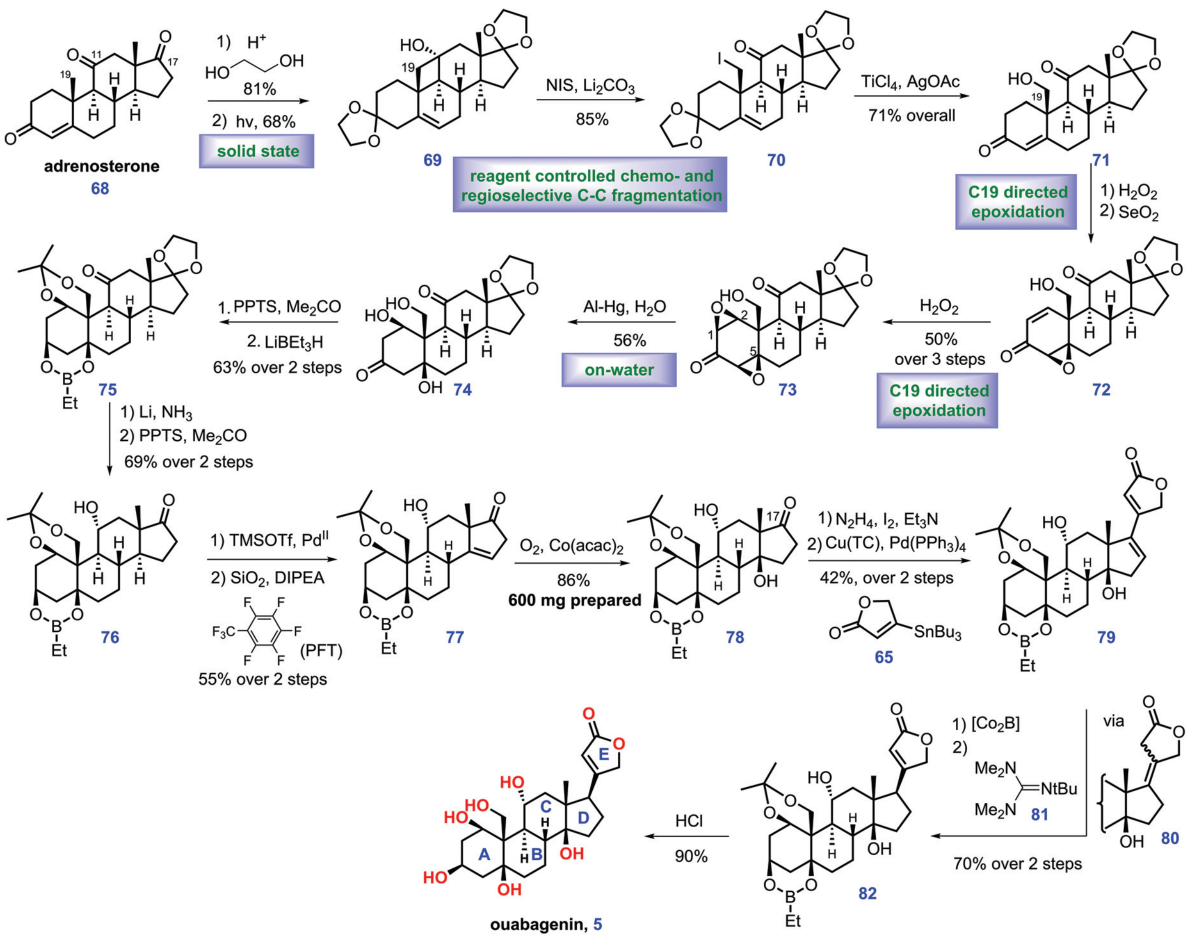
Subsequently, they planned to merge fragments **43** and **49** (Scheme 1b). Pleasingly, exposure of enol ether **49** to bromine afforded intermediate dibromide **50**, which was *in situ* treated with alcohol **43** *via* SN2 bromine displacement[11] to furnish acetal **51**. Treating bromide **51** with $BEt_3/(TMS)_3SiH$[12] initiated a carbon radical **52**, which underwent a radical addition to the C8–C9 double bond from the less hindered top face of the molecule, assembling tricycle **53**. With **53** in hand, the acid-mediated elimination of MeOH followed by the TBS protection of the C3 alcohol provided **54**. The removal of acetyl in **54** followed by the oxidation of the free hydroxyl groups gave ketone **55**. The authors closed ring C of the target *via* one-pot chemoselective C8 enol formation followed by treatment with C14 ketone, delivering **56** as the major product with good regio- and stereo-selectivity. Coupling precursor **64** could be prepared from **56** *via* a six-step operation, including removal of ketone, oxidative cleavage of alkene/hemi-acetylation, alcohol protection, stereo-selective Birch reduction and iodination.[13] Equipped with iodide **64**, they envisioned a Pd-catalysed Stille coupling reaction to append butanolide onto the steroid core. In practice, they observed that the treatment of **64** with stannane **65** under $[Pd(PPh_3)_4/CuCl/LiCl]$ produced adduct **66**. To complete the synthesis of **1**, the desired β-oriented stereochemistry at C17 should be established. Initial attempts for the straightforward hydrogenation of C16=C17 in **66** were found to be unfeasible, which only led to the undesired 17-*epi*-19-hydroxysarmentogenin after removal of TBS-protection. Ultimately, they discovered that introducing a bulky TMS group at C14 (**67**) was vital in shielding the convex face of the CD ring, thus providing the inverted α face selectivity of hydrogenation (dr = 6 : 1). Finally, the acidic-mediated de-protection of the primary alcohol achieved 19-hydroxysarmentogenin (**1**).

In Inoue's synthesis, they successfully completed the target from the commercially available (*S*)-perillaldehyde **36**. They tactfully adopted radical cyclization to install the desired C9 stereo-chemistry *via* clever substrate control. The ring C was fashioned stereo-selectively *via* judicious application of an aldol reaction. Smart manipulation of the steric hinder at the tertiary alcohol in **67** allowed for the installation of the desired the stereo-chemistry at C17, which would definitely inspire the syntheses of related natural products.

2.2 Baran's synthesis of ouabagenin (2013)

Ouabain was identified from the bark and roots of the ouabaio tree. It is widely utilized for the treatment of congestive heart failure.[14] It is also used as an adrenal hormone that naturally occurs in mammals. Besides, biological evaluation revealed that it demonstrated high inhibitory activity toward Na^+/K^+-ATPase.[15] Ouabain is constituted of ten stereo-genic centres, six hydroxyl groups and a β-oriented butanolide. The total synthesis of ouabain was first achieved by Deslongchamps's group (2007)[16] through a polyanionic cyclization methodology, which was highlighted in Heasley's review.[2] In 2013, Baran and co-workers described the scalable semi-synthesis of ouabagenin (**5**) from cortisone acetate **68**.[17] Key to Baran's synthesis is the strategic use of a redox relay and oxidative stereochemical relay (Scheme 2).

Their endeavours commenced with the commercially available cortisone acetate, which was converted into adrenosterone **68** *via* a known procedure.[17] After ketalization and recrystallization, the first redox-relay reaction was devised, which proceeded *via* the Norrish type II photochemical functionalization[18] of the angular C19 methyl group aided by C11 ketone. Notably, the above transformation only led to a moderate yield (43%) in the conventional solution (EtOH), which was attributed to the competitive formation of side products *via* the Norrish type I cleavage of the C9–C11 bond. Inspired by the work of Garcia-Garibay,[19] the authors successfully developed a solid-state (sodium dodecyl sulfate, SDS) irradiation of ketalized compound in aqueous suspension, which resulted in improved yield (68%). Subsequently, initial experiments to



Scheme 2 Baran's synthesis of ouabagenin (2013).

conduct oxidative fragmentation of the C11–C19 bond of **69** were unfruitful. Eventually, the authors identified that **69** could be transformed into **70** under Barluenga's reagent,[20] which, however, is costly. Accordingly, an inexpensive reagent, NIS,[21] was selected as an alternative. Then, $TiCl_4$-mediated selective deketalization of C3 ketone followed by AgOAc-promoted hydrolysis of C19 iodide provided enone **71**. At this juncture, the authors envisioned a next series of relay transformations, where the C19 hydroxyl moiety was switched into the β face of ring A *via* a diastereoselective stereochemical relay. In practice, H_2O_2 induced C19 hydroxyl-directed β-epoxidation of **71** followed by dehydrogenation of the C1–C2 bond, giving epoxide **72**, which served as the substrate for a second hydroxyl-directed epoxidation. Using this method, diepoxide **73** was accessible. Moving forward, the authors found that the reductive opening of diepoxide **73** on scale proved challenging. Although numerous conditions were screened, only a mixture of enones were obtained. Fortunately, the authors finally discovered that the aluminum amalgam-mediated reductive opening of **73** smoothly achieved the desired triol **74** under "on-water" conditions[22] (aqueous suspension). The selective protection of **74** to an acetonide followed by $LiBEt_3H$-induced reduction of the C3 ketone furnished **75**, where the hydroxyl at C1 and C5 was protected as an ethyl boronic ester. Li/NH_3 triggered the thermodynamic reduction of the C11 ketone followed by PPTS-mediated deketalization of the C17 ketone, affording **76**, thus setting the stage for the final redox-relay process. In real experiment, the authors attempted dehydrogenation of ketone **76** followed by olefin isomerization[23] to form enone **77**, which, however, resulted in low conversion and epimerization of the C14 stereo-centre. Pleasingly, the authors identified that fluorinated solvents could secure the reaction, while minimizing the undesired epimerization. Exposure of **77** to Mukaiyama hydration[24] conditions produced **78** with the desired tertiary alcohol installed (dr = 8 : 1, favored **78**). **78** is useful as it could be employed as a precursor to achieve plentiful analogues varied at C17. To complete the synthesis, it was necessary to attach a butenolide subunit to advance **78**. In practice, **78** was first promoted to vinyl iodide *via* Barton's method.[13] Then Pd-catalysed Stille-coupling reaction of the iodide compound with stannane **65** provided **79** with a full ring system established. In the final stage of the synthesis, direct reduction of the C16–C17 olefin of dienoate **79** in a productive manner failed since this reduction proceeded from the undesirable convex face of the molecule. Finally, the authors found that exposure of **79** to Co_2B[25] generated an intermediate, tetrasubstituted olefin **80**, which was further treated with Barton's base[26] **81** under heat. The resulting enolate **82** was obtained with the desired stereochemistry at C17 (dr = 3 : 1) favored. Finally, deprotection of all the hydroxyl groups in **82** completed ouabagenin (**5**).

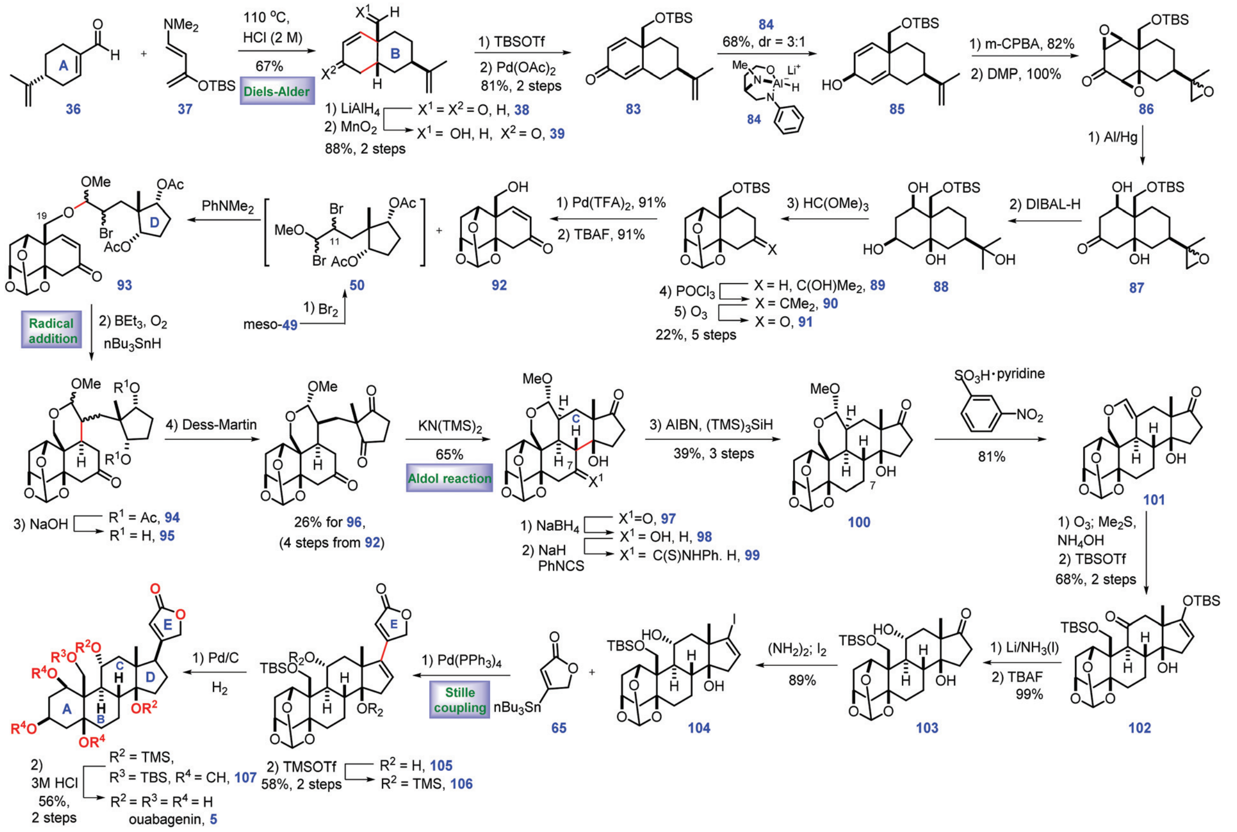
In Baran's work, the novel and outstanding redox relay and oxidative stereochemical relay showcase their potential in the elaboration of complex steroids. Notably, the key precursor of ouabagenin, **78**, could be prepared on scale, thus providing a versatile route to steroids analogues varied at C17. Most importantly, this work resulted in the discovery of new chemistry, such as "on-water" epoxide fragmentation and chemo-selective dienoate reduction, which will accelerate the synthesis of related natural products.

2.3 Inoue's synthesis of ouabagenin (2015)

In 2015, Inoue and co-workers also described the total synthesis of ouabagenin **5**, involving intramolecular radical cyclization and aldol reaction as key steps (Scheme 3).[27] Their pursuit of ouabagenin **5** began with the installation of a ring AB system of the target. Treatment of (*R*)-perillaldehyde **36** with Rawal's diene **37** under heat triggered the credible Diels–Alder reaction, leading to the desired *cis*-decalin with good regio- and diastereoselectivity, which was followed by deprotection *via* aqueous acid to give **38**. $LiAlH_4$-mediated reduction of two ketone groups, followed by chemo-selective oxidation of the allylic alcohol provided ketone **39**. TBS protection of the C3-enol and C19-hydroxy groups in **39** followed by Saegusa reaction[28] introduced dienone **83**. Equipped with **83**, the authors turned their attention toward the installation of the stereochemistry of C1- and 5-oxygen functional groups. Pleasingly, C3-β-alcohol-directed stereo-selective reduction of ketone **83** by chiral reagent **84**[29] arrived at desired **85** as a 3 : 1 diastereomeric mixture.

Moving forward, the epoxidation of **85** *via m*-CPBA followed by oxidation furnished tri-epoxide **86**. Sequential reductive opening of the two epoxides *via* Al/Hg,[30] stereo-selective reduction of C3 ketone, *ortho*-esterification of three *cis*-hydroxyl groups, dehydration of the tertiary alcohol and ozonolysis of the tetra-substituted olefin furnished orthoester **91**. Pd-catalysed dehydrogenation[31] of **91** followed by TBAF-mediated deprotection of TBS-ether provided the desired alcohol **92** with the requisite ring system AB installed. Learned from their previous work,[8] Inoue conducted dibromination of *meso*-**49**[32] that furnished intermediate **50**, which was *in situ* merged with **92** *via* SN2 bromine displacement, thus giving **93** as a diastereomeric mixture. The remaining C11-bromo group of **93** allowed the key radical cyclization reaction (Et_3B/*n*-Bu_3SnH/O_2) from the β-face of the C9-olefin,[33] leading to product **94** with the required C9 stereo-centre constructed. Removal of two Ac groups followed by DMP oxidation produced diketone **96**. With **96** in hand, the authors sought to develop conditions for construction of ring C of the target. They found **97** was subsequently fashioned *via* a $KN(TMS)_2$ (30 mol%) catalysed intramolecular aldol reaction where the ring C was formed. In the forward sense, their goal was to develop conditions for the deoxygenation of C7 at **97**, which was achieved *via* a three-step operation involving chemo-selective reduction at C7 ketone, derivation into thio-carbamate with thio-isocyanate and AIBN/$(TMS)_3SiH$-induced reductive cleavage of the C7-thiocarbamate. Using this method, **100** was accessible from **97** in 39% yield (3 steps).

Their efforts were then focused on the construction of the C11-functional group. Acid-mediated elimination of MeOH in **100** gave **101**. Ozonolysis of **101** followed by reductive workup and de-formylation gave the resultant hemiacetal product,



Scheme 3 Inoue's synthesis of ouabagenin (2015).

C17- and C19-oxygen of which was further capped as TBS ether **102** together with the liberation of the C11-ketone. Then they planned to install an equatorial C11-OH. In practice, they identified that the Birch reducing conditions (Li/NH_3) followed by deprotection of the C19 enol silyl ether could achieve the desired **103**. **103** was further developed to vinyl iodide **104**, setting the stage for a cross-coupling reaction. Inspired by their previous work,[8,17] they conducted a Pd-catalysed Stille coupling reaction[34] with stannane **65** to afford **105**, where the full ring system was installed.

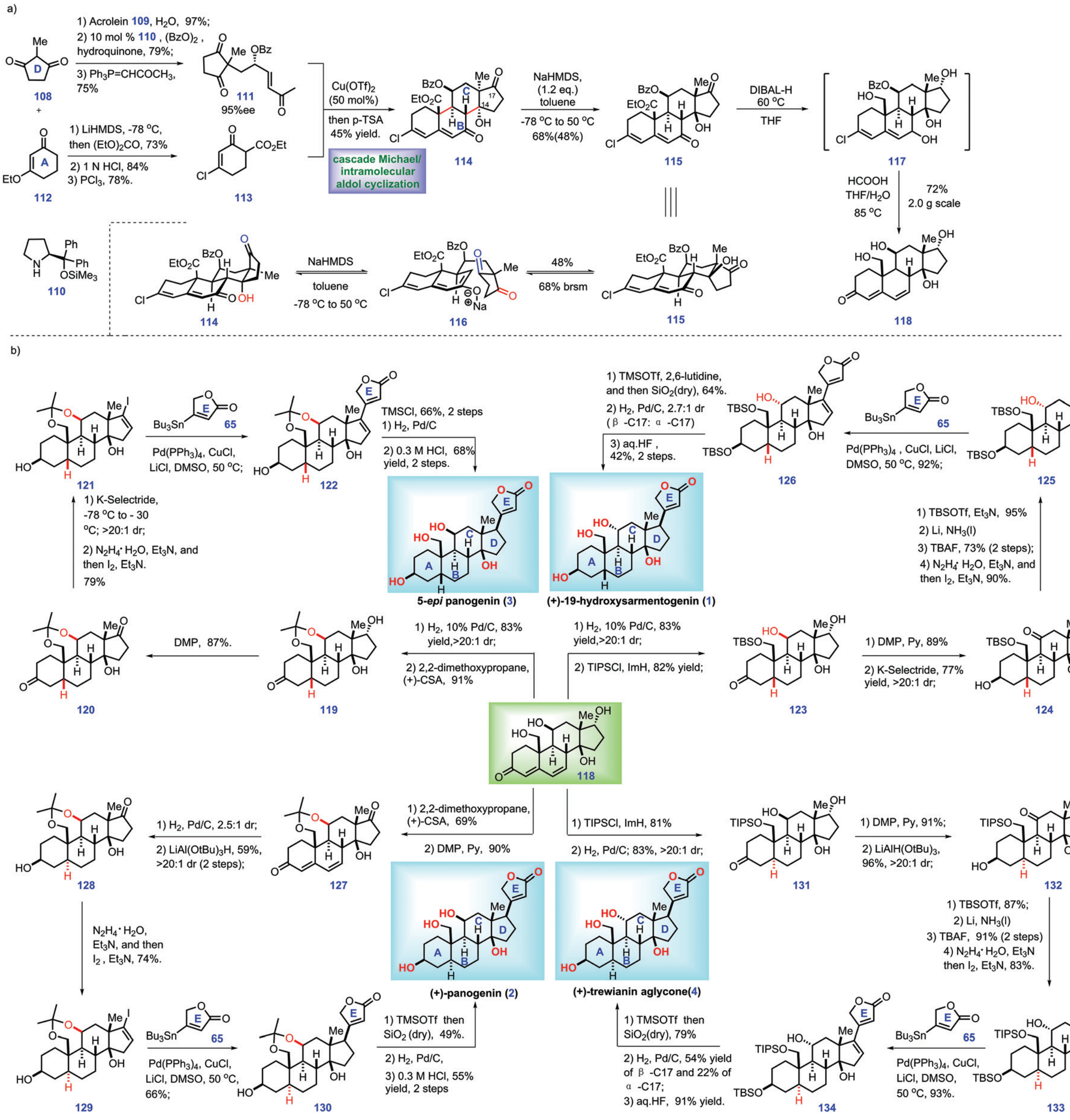
With access to **105**, what remained was the establishment of the C17 stereo-centre. Learning from their previous work,[8] the protection of the C14-hydroxy group with TMS-ether enabled the Pd-catalysed 1,4-reduction of enone **106** from the less steric concave α-face, thus yielding the desired **107**. To complete the synthesis, global removal of the protecting groups in **107** furnished the ouabagenin (**5**).

In Inoue's synthesis, the core strategy of ring formation was similar with their aforementioned work in the total synthesis of 19-hydroxysarmentogenin **1**,[8] both of which involved the Diels–Alder reaction to construct the ring AB system, a tactful SN2 bromine displacement to connect ring AB and ring D, the intramolecular Aldol reaction to install the ring C and a Pd-catalysed Stille coupling reaction to introduce lactone ring E. Besides, a clever C3-β-alcohol-induced di-epoxidation, followed by a reductive ring-opening reaction nicely installed both C1 and C5 hydroxyl groups. The triol was protected to orthoester **89**, which could minimize side reactions in the subsequent transformations.

2.4 Nagorny's synthesis of ouabagenin, sarmentologenin, 19-hydroxysarmentogenin, and 5-*epi*-panogenin and their derivatives (2019)

In 2016, Nagorny's group reported synthetic endeavours toward the total synthesis of cardiotonic steroids 19-hydroxysarmentogenin **1** and trewianin aglycone **4** *via* Cu(II)-catalysed asymmetric Michael addition/intramolecular aldol cyclization reactions as the core protocol.[35] In 2018, they documented the synthesis of cannogenol-3-O-α-L-rhamnoside **8** utilizing an identical strategy.[36] In 2019, they further described a full report on the total syntheses of ouabagenin **5**, sarmentologenin **6**, 19-hydroxysarmentogenin **1**, 5-*epi*-panogenin **3** and other cardiotonic steroid involved the above-mentioned Cu(II)-catalyzed Michael addition/intramolecular aldol cyclization reactions as key protocols (Scheme 4) and other cardiotonic steroids,[37] which has included their aforementioned work in 2016[35] and 2018.[36] Herein, we discuss their full paper (2019).[37]

In this work, the authors envisioned a convergent strategy to complete a series of cardiotonic steroids from a common core, steroid **118**. Accordingly, their project commenced with the assembly of **118** (Scheme 4a). Initially, 1,3-di-ketone **108** was advanced to enone **111** through a three-step manipulation



Scheme 4 Nagorny's synthesis of ouabagenin, sarmentologenin, 19-hydroxysarmentogenin, and 5-*epi*-panogenin and their derivatives (2019)-1.

involving a Michael addition[38] with acrolein **109**, an organocatalyst **110** catalysed enantioselective oxidation reaction[39] with benzoyl peroxide and a Wittig reaction with 1-(triphenylphosphoranylidene)-2-propanone. Instead, ethyl-vinyl ether **112** was progressed to β-ketoester **113** *via* acylation with diethylcarbonate, acid-hydrolysis of ethyl-vinyl ether and chlorination. Here, the authors sought to install the ring BCDE system of core **118**. In practice, key fragments enone **111** and β-ketoester **113** were successfully merged *via* a Cu(II)-catalysed asymmetric Michael addition reaction.[40] The resultant Michael adduct allowed for a subsequent *p*-TsOH-mediated double aldol cyclization cascade, leading to **114** with a tetracycle ring system installed.

Moving forward, they turned their attention toward the elaboration of **113** into common core **118**, which involved intermediate **115**. DFT calculations showed that diastereomer **115** was more stable than **114**. Hence, the authors planned to isomerize **114** into **115** *via* thermodynamic equilibrium. After screening extensive conditions, the author identified that the treatment of NaHMDS (1.2 eq.) with **114** at −78 °C to 50 °C initiated a retro-aldolization reaction, leading to **116**, which followed by intramolecular aldol condensation to fashion **115**. Notably, Na^+-containing bases demonstrated better reactivity than Li^+ and K^+ counter-cations. With access to **115**, the author devised a global reducing strategy followed by acidic workup to fulfil **118**. However, early attempts to employ $LiAlH_4$ led to complex results, while the reduction of C19 ester proceeded slowly with the use of $LiBH_4$ and DIBALH. Fortunately, treatment of **115** with DIBAL-H under heat (60 °C) afforded intermediate **117**, which was further treated with aqueous formic acid at elevated temperature (80 °C), thus allowing the core **118** .

With core **118** constructed, the authors then developed conditions for the convergent synthesis of cardiotonic steroids **1**, **2**, **3** and **4** (Scheme 4b). The authors envisioned that these four syntheses held some common characteristics as follows: (1) the α-C5 configuration (**1** and **3**) and β-C5 configuration (**4** and **2**) could be both established *via* diastereoselective reduction of **118**. (2) The C11 configuration position could be inverted (**4** and **6**) or retained (**2** and **3**). (3) A C17 butenolide moiety should be attached *via* Stille coupling in the final stage.[17]

With this in mind, the authors first targeted 5-*epi*-panogenin (**3**). Global hydrogenation of the diene motif in **118** followed by protection of the resultant diol (C11, C19) with 2,2-dimethoxypropane afforded acetonide **119** with a β-C5 stereo-centre built. In a parallel experiment, the site-selective protection of C19 hydroxyl in **118** with TBSCl furnished **123**.

Moving forward, DMP oxidation of **119** yielded **120**, which was then processed through the site-selective reduction of C3 ketone and a Shapiro reaction to give rise to vinyl iodide **121**. **121** was served as a substrate for the Pd-catalysed Stille cross-coupling reaction with stannane **65**, thus affording **122** with a full ring system fashioned. With access to **122**, what remained was to build the C17 stereo-centre. Similar to the work of Inoue and Baran,[8,16,17] the authors also failed to direct the hydrogenation of the Δ-olefin.[16,17] Pleasingly, when the C14 hydroxyl in **122** was protected with TMS ether, it allowed a Pd-catalysed hydrogenation reaction with a much higher stereo-selective mixture (25 : 1.0 : 2.8). Exposure of the resulting mixture to acidic conditions removed the acetonide protecting group, thus completing the 5-*epi*-panogenin (**3**).

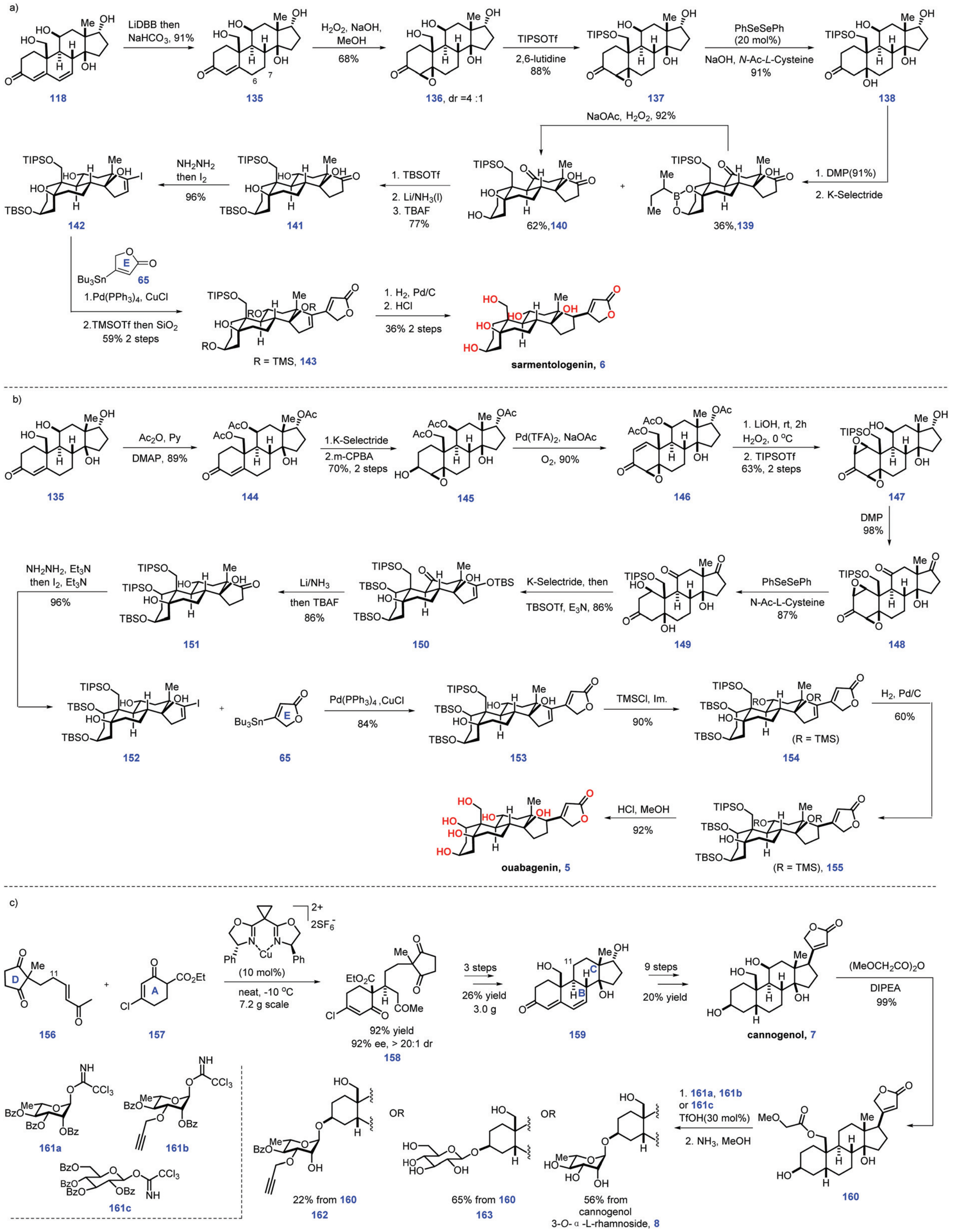
Moving forward, the authors then aimed for 19-hydroxysarmentogenin **1**. Compared with 5-*epi*-panogenin **3**, accomplishment of 19-hydroxysarmentogenin (**1**) was performed *via* similar operations but called for requisite manipulations to construct the α-C11 stereo-centre. In practice, global oxidation of alcohol in **123** followed by site-selective reduction of C3-ketone gave rise to **124**. Treating **124** with TBSOTf induced selective protection of C17 ketone, thus generating a TBS ether product. Li/NH_3 initiated the stereo-selective reduction of the C11 ketone followed by removal of the TBS protecting group, providing **125** with the requisite α-C11 hydroxyl group fashioned. Fragment **125** and stannane **65** were then connected *via* a similar Pd-catalysed Stille coupling to achieve **126**. With the full ring system in place, all that remained was to elaborate **126** into target **1**. Finally, 19-hydroxysarmentogenin (**1**) was procured *via* three additional manipulations, including TBS-protection of the C13 alcohol, hydrogenation of the Δ-alkene[16,17] and global deprotection of the alcohols.

Their goal then was to accomplish the panogenin (**2**) and trewianin aglycone (**4**), which featured a *trans*-A/B ring fusion and α-C5 stereo-centre. Initially, they targeted panogenin (**2**). The project commenced with the protection of **118** to form the acetonide product, which followed by C17 alcohol oxidation, thus affording ketone **127**. Stereoselective hydrogenation of **127** delivered the product with a fashioned *trans*-A/B ring (2.5 : 1 dr at C5). LiAl(OtBu)$_3$H-mediated stereoselective reduction of the C3 ketone in the above product gave rise to **128** (59%, two steps). Then **128** was advanced to vinyl iodide **129**, which was further transformed into panogenin (**2**) *via* the aforementioned protocol for 5-*epi*-panogenin (**3**).

Next, the authors focused their attention toward the synthesis of trewianin aglycone (**4**). Exposure of **118** to TBSCl/ImH masked the C19 alcohol of **118** as the TBS ether, thus allowing the following stereoselective hydrogenation. Pleasingly, the resultant *trans*-A/B ring fused **131** was generated with high diastereoselectivity (>20 : 1). Then, **131** underwent a two-step redox manipulation to form **132**. Finally, **132** was advanced to trewianin aglycone (**4**) *via* the abovementioned operations to panogenin (**2**).

Moving forward, the authors then envisioned an "oxidase phase" strategy to conquer sarmentologenin (**6**) and ouabagenin (**5**) (Scheme 5a). Initial experiments to expose **118** to the conventional reducing conditions such as selective hydrogenation, conjugate reduction and diimide reduction failed to give the target product. Fortunately, they eventually identified LiDBB was engaged in the reduction of the Δ alkene[6,7] in **118**, leading to the desired **135** after aq. $NaHCO_3$ workup. Epoxidation of enone **135** fashioned β-epoxide **136** as the major product (dr = 4 : 1). However, further advancement of **136** into **137** proved challenging since product **137** was feasible to undergo dehydration, thus returning to enone **135**. Unfortunately, common reducing conditions only led to decomposition of the reaction. Finally, the authors discovered that oxidase-mediated reducing conditions (PhSeSePh, NaOH, N-Ac-L-cysteine) could form the alcohol product. However, they failed to isolate the alcohol product due to its high hydrophilicity. To address this issue, the C19 alcohol of **136** was protected to form TIPS ether **137**, which was then smoothly advanced to sarmentologenin core **138**. Global oxidation of **138** afforded the ketone product, which was used as a precursor for a C3 ketone reduction, thus arriving at boronic ester **139** (36%) together with the desired **140** (62%). Note that boronic ester **139** could be converted into **140** *via* H_2O_2-mediated oxidation. **140** was progress to **141** *via* three additional sequences involving TBS protection of the C3 alcohol, β-selective reduction of the C13 ketone and de-protection of the C5, C14 TBS ether. Subjecting **141** to Shapiro reaction gave vinyl iodide **142**, which was followed by Pd-catalysed Stille coupling with stannane **65** and site-selective alcohol protection to construct **143**. To complete the synthesis of sarmentologenin **6**, the requisite C17 stereochemistry should be fashioned. In practice, Pd-catalysed stereoselective hydrogenation of **143** followed by an acid-mediated global deprotection reaction secured sarmentologenin **6**.

After that, their task turned to ouabagenin (**5**), which called for the installation of the C1 hydroxyl motif from sarmentologenin (**6**) (Scheme 5b). The authors conceived a bis-epoxidation of **118** or **135** followed by epoxide-reopening strategy to simultaneously introduce the desired double hydroxyl group. In real experiment, attempts to utilize this strategy to fulfil the target failed, which was attributed to the feasible aromatization of the steroidal ring A system.



Scheme 5 Nagorny's synthesis of ouabagenin, sarmentologenin, 19-hydroxysarmentogenin, and 5-*epi*-panogenin and their derivatives (2019)-2.

After considerable experiments, the authors eventually identified a stepwise sequence to enable the introduction of C1 and C5 oxygenation. Site-selective acetylation of the C11, C17 and C19 hydroxyls of **135** gave **144**, which was subjected to a two-step transformation involved α-face reduction of the ketone, followed by C3-directed epoxidation of alkene, resulting in **145**. Exposure of **145** to Pd-catalysed oxidative conditions furnished enone **146**. LiOH mediated the global removal of the acetate ester in **146** followed by C1–C2 epoxidation (H_2O_2) and selective protection of the C19 alcohol as TIPS ether furnished bis-epoxide **147**. The authors guessed that the TIPS protecting group could enhance the hydrophobicity of **147**, thus allowing the following steps to proceed smoothly. Oxidation of **147** led to triketone **148**, thus setting the stage for an epoxide opening reaction. The initial experiment showed the product **149** was sensitive to dehydrating conditions (basic or acidic media), leading to aromatization of ring A. Pleasingly, epoxide opening reactions could be achieved under the condition of (PhSeSePh, N-Ac-L-Cys, NaOH), which gave target **149** in good yield (87%). Note that cautious adjustment of the ratio of N-Ac-L-Cys to NaOH was crucial in minimizing the side reactions. Stereoselective reduction of the C3-ketone moiety of **150** *via* K-selectride generated the C3-hydroxyl product, which was advanced to the C3- and C17-silylated enol ether **151**. Following a similar protocol, **151** was processed through a five-step sequence, including stereoselective reduction of ketone, desilylation of the enol ether, Shapiro reaction, a Pd-catalysed coupling reaction with stannane **65**, TMS protection of the C5 and C11 alcohol and Pd-catalysed stereo-selective hydrogenation of the Δ alkene[16,17] to deliver **155**, which was subjected to global deprotection conditions (HCl/MeOH) to complete the ouabagenin (**5**).

Finally, the authors focused on cannogenol glycosides **8**, **162** and **163**, which lacked C11 oxygenation (Scheme 5c). Treatment of enone **156** with β-keto-ester **157** *via* a Cu-catalysed enantioselective Michael addition gave **158**. Based on the aforementioned protocol for its C11-hydroxyl analogue **118**, **158** could be smoothly advanced to enone **159** *via* three additional operations. Then, **159** was subjected to a 9-step transformation to produce the cannogenol (**7**). Treatment of the more reactive C19 hydroxyl in **7** with $(MeOCHCO)_2O$ led to **160**, thus setting the stage for the subsequent glycosylation of the C3 alcohol *via* trichloroacetimidate **161a**. The corresponding α-L-rhamnoside secured. Moving forward, removal of both the sugar benzoates and C19 methoxyacetate provided the cannogenol α-L-rhamnoside (**8**). Note that subjecting **160** to the condition of 50% ammonia in methanol initiated selective hydrolysis of the ester motif, leaving butanolide intact. Correspondingly, glycosides **162** and **163** could be made from **160**. Notably, α-L-rhamnosides of the steroids digitoxigenin,[41] bufalin,[42] and strophanthidol[43] could also be fashioned *via* a similar protocol. Then, the synthetic steroids were subjected to biological investigation. Pleasingly, the cannogenol-3-*O*-α-L-rhamnoside (**8**) and strophanthidol-3-*O*-α-L-rhamnoside exhibited excellent anticancer activity in the concentration range of 10–100 nM.

In Nagorny's synthetic campaign, the ring ABCD system was efficiently and elegantly established *via* a novel copper-catalysed intermolecular asymmetric cascade Michael/Aldol reaction with four desired stereocentres installed. More importantly, the key cascade reaction could be scaled up, thus allowing the preparation of enough materials for the later biological investigation. According to their ingenious design, the authors tactfully envisioned the key common intermediate **118**, which set the stage for the rapid and convergent syntheses of a series of related natural products. Additionally, enzyme chemistry was successfully utilized to promote the ring opening of the epoxide in the complex molecule synthesis, which provided enlightening value to conquer other limonoid-like compounds.

3. Sec limonoids

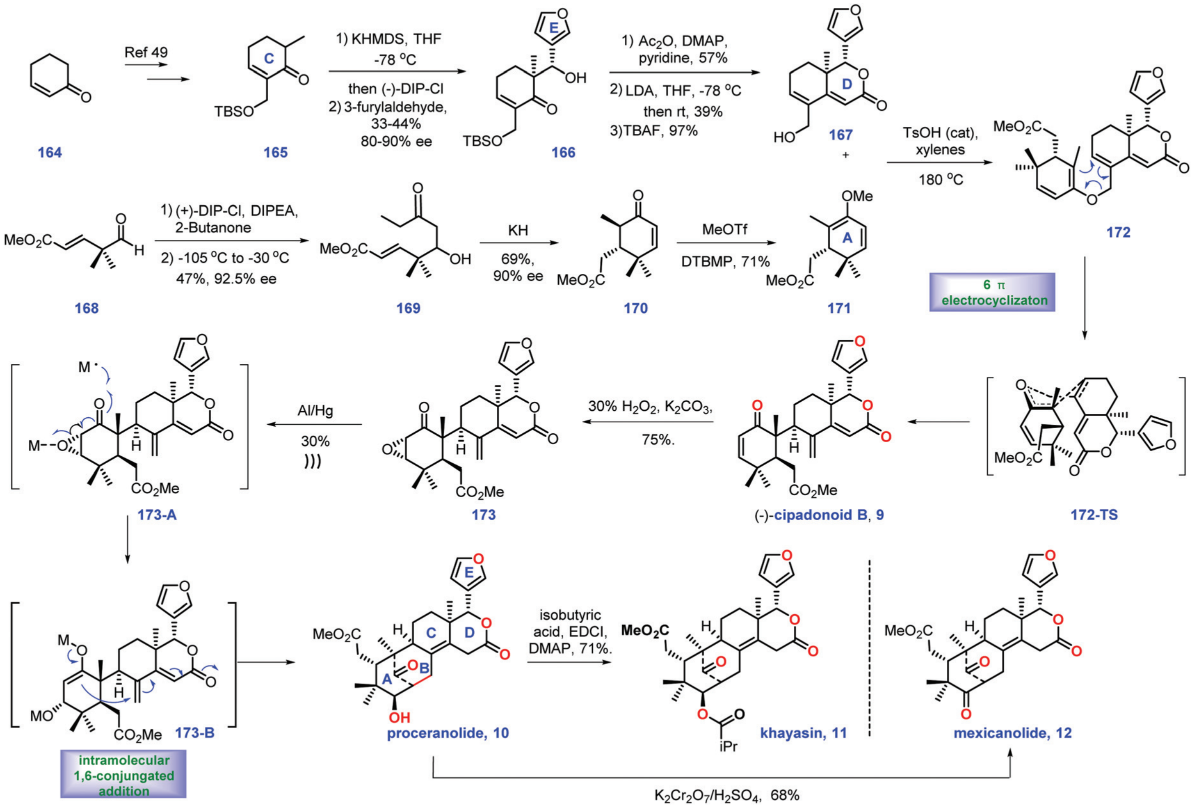
3.1 Williams's synthesis of (−)-cipadonoid B, khayasin, proceranolide, and mexicanolide (2012)

In 1966, Taylor's group isolated tetranortriterpenoid khayasin **11**, which belongs to the mexicanolide class of limonoids.[44] Khayasin **11** was utilized as an insecticide to kill coconut leaf beetle *Brontispa longissima*.[45,46] In 2011, Williams's group disclosed the racemic synthesis of cipadonoid B **9**.[47] In 2012, they further reported convergent asymmetric total synthesis of mexicanolide limonoids including (−)-cipadonoid B **9**.[48]

In 2012, Williams and co-workers reported the asymmetric total synthesis of khayasin **11** together with (−)-cipadonoid B **9**, proceranolide **10**, and mexicanolide **12** *via* a convergent strategy (Scheme 6).[48] Initially, they developed conditions for the asymmetric synthesis of intermediate (+)-azedaralide **167**. Enone **164** was firstly converted into **165** *via* known procedures.[49] Then [(−)-DIP-Cl] induced the asymmetric aldol reaction of **165** with 3-furylaldehyde, giving alcohol **166** in 33–44% yield with 80–90% ee. Then **166** was utilized as a substrate for a three-step sequence, including acetylation of alcohol, an aldol reaction and removal of TBS ether to form (+)-azedaralide **167**.

With access to (+)-**167**, their goal was to install the diene fragment **171**. Treatment of (+)-DIP-Cl and DIPEA with 2-butanone followed by addition to aldehyde **168** furnished **169** with 47% yield and 92.5% ee. With **169** in hand, KH initiated an intramolecular Michael reaction to construct cyclohexanone **173**/**170** as a 4 : 1 mixture of diastereomers (epimeric at C6). However, the above mixture was inconsequential, as both diastereomers could be transformed into (−)-vinyl ether **171** *via* treatment with methyl triflate.

Equipped with (+)-azedaralide **167** and (−)-vinyl ether **171**, they next devised to the asymmetric synthesis of (−)-cipadonoid B **10** *via* a cascade ketal-Claisen rearrangement reaction. In practice, subjecting **171** and **167** to acidic conditions under heat (TsOH, 180 °C, 4 h) initiated the cascade condensation to enol ether **172-TS**, which was *in situ* followed by rearrangement to arrive at the desired enantiopure (−)-cipadonoid B **9**.[47] DFT calculation demonstrated that the ketal-Claisen cascade favored the proposed transition state to minimize steric hinderance. Consequently, the authors turned their attention to



Scheme 6 Williams's synthesis of (−)-cipadonoid B, khayasin, proceranolide, and mexicanolide (2012).

other mexicanolide natural products. The regio- and stereoselective epoxidation of (−)-cipadonoid **9** yielded **173** with β oxygenation at C-3 installed. Al/Hg induced ring-opening of the epoxide[50] in **173** followed by intramolecular 1,6-conjugate addition of **173B** produced (−)-proceranolide **10**. Oxidation of (−)-proceranolide **10** formed (−)-mexicanolide **12**. Acylation of (−)-proceranolide **10** gave rise to (−)-khayasin **11**.

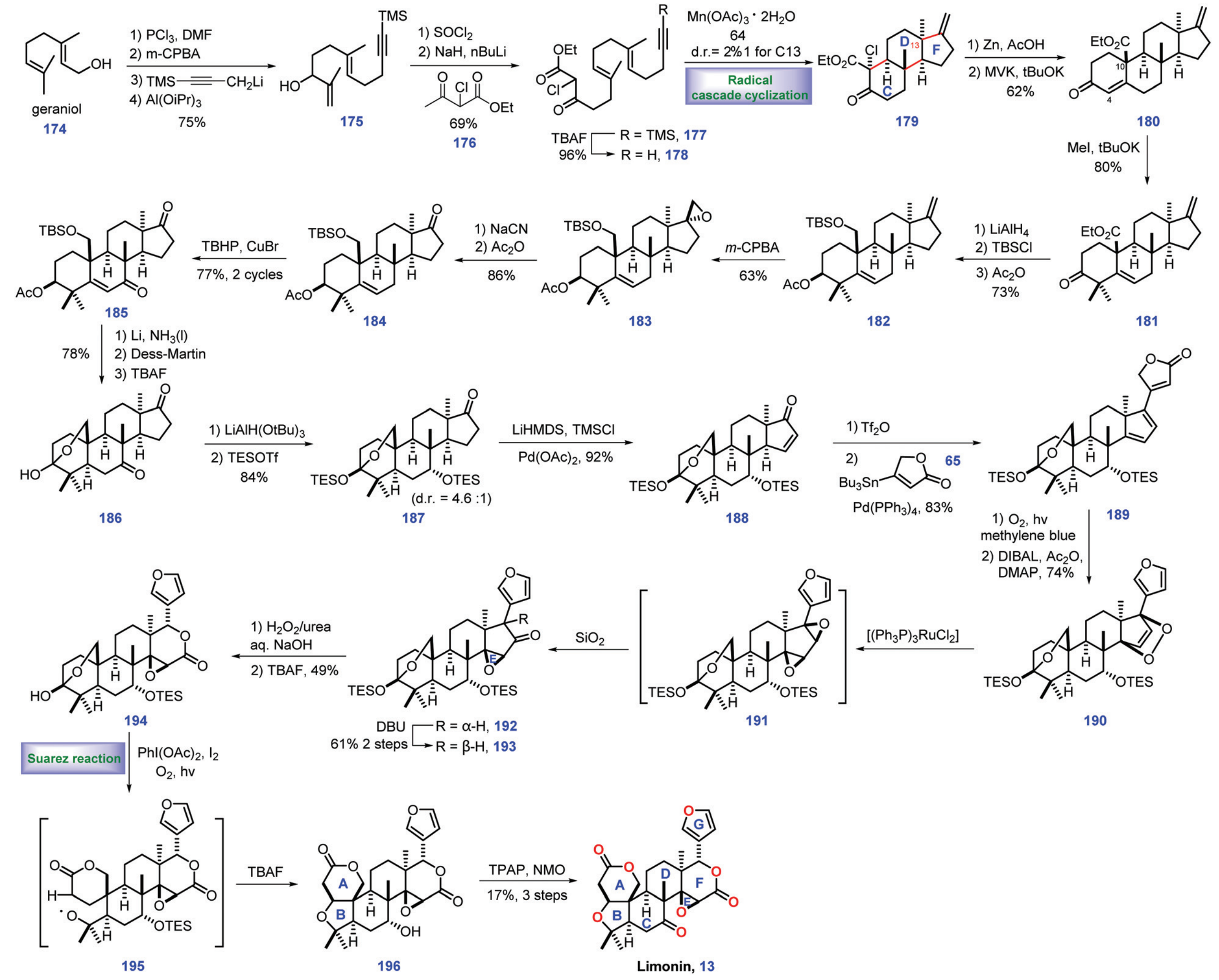
In this synthesis, the clever one-pot cascade ketal-Claisen rearrangement rapidly afforded (−)-cipadonoid B; however, its efficiency was unsatisfactory (25% yield). An impressive solving metal-induced radical skeleton rearrangement reaction smartly constructed the desired [3.3.1] framework, which enabled the collective synthesis of a series of mexicanolide natural products.

3.2 Yamashita's synthesis of limonin (2015)

Limonin **13** was discovered from the bitter components of the citrus fruit in 1841,[51] but its structure was confirmed until 1960, which contains an intact skeleton of 4,4,8-trimethyl-17-furyl-13a-androstane. Currently, hundreds of limonoids have been identified.[52] In 2015, Yamashita and co-workers first completed their synthetic efforts toward limonin **13**. Key to their success involved a tandem radical cyclization to install a ring CDF system as the core strategy (Scheme 7).[53] Their endeavours began with the installation of the ring CDF system from the commercially available geraniol **174**. Sequential alcohol chlorination, alkene region-selective epoxidation, propargylation and Ti(III)-mediated epoxide opening reaction generated allylic alcohol **175.** Exposure of **175** to $SOCl_2$ followed by treatment with the dianion of ethyl 2-chloroacetoacetate **176** and TBAF, gave alkynyl β-ketoester **178**.

With access to **178,** the authors focused on an efficient tandem radical cyclization strategy to fashion the ring CDF system. Eventually, they found a manganese-mediated condition [$Mn(OAc)_3 \cdot 2H_2O$] was capable of engaging the cascade cyclization, leading to the desired **179** with moderate diastereoselectivity at C7 (dr = 2.2 : 1).[54] Consequently, the authors then sought to assemble ring A of the target. Elimination of chloride in **179** *via* Zn/AcOH followed by Robinson cyclization with methyl vinyl ketone (MVK) smoothly forged tetracyclic **180** with ring A constructed. Double methylation of the C4 position of **180** afforded **181** in good yield (80%).

Here, the authors devised a cross coupling strategy to append a furan motif onto the core structure. Thus, the protocols for coupling precursor should be established. Initially, experiments to convert the *exo* methylene group in **181** into a ketone group *via* conventional oxidative cleavage conditions were found to be unfeasible. Instead, they switched to a five-step manipulation including reduction of the ester and C3-ketone, separate protection of the diol, epoxidation of the *exo* methylene and NaCN-mediated ring opening of the epoxide followed by elimination of CH_3CN to afford ketone **184.**[55] The copper-catalysed oxidation of **184** gave enone **185**,[56] which served as a substrate for three additional operations, including



Scheme 7 Yamashita's synthesis of limonin (2015).

Birch reduction, DMP oxidation and acetyl removal, to furnish hemiacetal **186** with an installed C5 stereocentre. The C7 ketone of **186** was chemoselectively reduced *via* LiAlH(O*t*Bu)$_3$ and the resultant bis-alcohol was further protected as TBS ether **187**. Ketone **187** was further advanced to enone **188** by Ito–Saegusa oxidation. Exposing this material to triflation conditions (DTBMP, Tf$_2$O) followed by a Pd-catalysed Stille coupling reaction with butenolide **65**gave the coupled product **189** with ring G established.

Moving forward, their next task was to set up the lactone moiety. In practice, **189** was subjected to singlet oxygen ($^1O_2$), triggering a [4 + 2] cycloaddition reaction, which was followed by two additional operations involving butanolide reduction and acetylation/elimination. The target endoperoxide **190** secured.[57] Exposure of **190** to [(Ph$_3$P)$_3$RuCl$_2$] initiated isomerization of the endo-peroxide moiety,[58] affording bis-(epoxide) **191**, which is *in situ* quenched by silica gel, inducing a 1,2-hydride shift to arrive at the undesired **192**. Notably, **192** could be isomerized under base (DBU) to form **193**/**192** as a 5.4 : 1 mixture in 61% yield (2 steps).

With the desired **193** in hand, a Baeyer–Villiger rearrangement was conducted followed by removal of TES ether, constructing epoxylactone **194** with lactone F formed. To complete the synthesis, installation of ring AB system of the target was necessary. **194** was exposed to Suarez reaction conditions,[59] [PhI(OAc)$_2$/I$_2$/O$_2$(10 atm)/*hv*], triggering the homolysis of the C3–C4 bond followed by C4 oxidation to give rise to alkoxy radical intermediate **195**. Intermediate **195** underwent a cascade 1,5-hydrogen abstraction, iodination and THF-ring formation to give **218** with the full ring skeleton established. Finally, only redox manipulations were required to access limonin **13**. TBAF-mediated de-protection of TES ether in **196** followed by Ley's oxidation[60] completed the synthesis of (−)-**13**.

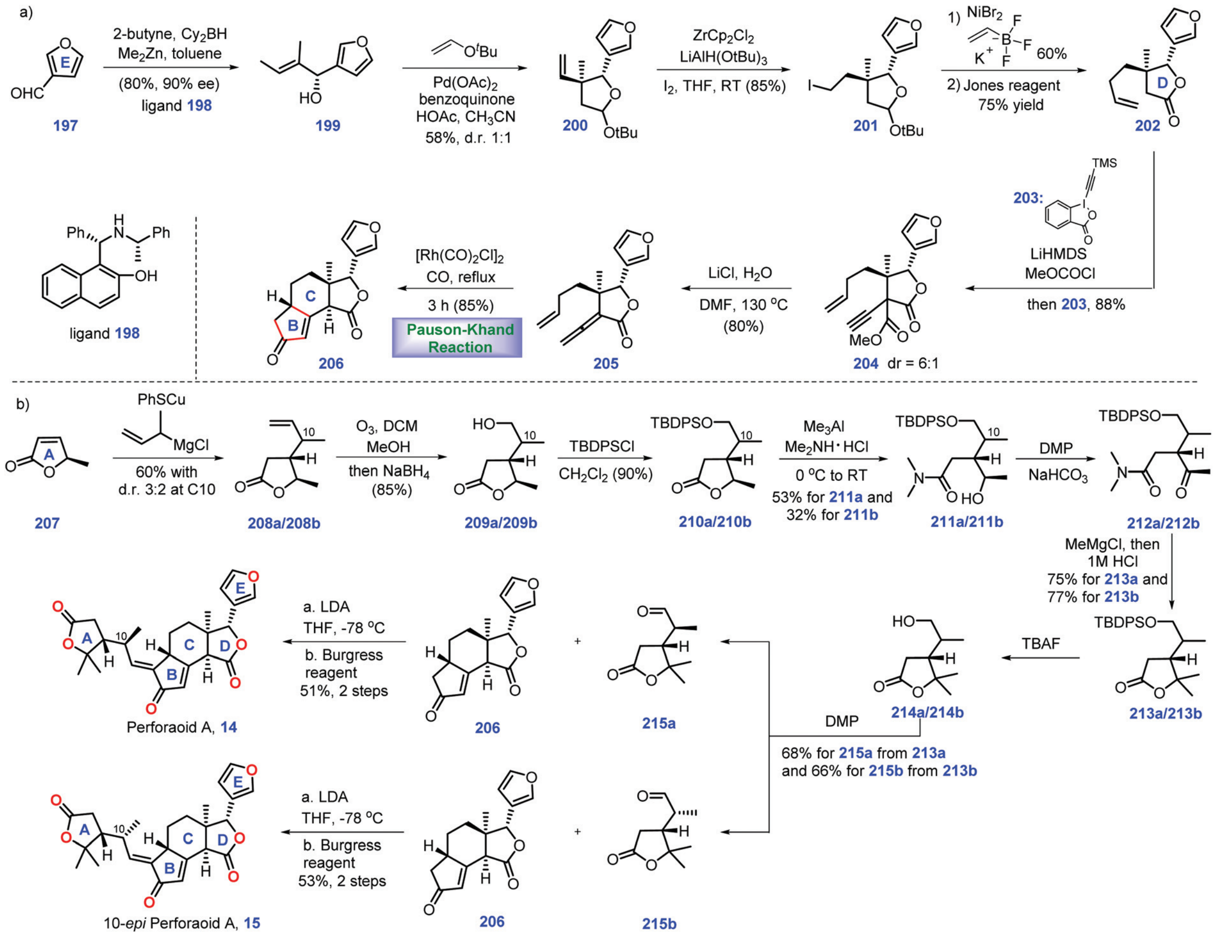
In Yamashita's synthesis, a well-designed Mn(OAc)$_3$-promoted radical cyclization rapidly assembled the CDF ring system with the desired stereochemistry installed, thus definitely accelerating the synthesis of intact limonoid natural products. A clever O$_2$-induced [4 + 2] cycloaddition followed by Ru-catalysed isomerization of endo-peroxide ingeniously assembled the required epoxide and subsequent lactone. The impressive Suarez reaction nicely fashioned the requisite ring AB system. Furthermore, some clever transformations (**189** → **190** and **194** → **196**) were also vital to the overwhelming success of their work.

3.3 Yang, Shen and Hao's synthesis of perforanoid A (2016)

Hao's group isolated a series of limonoids from Meliaceae and Simaroubaceae species, which showed diverse biological acitivities.[61,62] In 2016, they further identified a new limonoid, perforanoid A **14**, from this plant, which contains two lactone moieties, one all-carbon quaternary stereo-centre and a novel BCD tricyclic skeleton. Together with the isolation of perforanoid A **14**, Yang, Shen and Hao disclosed their efforts toward the first total synthesis of this molecule involving Rh-catalysed Pauson–Khand reaction as the key transformation (Scheme 8).[63]

Initially, their efforts focused on the establishment of the ring BCD system of the target (Scheme 8a). Treatment of furan-3-carbaldehyde **197** with 2-butenyl methyl zinc in the presence of chiral ligand **198**[64] initiated an enantioselective alkenylation reaction. The chiral secondary alcohol **199** was generated with good yield (80%) and high ee (90%). Taking inspiration from the work of Morken,[65] treatment of **199** with 2-methyl-2-(vinyloxy)-propane under Pd-catalysed oxidative cyclization,[66] [$Pd(OAc)_2$/BQ/AcOH], formed **200** with ring D installed. Then **200** was advanced to iodide **201** *via* Zr-mediated iodination. At this stage, the authors envisioned a cross-coupling reaction to introduce the terminal olefin. However, early efforts utilizing standard Suzuki, Negishi, and Kumada coupling conditions to transform iodide **201** into terminal olefin proved troublesome. Ultimately, it was found that Ni-catalysed coupling conditions[67] could furnish the target olefin, which subsequently underwent Jones oxidation to deliver γ-butyrolactone **202**. Moving forward, their goal was to set up an allene moiety. Exposure of **202** to excess LiHMDS generates a transient enolate, thus allowing the sequential coupling reaction with methyl carbonochloridate and Waser's reagent **203**[68] to furnish **204** as a 6 : 1 diastereomeric mixture. Note that the mixture of diastereomers in **204** proved inconsequential since both isomers could be converted into allene **205** *via* decarboxylation.

In the key step of the synthesis, the authors speculated a metal-catalysed Pauson–Khand reaction strategy to create the ring BC system of the target. Pleasingly, subjecting allene **205** to Rh-catalysed Pauson–Khand reaction conditions {$[Rh(CO)_2Cl]_2$/CO/toluene/120 °C} furnished tetra-cycle **206** (85%).



Scheme 8 Yang, Shen and Hao's synthesis of perforanoid A (2016).

Note that a low reaction concentration (0.008 M) was crucial to this transformation.

With tetra-cycle **206** in hand, their next task was the construction of ring A system, lactone **215a**/**215b** (Scheme 8b). The project commenced with the copper-mediated 1,4-addition of Grignard reagent to furanone **207**, leading to adduct **208a**/**208b** in 60% yield with a 3 : 2 dr value at C10. The mixture of **208a**/**208b** was subjected to olefin ozonolysis followed by aldehyde reduction, furnishing corresponding alcohol **209a**/**209b**, which was protected to TBS ether **210a**/**209b**. With access to **210a**/**209b**, $AlMe_3$-mediated amidation with $Me_2NH \cdot HCl$ allowed **211a** (53%) and **211b** (32%). To identify the stereochemistry of C10 in perforanoid A **14**, the authors transformed **211a** and **211b** into **215a** and **215b**, respectively. Dess–Martin oxidation of **212a** afforded ketone **212a**, which set the stage for the subsequent one-pot addition of MeMgCl followed by acid-mediated lactonization, forming lactone **213a** with ring A established. Notably, lactone **213b** could also be prepared from **213b** *via* the abovementioned routes. Equipped with **213a**/**213b**, redox manipulations were required to access **215a**/**215b**. Removal of TBDPS ether in **213a** followed by DMP oxidation gave rise to aldehyde **215a**. Identical manipulations were conducted for the synthesis of **215a** from **213b**. It is worth noting that the aldehyde was obtained without epimerization under DMP oxidation. Moving forward, the authors employed Mosher's method to determine the absolute stereochemistry at C10 in **215a** and **215b**, which was *S* and *R*, respectively.

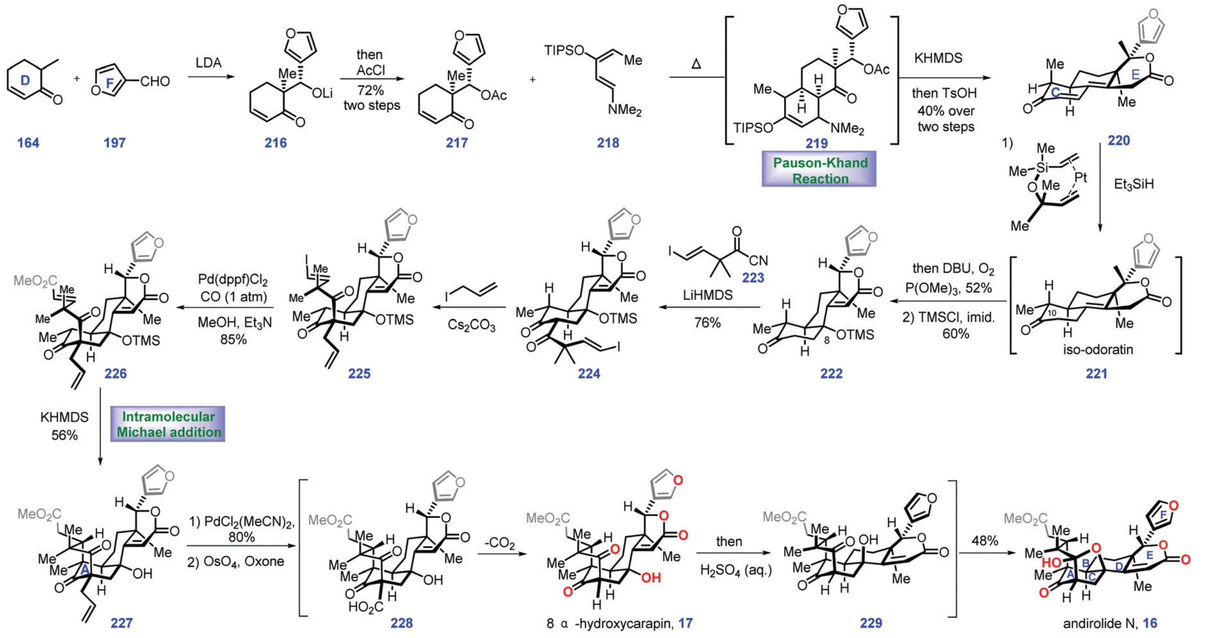
To complete the synthesis of perforanoid A **14**, they sought to append lactone ring A onto tetra-cycle **206**. Pleasingly, the authors found LDA-mediated aldol reaction of key fragment enone **206** with aldehyde **215b** followed by dehydration accomplished perforanoid A **14**. In a parallel experiment, **215b** provided 10-*epi*-perforanoid A **15**. Then the synthesized perforanoid A **14** was subjected to biological investigation, which demonstrated potent anti-tumor activities with IC_{50} values ranging from 3.91 to 6.17 μM.

In their synthesis, the successful and tactful utilization of the key PKR reaction ensured efficient completion of this synthesis in 10 steps. A clever Pd-catalysed oxidative cyclization strategy was also tactfully executed to establish ring D. The efficient PKR reaction together with elegant Pd-catalysed oxidative cyclization will undoubtedly enrich the synthetic strategy in limonoid synthesis.

3.4 Newhouse's synthesis of (±)-andirolide N and 8α-hydroxycarapin (2017)

Screening the extracts of flowers of a mahogany tree from the Amazonian rainforest (*Carapa guianensis*) by Tanaka and co-workers resulted in the isolation of andirolide N **16**,[69,70] a limonoid tetranortriterpenoid natural product, which featured a bicyclo[3.3.1]nonane core with bridged tetrahydrofuran ring system. In 2017, Newhouse and co-workers reported their efforts toward the total synthesis of (±)-andirolide N **16** and 8α-hydroxycarapin **17** *via* intermolecular Diels–Alder reaction and stereoselective intramolecular Michael addition as the key protocols (Scheme 9).[71]

The project started at the synthesis of iso-odoratin **221**. Treatment of the known compound **164**[72] with LDA led to a transient lithium enolate, thus allowing a diastereoselective aldol reaction with 3-furaldehyde **197**. The resultant alkoxide **216** was protected with AcCl to obtain furan **218,** which served as a precursor for a thermal Diels–Alder reaction with Rawal-type diene **218**. The cyclo-adduct **219** was generated as a mixture of diastereomers. Treating **219** with KHMDS triggered an intramolecular aldol reaction followed by β-elimination of



Scheme 9 Newhouse's synthesis of (±)-andirolide N and 8α-hydroxycarapin (2017).

the dimethylamino group. The resulting product was desilylated and dehydrated under TsOH to deliver lactone **220** as a mixture of diastereomers at C10 (1 : 1 dr), which proved inconsequential since both of these mixtures could be transformed into iso-odoratin **221** as a single diastereomer *via* a hydrosilylation reaction (Karstedt's catalyst, Et_3SiH).[73]

With **221** in hand, their attention turned toward completion of (±)-andirolide N **16**. Installation of a hydroxyl group at C8 in the limonoid framework posed a challenge in the semi-synthesis.[74] Fortunately, the authors identified that subjecting the crude iso-odoratin **221** to alkene hydration conditions [$P(OMe)_3$/DBU/O_2] followed by alcohol protection furnished **222** with the desired C8 hydroxyl secured. With access to **222**, they sought to construct the bicyclo-[3.3.1]nonane framework of the target. Exposing **222** to LiHMDS initiated the transient lithium enolate, which was *in situ* treated with acyl cyanide **223** to achieve di-ketone **224**. The authors speculated that the devised acylation strategy[75] minimized the retro-aldol and aldol condensation side reactions. Furthermore, it was found that the blocked α-position of the 1,3-diketone[76] is crucial in the subsequent Michael addition to form the bicyclo-[3.3.1]nonane skeleton. After extensive attempts, the authors discovered that a carbon-based blocking group could be engaged in the formation of the bridged bicycle. In practice, **224** was processed through α-allylation to deliver **225**. In this key transformation, the allylic group approached di-ketone **224** from the less hindered convex face, adopting the favored geometry for the synthesis of the bridged ring system.

Stepping forward, their next objective was to install the Michael addition precursor. Here, the authors devised a palladium-catalysed carbomethoxylation reaction, which successfully assembled **226** from **225**. In the key step of this synthesis, exposure of **226** to KHMDS triggered an intramolecular Michael addition. The sterically congested **227** was generated with the bicyclo[3.3.1]nonane motif installed. With **227** in hand, a Pd-catalysed alkene isomerization[77] followed by oxidative cleavage[78] gave rise to **228**, which served as a substrate for spontaneous decarboxylation, resulting in 8α-hydroxycarapin **17**. To complete the synthesis of (±)-andirolide N **16**, inversion of the tertiary alcohol was requisite. Pleasingly, exposing **17** to acidic aqueous conditions furnished the diastereomeric alcohol of 8α-hydroxycarapin, **229**. The authors reasoned that a stabilized carbocation conjugated to the neighboring enolate accounted for this stereochemical inversion. Finally, ketalization of alcohol **229** completed the synthesis of the thermodynamically favored (±)-andirolide N **16**.

In Newhouse's synthesis, both the stereoselective Diels–Alder reaction and well-designed intramolecular Michael addition enabled completion of the target in only 12 steps from commercially available materials. Some ingenious stereocontrol reactions (**224** → **225** and **17** → **229**) were vital to the overwhelming success of this work. The advanced intermediate iso-odoratin **221** could be obtained in a batch of 15 g, which supplies sufficient materials to fulfil the target molecules.

3.5 Newhouse's synthesis of xylogranatopyridine B (2018)

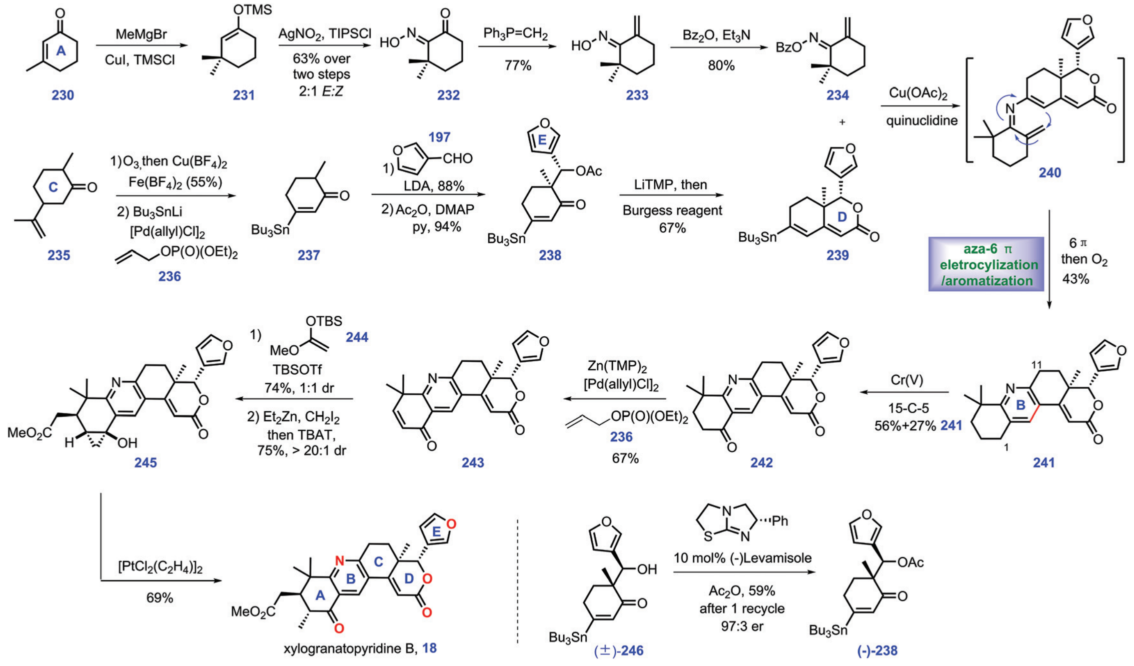
In 2014, xylogranatopyridine B **18**, a structurally unique limonoid identified from the leaves of a Chinese mangrove tree (*Xylocarpus granatum*),[79] which featured a pyridine ring in its core. In 2018, Newhouse and co-workers reported the total synthesis of (−)-xylogranatopyridine B **18**, involving aza-6π-electrocyclization/oxidative aromatization as a key transformation (Scheme 10).[80] Initially, they targeted an enone functionalization reaction, where reliable conditions were established to achieve the construction of oxime **234**. Treatment of 3-methyl-2-cyclohexenone **230** with MeCu initiated the 1,4-addition. The stannane precursor facilitated the synthesis of xylogranatopyridine B. In practice, the project commenced with the resulting copper enolate *in situ* trapped with TMSCl to afford enoxysilane **231**, which served as a precursor for Yamamoto's oxime formation reaction ($AgNO_2$/TIPSCl),[81] leading to α-keto oxime **232**. Then, **232** was advanced to oxime **234** *via* a two-step conversion, including ketone methylenation and *O*-benzoylation.

Then, their synthetic efforts turned to assembly of fragment stannane **239**. The project began with the commercially available dihydrocarvone **235**. Ozonolytic fragmentation[72] of **235** followed by Pd-catalysed oxidative stannylation[82] generated stannane **237**.

Exposure of **237** to LDA yielded lithium enolate, which was subsequently treated with 3-furaldehyde **219** to undergo a diastereoselective aldol reaction, followed by its capture by acylation to furnish **238**. With **238** in hand, enone fragment **239** was assembled *via* LiTMP-promoted intramolecular aldol reaction followed by trapping with Burgess reagent.

With fragments **234** and **239** in hand, the authors envisioned an aza-6π-electrocyclization and aromatization strategy to install pyridine ring C. However, initial screenings to merge these two fragments *via* Chan–Lam coupling conditions[83,84] proved challenging since oxime **234** and stannane **239** decomposed during the reaction. Fortunately, it was discovered that when the aforementioned amine additives[85] were replaced with quinuclidine, the key aza-6π electrocyclization/aromatization ensued, thus forming **241** with the full ring system established. Notably, when each of the oxime isomers were separately evaluated in the Chan–Lam coupling, both reactions proceeded smoothly, which was attributed to the thermal isomerization of either **234** or **240** in the reaction. Accordingly, the authors applied the isomeric mixture of **234** in this transformation.

With installed **241**, they next focused on developing conditions to achieve the selective oxidation of benzylic at C1 over C11. They speculated that the *meta*-position (C1) of pyridine was more electron-rich than its *ortho*-position (C11).[86] Hence, various oxidants were evaluated to achieve this transformation. Ultimately, they identified that a Cr(v) complex[87] was capable of engaging this chemo-selective oxidation, yielding ketone **242** in 56% yield together with 27% recovered **241**. According to the protocol from their previous work,[82] a Pd-catalysed α,β-dehydrogenation of ketone **242** afforded enone **243**, which served as substrate for a Mukaiyama–Michael reaction with



Scheme 10 Newhouse's synthesis of xylogranatopyridine B (2018).

enoxysilane **244**, resulting in a 1 : 1 diastereomeric mixture of enolate at C5. However, the subsequent capture of the transient enolate *via* methylation failed since the target **18** was less stable in basic conditions. Alternatively, they devised a Simmons–Smith cyclopropanation strategy, a neutral condition, to circumvent this issue. Exposure of the transient enolate to ZnEt$_2$/CH$_2$I$_2$ initiated cyclopropanation with excellent diastereoselectivity (>20 : 1 dr). Then, the TBAT-promoted deprotection of the siloxycyclopropane gave a single diastereomer **245** together with a mixture of C5 epimers (combined 75% yield).

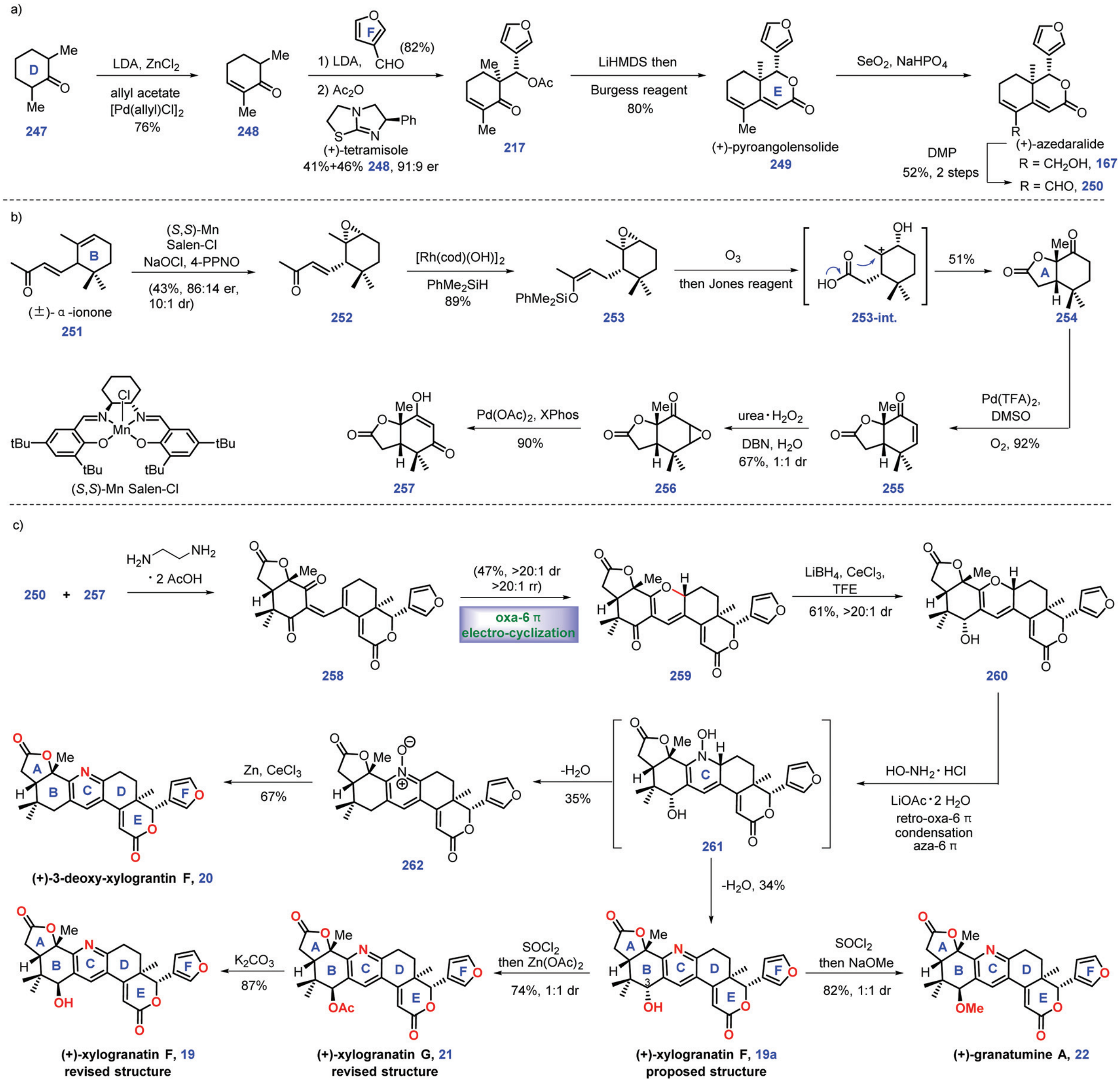
Finally, they conducted a cyclopropanol opening reaction *via* Zeise's dimer, [PtCl$_2$(C$_2$H$_4$)]$_2$,[88] to complete xylogranatopyridine B **18**. It is worth noting that they further prepared chiral acetate (−)-**238** (43%, 94% ee) on a decagram scale *via* Birman's acylative kinetic resolution of alcohol (±)-**246**.[89] The chiral (−)-**238** secured (−)-xylogranatopyridine B **18**. In Newhouse's synthesis, xylogranatopyridine B **18** was achieved *via* the longest linear 11 steps from commercially available materials. A credible aldol reaction was devised to join ring D and ring E. A novel enone functionalization strategy was devised to prepare the stannane compound (ring A), which was successfully utilized to merge with ring CDE *via* a Pd-catalysed Chan–Lam coupling reaction. The impressive aza-6π electrocyclization/oxidative aromatization nicely installed the core pyridine ring C, thus providing a reliable platform for the synthesis of other pyridine-based limonoids.

3.6 Newhouse's synthesis of (+)-granatumine A and related bislactone (2019)

In 2014, Guo and co-workers identified a bislactone limonoid alkaloid named granatumine A **22** from Chinese mangrove (*Xylocarpus granatum*). Biological investigation demonstrated that it exhibited moderate inhibitory activity against PTP1B.[79] In 2019, Newhouse's group reported the first total synthesis of (+)-granatumine A **22** and related bislactone[90] employing Pd-catalysed ketone α,β-dehydrogenation and convergent Knoevenagel condensation/carbonyl-selective electro-cyclization as key protocols (Scheme 11). At the beginning, the authors targeted azedaralide derivative **250** (Scheme 11a). Dehydrogenation of ketone **247** to **248** *via* known literature procedures,[101] such as Birch reduction or bromination/elimination methods,[91] proved unsuccessful.

Inspired by their original work,[82] palladium-catalysed α,β-dehydrogenation of ketone **247** successfully delivered enone **248**. In this transformation, they successfully developed a less expensive reaction condition, which utilized allyl acetate as an oxidant, LDA as a base and 1 mol% loading of palladium salt as catalyst. Treatment of enone **248** with 3-furaldehyde under (+)-tetramisole[89] induced an acylative kinetic resolution, leading to acetoxy **217** in 41% yield with 82% ee. Note that the undesired enantiomer could be recovered as **248** *via* a retro-aldol reaction. LiHMDS-initiated intramolecular aldol reaction of **217** followed by dehydration (Burgess Reagent) furnished (+)-pyroangolensolide **249**, which served as a precursor for the subsequent methyl site-selective allylic oxidation, thus generating (+)-azedaralide **167**. Dess–Martin oxidation of the resulting alcohol in **167** formed aldehyde **250**.

With aldehyde **250** in hand, the authors set about for the construction of 1,3-diketone **257** (Scheme 11b). Upon subjecting (±)-α-ionone **251** [92] to Jacobsen's epoxidation conditions,[93] direct kinetic resolution ensued, thus providing the desired epoxide (−)-**252** (43%, 86 : 14 er, 10 : 1 dr). [RhCl(OH)]$_2$ cata-



Scheme 11 Newhouse's synthesis of (+)-granatumine A and related bislactone (2019).

lysed the hydrosilylation[94] of enone **252** to give enoxysilane **253**. Treatment of **253** with ozone followed by Jones oxidation furnished ketone **254**. The authors envisioned that intermediate **253-int** was responsible for this transformation, where acid-mediated opening of the epoxide followed by its capture by carboxylic acid and oxidation of the resultant secondary alcohol occurred. Inspired by the work of Stahl,[31] the Pd-catalysed oxidative dehydrogenation of **254** furnished enone **255**, which was subjected to nucleophilic epoxidation conditions (urea H_2O_2, DBN), forming epoxide **256** as an inconsequential 1 : 1 diastereomeric mixture.

Here, they sought to install the core tetra-substituted pyridine ring of the target (Scheme 11c). In practice, they anticipated to utilize a Pd-mediated α,β-epoxy ketone opening reaction[95] of epoxide **256** to construct which, however, **257** was unsuccessful. After extensive experiments, they found that phosphine ligands XPhos were capable of engaging this transformation, thus affording **257** in good yield (90%).

Pressing forward, key fragments di-ketone **257** and aldehyde **250** were then merged *via* Knoevenagel condensation[96] to give enedione intermediate **258**, followed by the vital oxa-6π electrocyclization[97] under thermal conditions to install 2H-pyran **259** as the kinetically and thermodynamically favored product, which was further confirmed *via* DFT calculation. The C3 ketone in **259** was converted into allylic alcohol **260** *via* site-selective Luche reduction. Notably, the utilization of less nucleophilic solvents, such as CF_3CH_2OH, was crucial in minimizing the decomposition of the reactants.

With alcohol **260** in hand, the authors then constructed the final pyridyl ring through treatment with hydroxylamine under reflux, giving the originally proposed structure of (+)-xylogranatin F **19a**. Then, they turned their synthetic efforts toward

(+)-granatumine A **22**. Initially, their attempts to treat derivative **19a** with methoxide *via* SN2 displacement proved challenging since an SN1 solvolysis pathway dominated in this transformation. Ultimately, the one-pot chlorination of benzylic alcohol **19a** followed by methanolysis completed the synthesis of (+)-granatumine A **22**. Although the pyridine N-oxide in **262** could be smoothly reduced[98] to 3-deoxy-xylogranatin F **20**, the following benzylic oxidation of **20** into (+)-xylogranatin F **19a** proved troublesome due to the increased steric demand and enhanced deactivation energy by inductive effects. Note that the authors discovered the NMR structure prediction calculations were not in accordance with the originally proposed structure of xylogranatin F **19a**. Accordingly, they sought to its chemical synthesis to address this unclarified issue. Learning from their proposed biosynthesis, they hypothesized that the correct structure was the C3-epimer of **19**. In practice, the $SOCl_2$-mediated chlorination of alcohol **19** followed by Zn$(OAc)_2$-promoted substituted reaction completed the synthesis of (+)-xylogranatin G **21**. Ester hydrolysis of **21** furnished **19**, whose spectral data was in accordance with that reported for (+)-xylogranatin F **19**.

In Newhouse's synthesis, the elegant utilization of Knoevenagel condensation/carbonyl-selective electrocyclization in conjunction with a modified Pd-catalysed ketone α,β-dehydrogenation provided an efficient and credible platform for the synthetic campaign of related limonoid molecules. A clever ring-opening of epoxide followed by trapping with carboxylic acid rapidly enabled the desired *cis*-lactone. Impressively, the key precursor **250** could be rapidly constructed in 6 steps, thus allowing the complete synthesis of (+)-xylogranatin F **19** in 10 steps.

4. Highly decorated limonoids and limonoid-like natural products

4.1 Watanabe's formal synthesis of azadirachtin (2015)

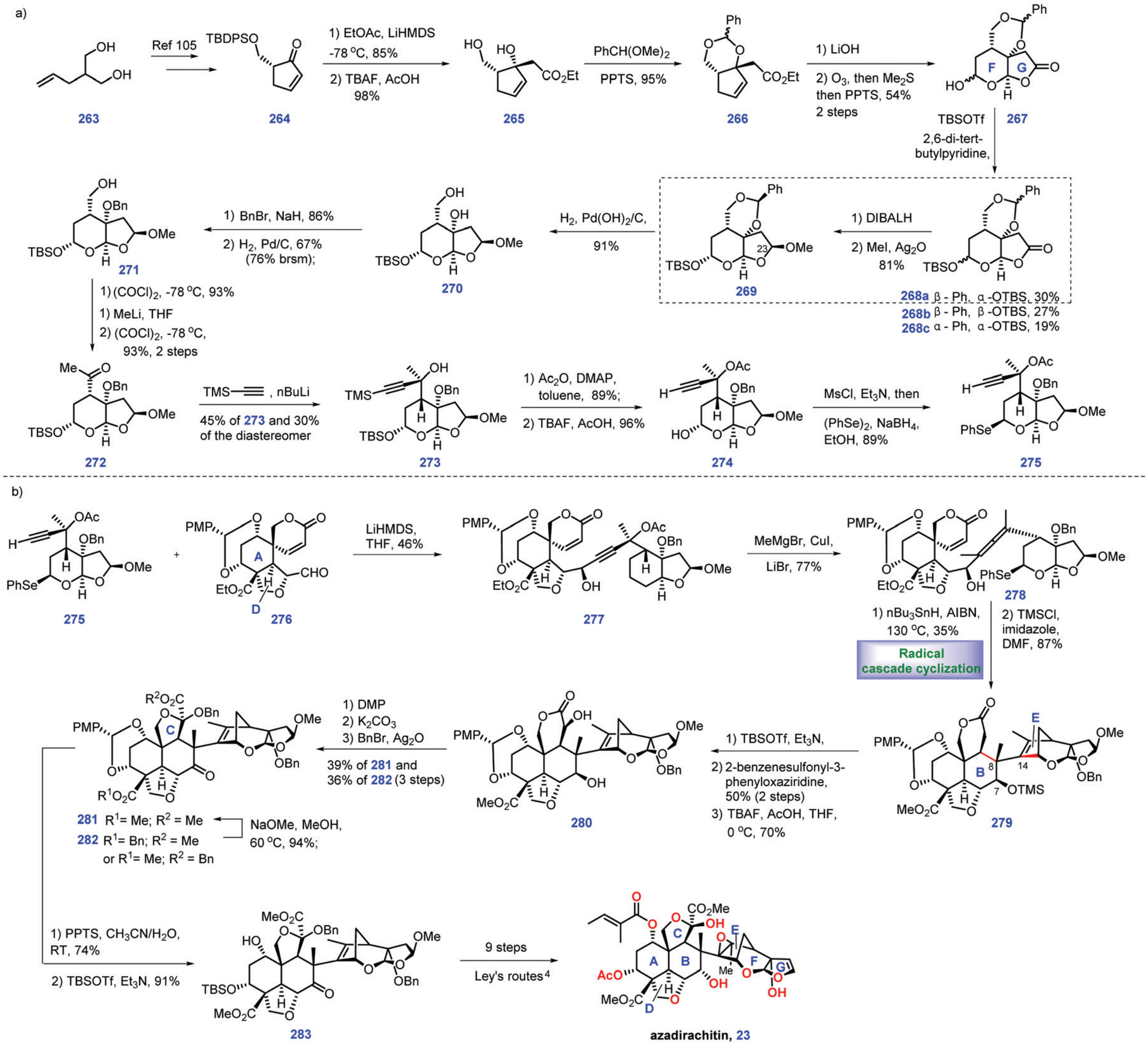
In 1968, azadirachtin **23** was isolated from the neem tree Azadirachta indica A. Juss (Meliaceae). It featured sixteen contiguous stereogenic centers with multiple oxygen-containing functional groups.[99] However, its accurate structure was not determined until 1987.[100] Biological evaluations have demonstrated that it possesses antifeedant and growth disruption properties against insect species.[101] The key challenge in the synthesis of **23** involves the installation of the sterically hindered C8–C14 bond. Numerous synthetic endeavours for azadirachtin **23** have been demonstrated.[102] However, only Ley's group achieved its landmark total synthesis in 2007, which has been discussed in Heasley's review (2011).[102] In 2015, Watanabe and workers disclosed another protocol to fulfil the asymmetric formal synthesis of azadirachtin **23**, involving a novel radical initiated cascade cyclization reaction as a key step to install the challenging C8–C14 bond (Scheme 12).[103] Knowing that Watanabe's synthesis of fragment **276**[104] has been discussed in Heasley's review,[2] it will not be duplicated here.

Watanabe's efforts to construct fragment **275** commenced with diol **263**, which was first converted into the known (*R*)-**264**[105] (Scheme 12a). **264** served as substrate for an aldol reaction with ethyl acetate to arrive at **265** (Scheme 16a). Initial experiments to protect the tertiary alcohol with benzyl ether proved troublesome. In comparison, the authors devised an alternative route where the TBS ether was deprotected followed by masking the resultant diol as cyclic acetal **266.** Hydrolysis of ester **266** resulted in an acid product, thus allowing ozonolysis of the double bond, followed by PPT-promoted hemi-acetylation. Compound **267** was obtained with four inseparable diastereomers. Treatment of **267** with TBSOTf afforded the desired **268a** and undesired **268b**/**268c**. The authors noted that a bulkier base, 2,6-di-*tert*-butylpyridine, played a key role in generating the product with good yield.

Stepping forward, the authors planned to establish conditions for the conversion of the lactone moiety into methyl acetal. According to the protocol of Ley's work,[4] utilization of β-acetal at C23 **268a** was engaged in a one-pot reduction/methylation to give **269**. However, treating **268b** and **268c** with the same conditions as **268a** only gave the products as 1.1 : 1 and 1.3 : 1 diastereomeric mixtures, respectively. Initially, exposure of **269** to DIBAL failed to give **271**. Instead, **269** could be processed through three additional manipulations, involving Pd-catalysed de-protection of cyclic acetyl, benzyl protection of diol and selective de-protection of primary alcohol to form **271**. Sequential Swern oxidation of the primary alcohol, addition of MeLi to the aldehyde and Swern oxidation of the second alcohol afforded ketone **272**. Reacting **272** with lithium trimethylsilylacetylide delivered tertiary alcohol **273** (45%), together with its diastereomer (30%). **273** was treated with Ac_2O and the resultant product was subjected to the global deprotection of silyl ether to yield **274**. Mesylation of the alcohol in **274** followed by displacement with a phenylseleno group provided fragment **275**.

Pressing forward, their goal was to incorporate fragment **276** and selenium **275** (Scheme 13b). Treatment of **275** with LiHMDS generated lithium acetylide, thus allowing for a nucleophilic addition with aldehyde **276**.[104] Pleasingly, the coupling product **277** was obtained in 46% yield. Exposing **277** to a methyl-copper reagent triggered an SN2′ reaction, furnishing allene **278**,[106,107] which functioned as a radical cyclization precursor. After extensive investigation, the authors discovered that DMF was the optimal solvent for this reaction.

Here, their next task was to develop conditions for the crucial radical cyclization. After extensive screening, the authors eventually identified the conditions (nBu$_3$SnH, AIBN, DMF/130 °C) was capable of engaging the key radical cyclization, leading to the cyclized product with the key C8–C14 bond established. TMS protection of the alcohol in above cyclized product generated **279**, which could be utilized as a substrate for treatment with TBSOTf, thus providing the resultant silyl ketene acetal compound, which was subsequently oxidized by the Davis reagent to form the alcohol product. The authors noted that the free hydroxyl group at C7 resulted in the decomposition of the reactants. Subsequently, global removal



Scheme 12 Watanabe's formal synthesis of azadirachtin (2015).

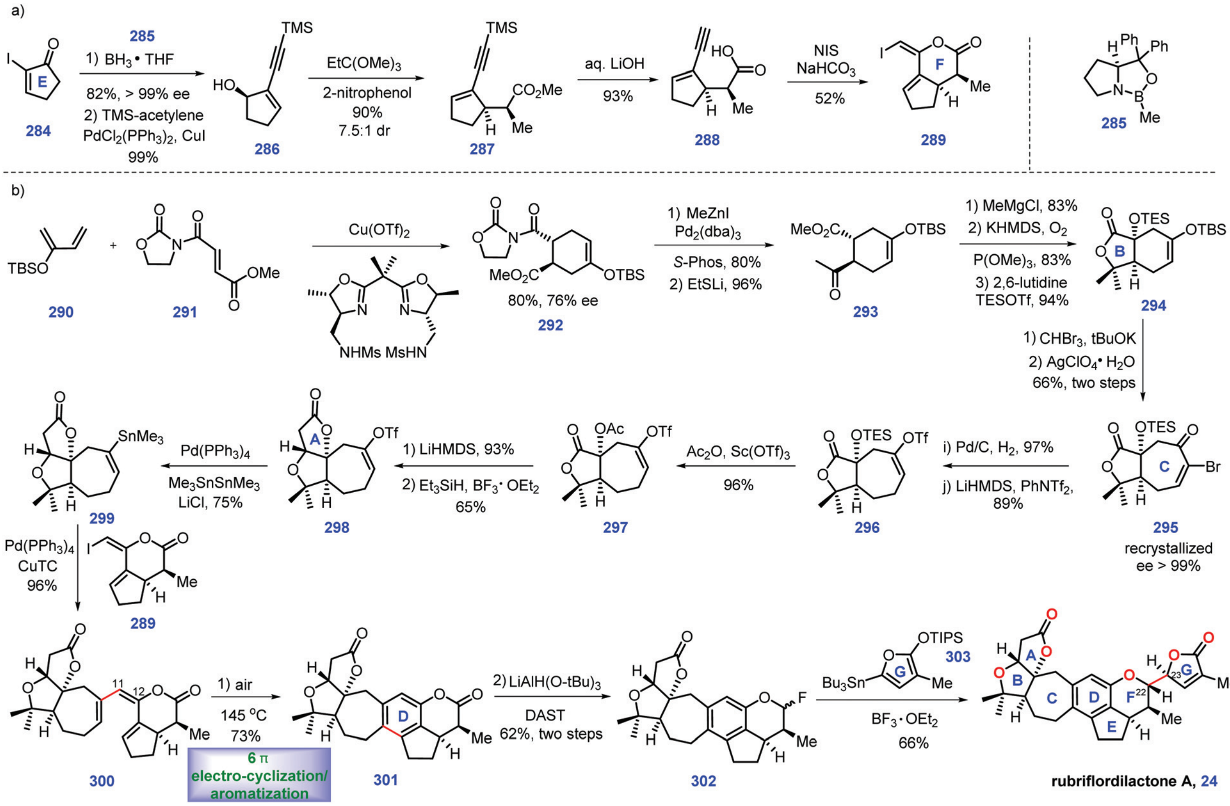
of the silyl ether protecting group provided **280.** DMP oxidation of **280** followed by methanolysis furnished the cyclic hemiacetyl product, which was further treated with BnBr/Ag_2O to furnish **281** together with benzyl ester **282.** It is notable that **282** could be recycled to **281** *via* methanolysis. In the final stages of the synthesis, PPTS promoted deprotection of *p*-methoxy-benzylidene acetal followed by the site-selective protection of C3 alcohol with TBSOTf to complete **283.** According to the protocol of Ley's work,[4] **283** could be advanced to azadirachtin **23** *via* a 9-step sequence. One contribution of Watanabe's synthesis was the development of a rapid route to obtain the optically active right-hand segment. Their effort qualifies as a landmark in the synthesis of azadirachtin due to its successful connection of the highly steric ring B and ring E system *via* a genius key intramolecular tandem radical cyclization.

4.2 Li's synthesis of rubriflordilactone A (2014)

Some of nortriterpenoids can be considered as limonoid-like natural products, which are widely distributed in *Schisandra* plants.[108] They have attracted increasing synthetic attention from the researchers[109] due to their diverse and excellent biological activities. Yang's group has made significant progress in the total syntheses of several schinortriterpenoids,[110–113] including schindilactone A (2011),[110] propindilactone G (2015),[111] lancifodilactone G acetate (2017)[112] and 19-dehydroxyarisandilactone A (2017),[113] all of which were highlighted in their recent report (2019).[114] Hence, we will not duplicate the abovementioned works in this review.

In 2006, Sun and co-workers reported isolation of rubriflordilactones A and B from *Schisandra rubriflora*,[115] which have widespread use in traditional Chinese medicine to treat illness. Structurally, they feature a 5/7/5/5/5-fused pentacyclic ring system. Biological investigation showed that rubriflordilactone B **32** was found to show potent anti-HIV activity.

In 2014, Li and co-workers described the total synthesis of rubriflordilactone A **24** (Scheme 13).[116] According to their successful experience[117] in utilizing the 6π-electrocyclization/aromatization strategy to install the complex natural products,



Scheme 13 Li's synthesis of rubriflordilactone A (2014).

they managed to employ this protocol in the synthesis of rubriflordilactone A **24**. Their efforts began by forming fragment **289** (Scheme 13a). CBS (**285**)-mediated 1,2-reduction of enone **284** followed by Sonogashira coupling with TMS-acetylene gave **286**. Subjecting alcohol **286** to John–Claisen rearrangement conditions[118] [2-nitrophenol (2 mol%), EtC(OMe)$_3$, 100 °C] gave methyl ester **287**, which was employed as a substrate for a saponification reaction, leading to acid **288**. Stereospecific iodolactonization[119] of **288** transformed it into E-alkene **289** with the desired ring F installed. The authors noted that **289** should be prepared *in situ* since it is unstable when preserved.

Equipped with **289**, their goal was to assemble fragment **299** (Scheme 13b). Treating diene **290** with dienophile **291** *via* a Cu-catalysed asymmetric Diels–Alder reaction[120] furnished chiral **292** with 76% ee. LiSEt-mediated removal of the oxazolidinone moiety in **292** followed by a Pd-catalysed Negishi cross coupling reaction[121] with Me$_2$Zn resulted in ketone **293**. Inspired by Yang's synthesis of schindilactone A,[110] **293** was then processed through three additional operations, involving nucleophilic addition of methyl Grignard reagent to ketone followed by *in situ* lactonization, α-hydroxylation of lactone and TBS protection of the resultant alcohol to form lactone **294**. **294** was then converted into bromoenone **295** *via* a two-step transformation. Notably, **295** could be recrystallized to receive the near optically pure **295** (>99% ee). Subjecting enone **295** to 1,4-reduction conditions (Pd/C, H$_2$) allowed *in situ* debromination to transform it into cycloheptanone which served as a precursor for a triflation reaction, thus generating **296** with excellent regioselectivity. The authors speculated that the steric difference between the α and α′ positions of the carbonyl accounted for this selectivity. Replacement of the TES ether in **296** with an acetate group yielded acetate **297**, thus setting the stage for intramolecular Dieckmann condensation. BF$_3$·OEt$_2$/Et$_3$SiH-mediated[122] deoxygenation of the resultant hemi-ketal species gave **298**. With access to **298**, Pd-catalysed Stille cross-coupling reaction[123] with Me$_3$SnSnMe$_3$ afforded stannane **299**.

Equipped with **299** and **289**, the authors devised a coupling reaction to merge fragments **299** and **289**. After extensive screenings, they identified that Pd(0)/CuTC[124] was capable of engaging the Stille-Migita reaction, providing target triene **300** in high yield (96%). Here, their goal was to develop conditions to fulfil the key π-electrocyclization/aromatization protocol. The authors envisioned that rigid E-geometry of the C11–C12 bond was crucial to the cyclization. Pleasingly, exposure of triene **300** under heat at air atmosphere triggered cascade 6π-electrocyclization/aromatization, thus forming arene **301**. LiAlH(O*t*-Bu)$_3$[125] mediated the regioselective reduction of C26 ketone, which generated a mixture of **301** together with its ring-opened aldehyde. With access to **301**, the final step was to attach the lactone motif appendage onto C22. However, exposure of the abovementioned mixture **301** with siloxy furan did not deliver the coupling product but an open-chain alcohol. The author reasoned that the ring strain of the 6,5,6-

tricyclic system in conjunction with the easily dissociated tendency of the phenoxide moiety accounted for this outcome. Here, they added DAST[126] to this mixture of lactol/aldehyde, which successfully gave fluoride **302**. Meanwhile siloxy furan was elaborated to the electron-richer donor stannane **303**.[127] Ultimately, the treatment of fluoride **302** with stannane **303** *via* $BF_3 \cdot OEt_2$-mediated[128] SN2 displacement gave rubriflordilactone A. To confirm the stereochemistry of the final step, a model reaction was conducted, and the resultant product was confirmed by X-ray crystallographic analysis.

In Li's synthesis, the authors showcased the powerful convergent synthetic strategy in the quick assembly of complex molecules. Relying on the authors' insightful consideration, the tricky lactone F was successfully incorporated onto the core substructure. It is of great significance that the elegant application of the 6-π-electrocyclization/aromatization in this synthesis demonstrates the viability of this strategy in total synthesis.

4.3 Anderson's synthesis of (+)-rubriflordilactone A (2015)

After Li's synthesis (2014), Anderson and co-workers also reported the total synthesis of (+)-rubriflordilactone A[109] **24** (2015). Critical to the success of their endeavour was the strategic use of palladium- or cobalt-catalysed cyclotrimerization as key steps (Scheme 14).[115,129]

The project started with the construction of fragment terminal alkyne **309** (Scheme 14a). Esterification of (*S*,*E*)-pent-3-en-2-ol **305** with carboxylic acid **304** gave ester **306**, which was subjected to Ireland–Claisen rearrangement conditions followed by workup. The target acid **307** was obtained in high yield (96%) and excellent diastereoselectivity (dr > 20 : 1). Then **307** was transformed into benzyldimethylsilyl alkyne **308**,[116] the *para*-methoxybenzyl ether moiety of which was subsequently converted into terminal alkyne **309**.

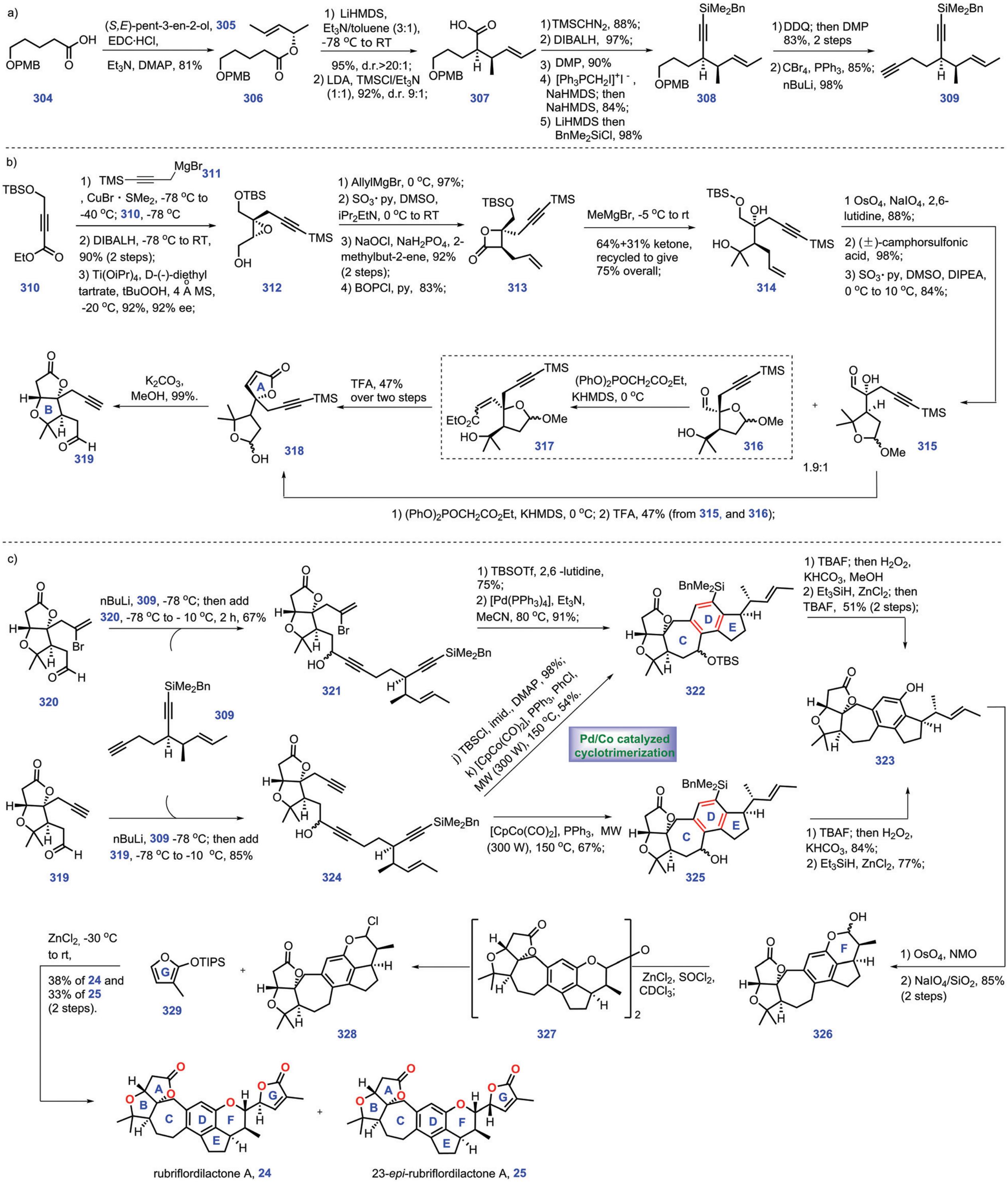
With fragment **309** in hand, they turned their attention to the synthesis of bicyclic alkyne-bearing aldehyde **319** (Scheme 14b). Their efforts began with ester **310**, which could be transformed into epoxide **312** *via* three additional operations involving alkyne carbocupration,[33,130] ester reduction and Sharpless asymmetric epoxidation.[131] Then epoxide **312** was advanced to lactone **313** through epoxide ring-opening, alcohol oxidation and β-lactonization. Treatment of **313** with methylmagnesium bromide initiated double nucleophilic addition, affording **314** with the *gem*-dimethyl group of the ring B installed. Alkene **314** was then processed through alkene oxidative cleavage, acetalization and alcohol oxidation to deliver aldehyde regioisomers **315** and **316**. Although this transformation was generated as a mixture of acetyl isomers, it proved inconsequential since both isomers could be converted into aldehyde **319**. In a real experiment, upon treatment of aldehyde **315** with $(PhO)_2POCH_2CO_2Et$, Ando olefination ensued, thus affording the alkenyl product, which served as a precursor for the acid-promoted hydrolysis of the acetal. The desired **318** was secured. Meanwhile conversion of **316** into lactol **317** was accomplished by Ando olefination.[132] TFA-mediated hydrolysis of acetal in **317** followed by lactonization led to aldehyde **318**. Exposure of **318** to base conditions (K_2CO_3/MeOH) initiated intramolecular oxy-Michael addition spontaneous lactonization to form **319** with ring AB established. Note that bromide **320** could also be prepared *via* the abovementioned protocol.

Stepping forward, their next task was to merge fragment **320** with **309** (Scheme 14c). Exposure of diyne **309** to *n*BuLi followed by treatment with aldehyde **319** furnished alcohol **321**. Here, they arrived at the key step of the synthesis. Inspired by their previous work,[133] protected propargylic alcohol was crucial to enable this key cyclization. Accordingly, TBS protection of the free alcohol in **321**, followed by a Pd-catalysed cyclization reaction installed the core ring ABCDE pentacycle **322**, which was then advanced to the fully functionalized **323** *via* phenol oxidation and benzyl deoxygenation.[134] Alternatively, the authors also envisioned a cobalt-catalysed cyclotrimerization strategy.[135] In practice, treating diyne **319** with aldehyde **320** gave rise to triyne **324**, thus allowing a subsequent cobalt-catalysed cyclotrimerization reaction under microwave heating, which led to pentacycle **325**. **325** could also be processed through a two-step process *via* Tamao oxidation followed by benzylic deoxygenation to arrive at penta-cycle **323**. Meanwhile, **324** could also be advanced to **322** *via* silylation of the alcohol followed by cobalt-catalysed cyclotrimerization.

With access to penta-cycle **323**, what remained was to install the ring FG system of the target. A two-step oxidative elaboration of **323** furnished lactol **326**, which was subsequently treated with a mixture of $SOCl_2/ZnCl_2$, thus generating chloropyran **328**, presumably *via* the quick formation of dimeric intermediate **327**. To complete the synthesis, a butenolide motif should be attached onto the core structure, chloropyran **328**. Pleasingly, treatment of **328** with siloxyfuran **329** under zinc(II) chloride[136] secured the desired cross-coupling reaction, thus providing rubriflordilactone A **24** (38%) together with its C23-epimer **25** (33%). In Anderson's synthesis, it is of significance that several stereocentres were wisely installed *via* credible transformations, such as substrate-controlled Claisen rearrangement and hydroxyl-induced titanium-catalysed asymmetric epoxidation, both of which enabled the preparation of the chiral building block in a large quantity. An ingenious metal-catalysed cyclotrimerization efficiently assembled the ring CDE system which is believed to pave the way for achieving other related natural products.

4.4 Tang's synthesis of (+)-rubriflordilactones B and C (2015)

In 2012, Sun's group identified schilancitrilactones B (**26**) and C (**27**) from the stems of *Schisandra Lancifolia*.[137] Biological investigation revealed that schilancitrilactone C demonstrated good inhibiting activity toward HIV-1, while schilancitrilactone B was inactive. In 2016, Tang and co-workers described the first total synthesis of schilancitrilactones B and C. Critical to the success of this synthesis is the beautiful use of intramolecular radical cyclization to assemble a seven-member ring, late-stage iodination, and intermolecular radical C–C bond formation (Scheme 15).[138]

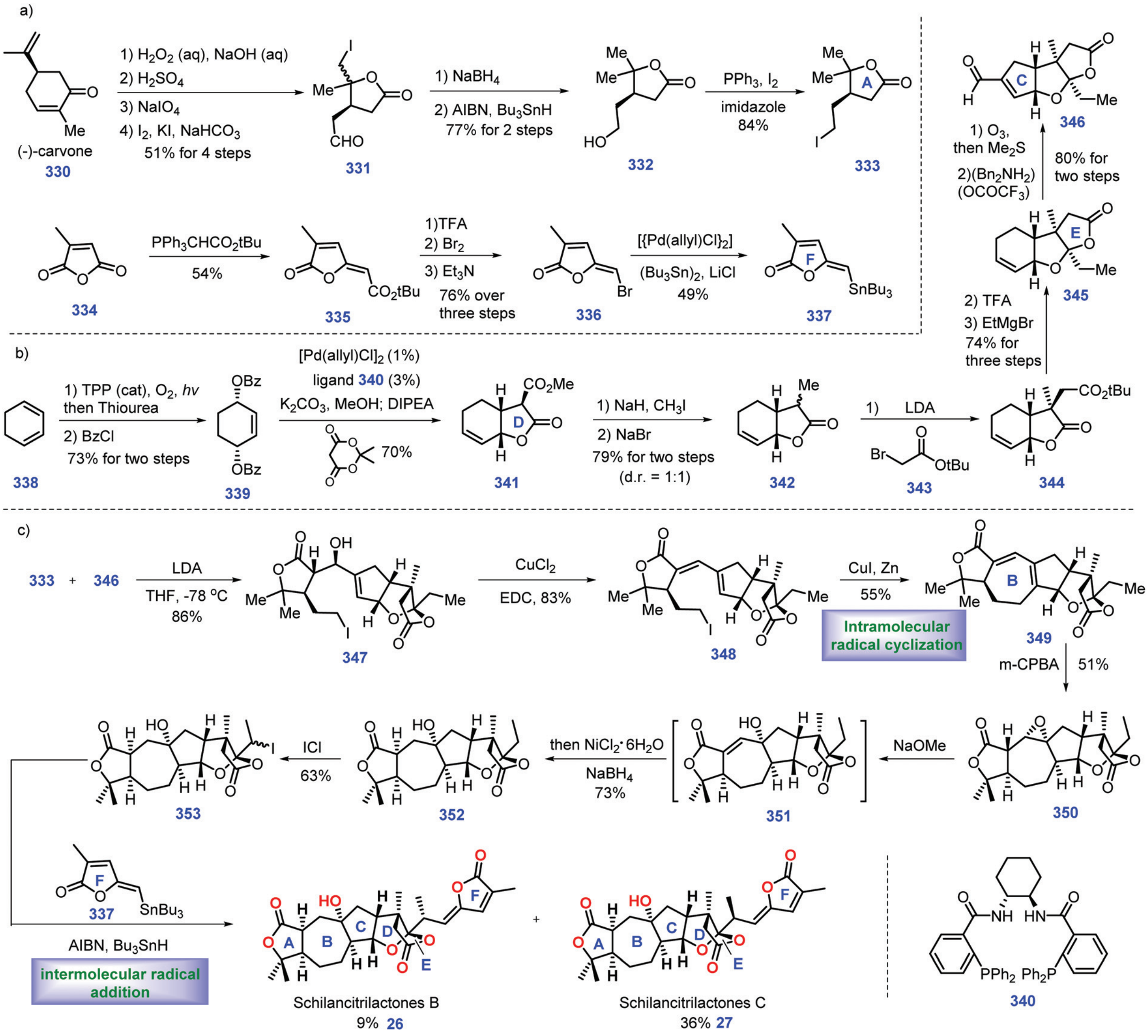


Scheme 14 Anderson's synthesis of (+)-rubriflordilactone A (2015).

Their synthetic efforts began with the construction of alkyl iodide **333** (Scheme 15a). Inspired by the work from Fukuyama's group,[139] L-carvone (**330**) was first converted into aldehyde **331** *via* a four-step manipulation,[140] including enone epoxidation, epoxide hydrolysis, diol oxidative cleavage and alkene iodo-lactonization.

Reduction of aldehyde **331** gave an alcohol compound, which served as a substrate for deiodination reaction under AIBN/Bu$_3$SnH. The resulting **332** was obtained in 90% yield. **332** was then subjected to Appel conditions to produce iodide **333**.

With **333** in hand, the authors turned their attention toward the construction of lactone **337** (Scheme 15a). Initially,



Scheme 15 Tang's synthesis of schilancitrilactones B and C (2015).

citraconic anhydride was accessed through a four-step reliable transformation to generate bromide **336**. Pd-catalysed stannylation[141] of **336** with $(Bu_3Sn)_2$ led to stannane **337**.

Moving forward, they next planned to establish fragment **346** (Scheme 15b). Taking inspiration from the work of Trost,[142] 1,3-cyclohexadiene **338** was funnelled into lactone **341** *via* a three-step sequence. **341** was then exposed to NaH/CH_3I, inducing C23 methylation, then followed by an NaBr-triggered decarboxylation reaction. The resulting **342** was accessible in 79% yield (dr = 1 : 1).

Exposure of **342** to LDA generated transient lithium enolates, which *in situ* reacted with *tert*-butyl bromoacetate **343** *via* alkylation to furnish **344**. Trifluoroacetic acid-mediated hydrolysis of the esters followed by treatment with ethyl magnesium bromide yielded **345** with the desired ethyl group installed. Ozonolysis of **345** followed by intramolecular aldol condensation produced aldehyde **346** with ring C installed.

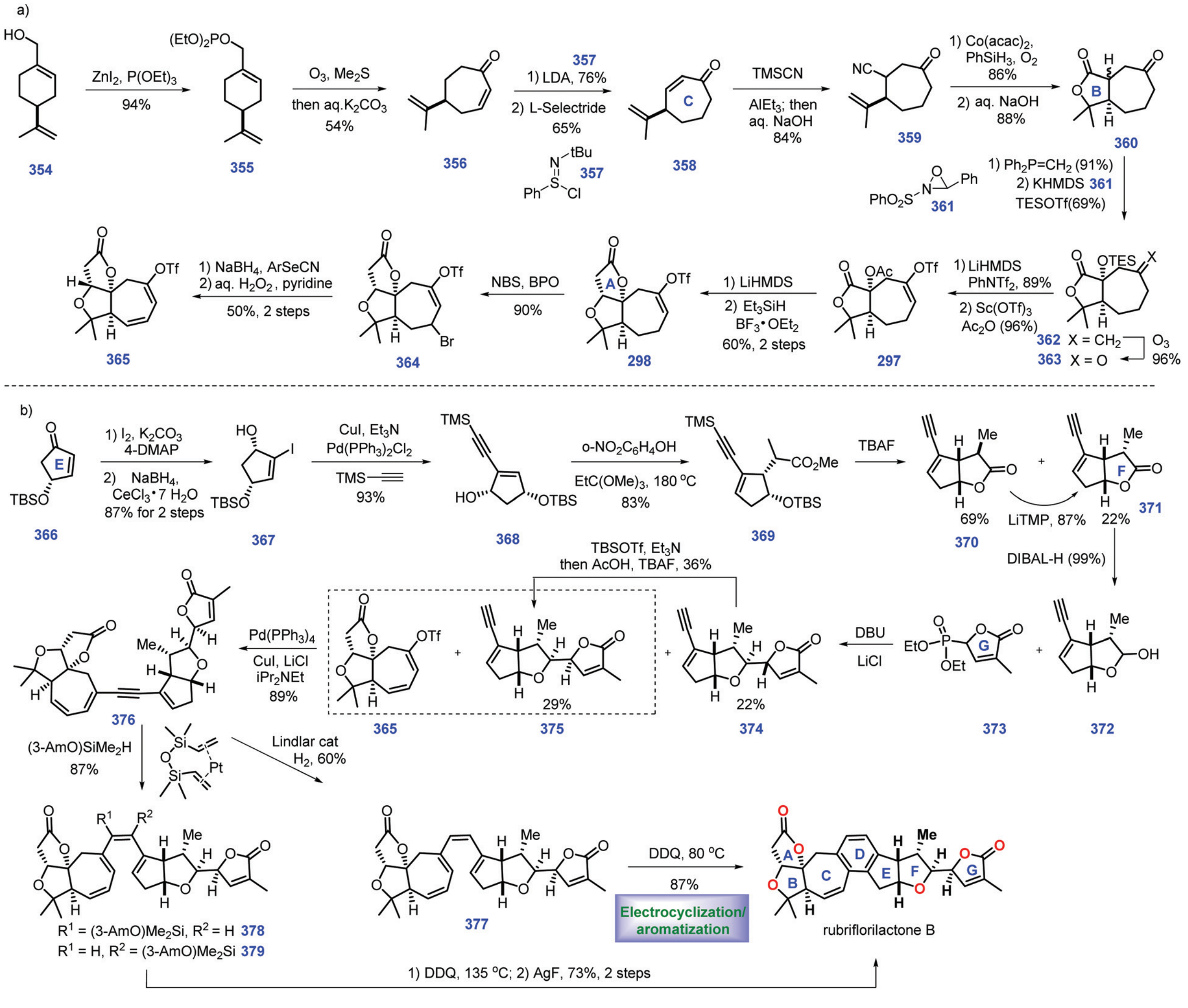
Equipped with fragments **333**, **337**, and **346**, the authors then developed conditions for the total synthesis of schilancitrilactones B **26** and C **27** (Scheme 15c). The authors first envisioned to merge **333** and **346**. In practice, exposing iodo compound **333** under LDA followed by treatment with aldehyde **346** generated alcohol **347** with an excellent dr value (17 : 1). Then $CuCl_2$-mediated dehydration[143] of **347** formed enone **348** as a 2 : 1 inseparable mixture, thus setting the stage for the key radical cyclization. Early screening to employ AIBN/nBu$_3$SnH only resulted in the decomposition of **348**. Besides, photoredox catalysis[144] was also found to be unfeasible. Ultimately, they discovered that Luche's condition[145] (CuI, Zn under ultrasound) was capable of being converted **348** into the desired cyclized product **349** with the formation of ring B. *m*-CPBA-mediated epoxidation of **349** resulted in **350**, which served as precursor for a cascade ring opening reaction/reduction (NaOMe, $NiCl_2·6H_2O/NaBH_4$), thus constructing alcohol **352**. In the final stage of the synthesis, the authors focused on appending a lactone motif onto the advanced core **352.** ICl-mediated iodination[146] at C20 in **352** provided iodo **353,** which was further treated with stannane **337** under AIBN/Bu_3SnH to complete the synthesis of schilancitrilactones B (**26**, 9%) and C (**27**, 36%).

In Tang's synthesis, the seven-membered ring was assembled brilliantly by judicious application of an intramolecular radical cyclization. A tactful late-stage iodination set the stage for the following clever intermolecular radical addition reaction, thus nicely appending the lactone motif. The above impressive strategy provides an attractive and viable alternative to the challenging late-stage connection of the fully functionalized core and lactone motif in the synthesis of complex limonoid-like natural products.

4.5 Li's synthesis of (+)-rubriflordilactone B (2016)

Following their brilliant work on the synthesis of (+)-rubriflordilactone A **24**,[116] Li and co-workers further documented their efforts toward the first and asymmetric total synthesis of (+)-rubriflordilactone B **32.**[147] Critical to the success of their endeavour was the strategic use of the 6π-electrocyclization–aromatization strategy as the key step (Scheme 16).

Their pursuit of **32** began with the preparation of fragment **365** (Scheme 16a). Subjecting **354** to Arbuzov-type reaction conditions gave rise to phosphonate **355,** which served as substrate for an ozonolysis and intramolecular HWE reaction. The resulting product, cycloheptenone **356,** was obtained in 54% yield. Mukaiyama dehydrogenation[148] of **356** generated dienone, which was followed by L-selectride-induced regioselective 1,4-reduction, thus giving the desired enone **358.** Exposure of **358** to *in situ*-prepared Et_2AlCN followed by base treatment furnished nitrile **359.** Mukaiyama hydration of **359** provided a tertiary alcohol,[24] which served as a precursor for a lactonization reaction under base conditions to transform it into lactone **360** with ring B installed. Notably, a low concentration of **359** was vital for inhibiting the undesirable bimolecular radical addition process. With **360** in hand, sequential ketone methylenation, α-hydroxylation of the lactone enolate and silylation of the alcohol gave **362** over three steps.



Scheme 16 Li's synthesis of (+)-rubriflordilactone B (2016).

Exposing this material to ozonolytic conditions afforded ketone **363**. Triflation (KHMDS, $PhNTf_2$) of **363** followed by displacement of silyl ether with an acetate group gave **297**. LiHMDS-mediated intramolecular Dieckmann condensation of **297** followed by $BF_3 \cdot OEt_2$-induced 1,4-reduction furnished lactone **298** with the ring A formed. Subjecting **298** to the conditions of NBS/BPO/85 °C triggered radical bromination at the less hindered C7, thus generating bromide **364**, which served as a precursor for selenidation, followed by oxidation and elimination reaction to afford diene **365**.

With diene **365** in hand, their attention then turned to assembly of fragment **375** (Scheme 16b). In practice, iodination of known enone **366** followed by Luche reduction delivered alcohol **367**. Pd-catalysed Sonogashira coupling of **367** with TMS–acetylene led to **368**, which was utilized as a precursor for a Johnson–Claisen rearrangement[149] to furnish ester **369**. TBAF-mediated cascade desilylation/lactonization of **369** resulted in a pair of chromatographically separable epimers, **370** and **371**. Fortunately, the authors found that the undesirable **371** could be converted into **370**. DIBAL-H induced reduction of **370** generated lactol **372**, which was treated with phosphonate[150] under Masamune–Roush conditions to construct a pair of epimers, **374** and **375** with ring G system attached. Pleasingly, the undesired **374** could be partially advanced to **375**, which functioned as a coupling precursor.

Subsequently, the authors sought to develop conditions for the completion of rubriflordilactone B **32**. In practice, the authors first attempted to connect key fragments **365** with **375** *via* a Pd-catalysed Sonogashira coupling reaction, which readily provided triene-yne **376** in 89% yield. However, initial efforts to semi-hydrogenate **376** suffered from low reaction reproducibility and less product stability. Here, hydrosilylation of **376** using Karsted catalyst[151] was successfully introduced, thus allowing **378** and **379** to be obtained as a 1 : 1 mixture. This proved inconsequential since both mixtures could be converted into rubriflordilactone B. In a real experiment, upon subjecting **378** and **379** to heat (135 °C), 6π-electrocyclization/aromatization ensued, thus providing mixed penta-substituted arenes, which were then desilylated *via* AgF to complete the target with the key ring B generated. However, the authors discovered the spectra of the synthetic product were not identical to the authentic material. Although they further synthesized 23-*epi*-rubriflordilactone B, its spectra also did not match that of the isolated material. From a strategic perspective, the clever electrocyclization–aromatization sequence exemplified in this work is efficient and tactful, which provides a creative strategy to assemble a benzene ring in complex molecules. The successful utilization of the hydrosilylation approach is critical to the overwhelming success of this process. Although the synthetic products did not match the authentic material, the established strategies in this work showcase the potent access to various diastereomeric structures of **32**, which may help elucidate the true structure of isolated *pseudo*-rubriflordilactone B in the future.

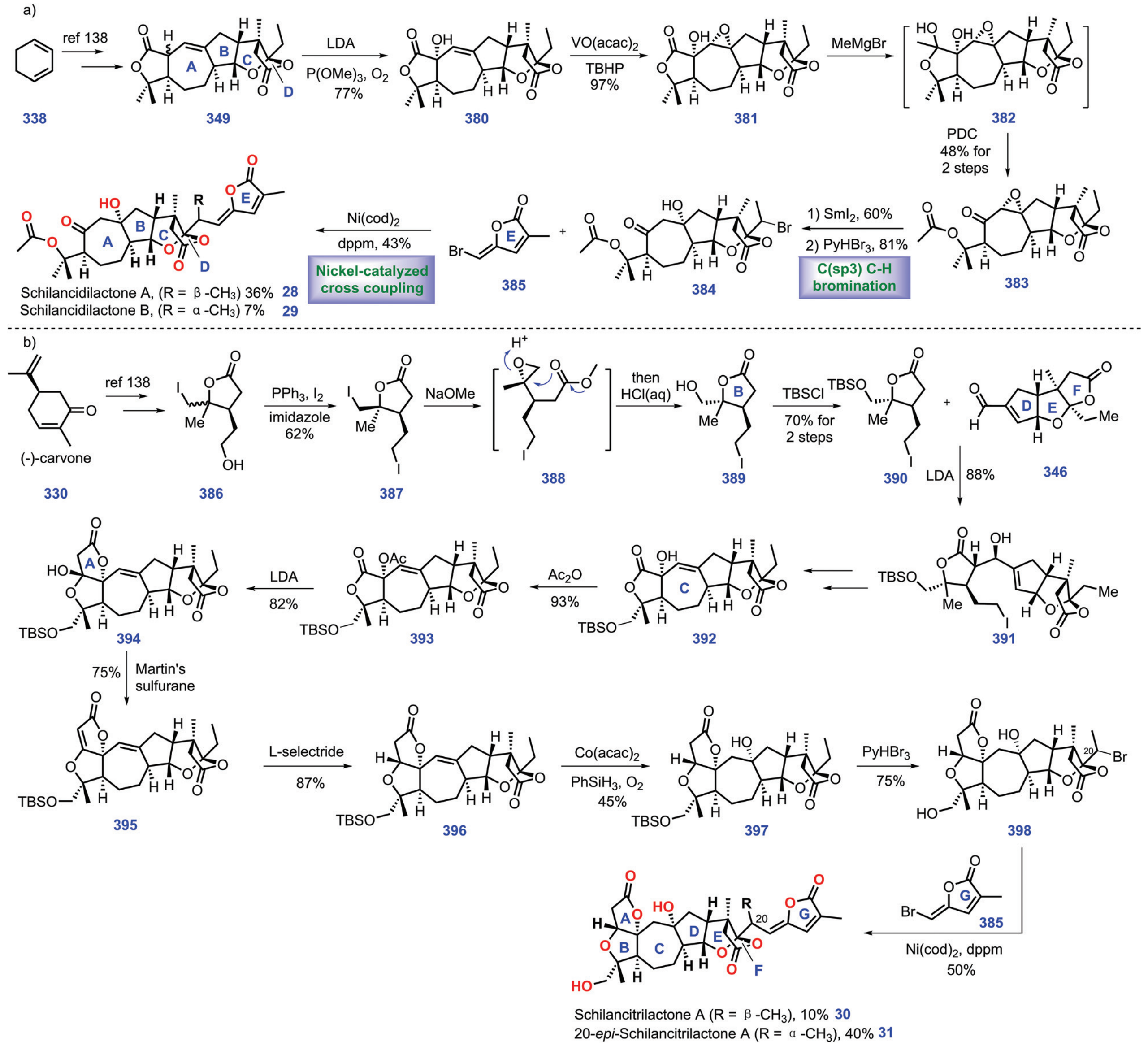
4.6 Tang's syntheses of schilancidilactones A and B, schilancitrilactone A, and 20-epischilancitrilactone A (2017)

In 2009, Sun's group identified schilancidilactones A and B and schilancitrilactone A (1–3), from the stems of *Schisandra lancifolia*.[137] Schilancidilactone A was reported to demonstrate inhibiting activity toward HIV-1, while schilancitrilactone A exhibited antifeedant activity. Following their previous successful work on the total syntheses of schilancitrilactones B **26** and C **27**,[138] Tang's group further disclosed their synthetic efforts toward the total synthesis of schilancidilactones A **28** and B **29**, schilancitrilactone A **30**, and 20-*epi*-schilancitrilactone A **31**, involving a late-stage nickel-catalysed cross coupling strategy as a novel step (Scheme 17).[152]

The task commenced with the known compound **349**,[138] which could be prepared *via* diene **328** (Scheme 17a). **349** was then treated with LDA followed by exposure to $O_2/P(OMe)_3$. Consequently, alcohol **380** was accessible in 77% yield. VO$(acac)_2$/TBHP-mediated epoxidation of **380** gave rise to epoxide **381**, which was reacted with methyl magnesium bromide, inducing a nucleophilic addition reaction. The resulting alcohol **382** was *in situ* oxidized by PDC to transform it into **383**. SmI_2-induced reductive ring opening[153] of **383** afforded **384**, which served as a substrate for the $PyHBr_3$-mediated[154,155] late stage C(sp3)–H bromination at C20, generating bromide **384**.

With access to bromide **384**, the authors then sought to complete the total synthesis of schilancidilactones A **28** and B **29**. Initially, they anticipated to utilize the radical addition strategy to generate the C20–C22 bond.[138] Unfortunately, their attempts to employ typical radical conditions and photoredox catalysis[144] did not succeed in delivering schilancidilactones A **28** and B **29**. Taking inspiration from recent progress in the nickel-catalysed cross coupling of alkyl halides,[156] the authors speculated whether key fragments **384** and stannane **385** could be merged *via* a nickel catalysed cross-coupling reaction. In practice, the authors pleasingly identified that $Ni(cod)_2$/dppm was capable of engaging the cross-coupling reaction, thus providing schilancidilactones A **28** and **B 29** in 36% and 7% yield, respectively.

Here, their goal then was to complete the synthesis of schilancitrilactone A **30** and 20-*epi*-schilancitrilactone A **31**. Their efforts commenced with the formation of fragment iodide **390**. The known compound **386** was prepared from (−)-carvone **330** (Scheme 17b).[138] Then **386** was converted into iodide **387** *via* Appel reaction. NaOMe-mediated methanolysis of **387** gave rise to epoxide **388**,[157] which was rearranged to lactone **389** *via* acid-promoted selective epoxide opening and cyclization. Alcohol **389** was further protected to TBS ether **390**. Moving forward, the authors turned their attention to complete the synthesis of schilancitrilactone A **30** and 20-*epi*-schilancitrilactone A **31**. Learning from their previous experiences in the synthesis of schilancitrilactones B **26** and C **27**,[138] exposure of **390** to LDA induced transient lithium enolate, which was *in situ* treated with known aldehyde **346**, thus providing alcohol **391**. Then **391** was advanced to allylic alcohol **392**.[138] Alcohol **392**



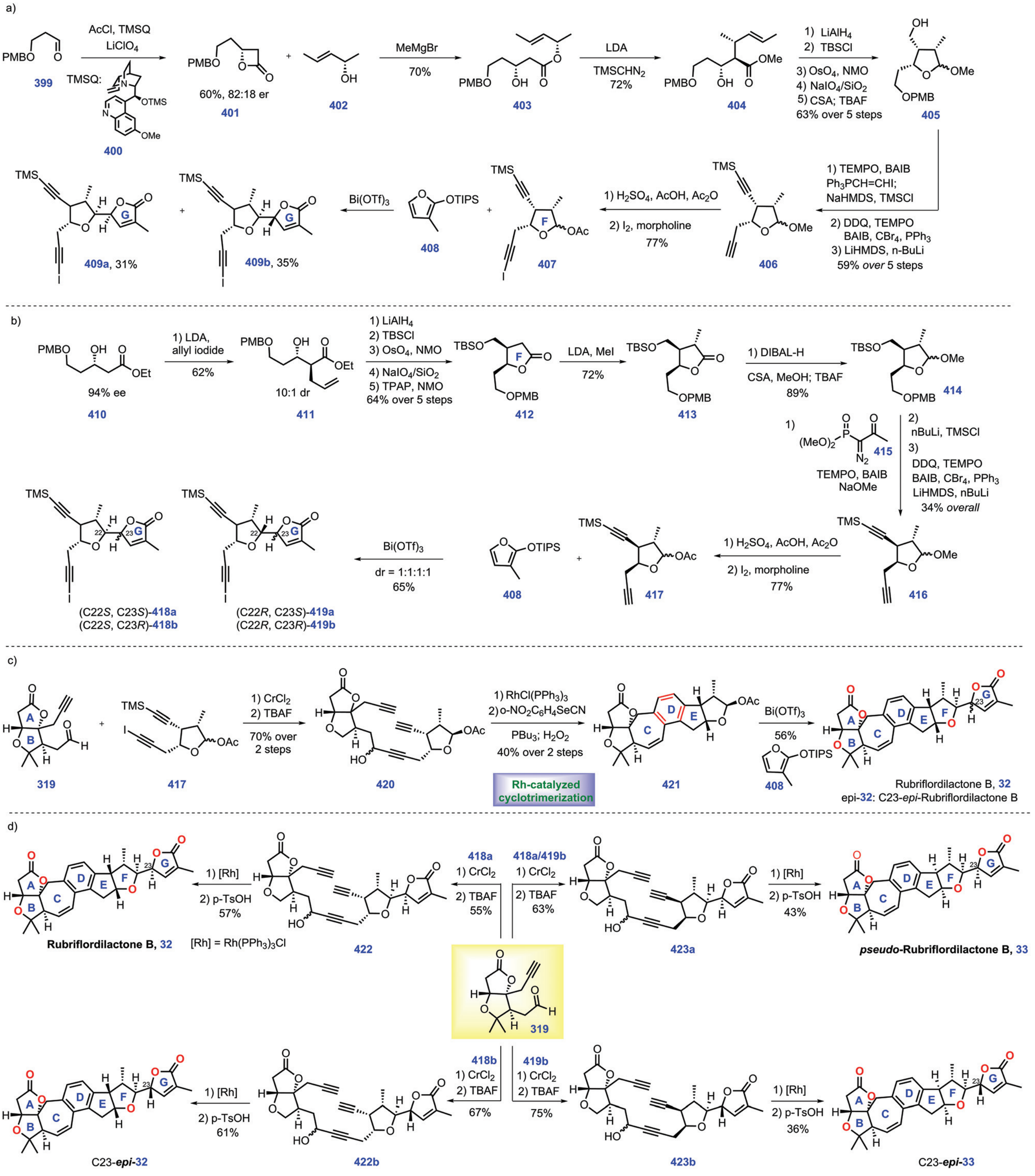
Scheme 17 Tang's synthesis of schilancidilactones A and B, schilancitrilactone A, and 20-*epi*schilancitrilactone A (2017).

was protected to acetate **393**, which was utilized as a precursor for LDA-promoted Dieckmann-type condensation.[111] The desired lactone **394** was received in 90% yield. Martin's sulfurane-mediated dehydration[143] of **394** furnished enone **395**. L-Selectride-induced selective reduction of **395** produced **396**. Exposing **396** to Mukaiyama conditions [Co(acac)$_2$, PhSiH$_3$, and O$_2$][24] installed a tertiary alcohol in C9. PyHBr$_3$-mediated C(sp3)–H bromination of **397** afforded **398**. To complete the synthesis, the installation of a butenolide motif onto the core structure was required. Pleasingly, the authors found that the nickel-catalysed cross-coupling of **398** with stannane **385** successfully delivered schilancitrilacetone A **30** together with its C20-epimer **31**.

In Tang's synthesis, the authors devised a clever nickel-catalysed cross-coupling to merge the advanced core and lactone motif, which showcased an attractive alternative to synthesize related natural products. Moreover, skillful utilization of late-stage C(sp3)–H halogenation provides an efficient and credible platform for the synthetic campaign of related Schisandraceae triterpenoids, thus facilitating their further biological evaluation.

4.7 Anderson's synthesis of (−)-rubriflordilactone B and (−)-*pseudo*-rubriflordilactone B (2019)

Li *et al.* noted in their original work that their synthetic rubriflordilactone B **32**, which was confirmed by X-ray crystallographic analysis,[147] did not match that isolated by Sun's group.[115] Then DFT calculation by Kaufman and Sarotti showed that the difference between these two forms of rubriflordilactone B **32** lies at C16 and C17 in ring EF.[158] To address this issue, Anderson and co-workers reported synthetic endeavours toward the total synthesis of (−)-rubriflordilactone B **32**



Scheme 18 Anderson's synthesis of (−)-rubriflordilactone B and (−)-*pseudo*-rubriflordilactone B (2019).

and (−)-pseudo-rubriflordilactone B **33**, utilizing rhodium-catalysed alkyne cyclotrimerization as the key strategy (Scheme 18).[159]

The project commenced with the installation of the ring FG system of the target (Scheme 18a). Aldehyde **399** was treated with ketene *via* TMSQ **400**-mediated enantioselective [2 + 2] cycloaddition[160] to produce chiral β-lactone **401** (60%, 64% ee). Exposure of chiral allylic alcohol **402** to MeMgCl led to magnesium alkoxide, thus allowing an *in situ* ring-opening reaction with **401**. The desired enantio-enriched alcohol **403** was obtained. Dianionic Ireland–Claisen rearrangement of **403** followed by quenching with TMS-diazomethane gave ester **404** with two desired stereocentres in ring-F. Then sequential ester reduction, TBS-protection of alcohol, oxidative cleavage of alkene, hemi-acetylation and removal of TBS ether provided furan **405**. Equipped with **405**, the two oxygen-containing edge chains were then converted into diyne **406** *via* several requisite functional group transformations. Acetoxylation of diyne **406** led to the acetal product, which was then treated with I_2/morpholine, generating iodoalkyne **407**.

With access to **407**, the authors then sought to assemble butenolide ring G. In the experiment, they identified that the treatment of **407** with siloxyfuran **408**[161] in the presence of Bi$(OTf)_3$ led to **409a** (31%) and **409b** (35%). Although the desired stereocentre at ring F (C22) could be well controlled, it proved challenging in inducing the stereocenter on ring G (C23), which only generated a mixture of stereoisomers (1 : 1). Considering that **409a** only secured rubriflordilactone B **32**, the synthesis of *pseudo*-rubriflordilactone B **33** called for an alternative synthetic protocol (Scheme 18b).

Then the project began with enantioenriched β-hydroxyl ester **410**, which was obtained from a known β-ketoester[162] *via* Noyori's asymmetric hydrogenation.[163] Treatment of **410** with LDA followed by allylation furnished **411** with good diastereoselectivity (10 : 1), which was transformed into lactone **412** *via* the aforementioned sequences. Diastereoselective methylation of lactone **412** with CH_3I in the presence of LDA afforded **413** with a pleasing dr value (10 : 1). Reduction of lactone in **413** followed by TBAF-mediated deprotection of TBS ether delivered acetal **414**. With access to **414**, alkyne **417** was achieved *via* similar manipulations, which was employed for synthesis of **409a**/**b**. Note that exposure of **417** and **408** to Bi$(OTf)_3$ failed to induce stereo-control, thus leading to four diastereomeric diynes **418a**/**b** and **419a**/**b** with an approximately equimolar ratio (1 : 1 : 1 : 1) where **418a** and **419a** were confirmed *via* X-ray analysis, while **418a** and **419b** were inseparable.

Here, the authors arrived at the key stage of this work. To evaluate the viability of core alkyne cyclotrimerization and furan addition, a model reaction was conducted, which proceeded smoothly with the desired ring CDEFG installed. In a real experiment, treatment of **407** with aldehyde **319**[109] *via* Nozaki–Hiyama–Kishi conditions ($CrCl_2$) followed by TBAF-mediated deprotection of TMS ether gave cyclized precursor **420**, which was subjected to the key rhodium-catalysed cyclotrimerization reaction (Scheme 18c),[164] successfully installing the desired hexacycle. However, upon subsequent treatment of the hexacycle with Martin sulfurane, it failed to undergo dehydration, which may be attributed to steric hindrance. Fortunately, they found that exposing the hexacycle to Grieco's protocol[165] induced a dehydration reaction to provide **421**. In the final step, treating **421** with furan **408** in the presence of Bi$(OTf)_3$ completed the total synthesis of rubriflordilactone B **32** together with its C23-epimer (*epi*-**32**) as a 1 : 1 mixture. Unfortunately, the authors found it difficult to isolate **32** and C23-isomer **32**.

To address this issue, they envisioned attachment of a butenolide motif in an earlier stage, thus allowing for a more convergent synthesis (Scheme 16d). In practice, subjecting **319** with **408a** or **408b** to Nozaki–Hiyama–Kishi reaction followed by the removal of silyl enol ether gave **422a** and **422b**, respectively. Moving forward, Rh-catalysed cyclotrimerization of **422a** and **422b** followed by dehydration resulted in the formation of rubriflordilactone B **32** and *epi*-**32**, respectively. Exposure of aldehyde **319** with **408a**/**409b** and **408b** to the abovementioned protocol completed the synthesis of *pseudo*-rubriflordilactone B **33** and *epi*-**33**. Pleasingly, they found that the NMR spectroscopic data of synthetic *pseudo*-rubriflordilactone B **33** was identical to that of the isolated material, thus demonstrating the DFT-predicted stereochemistry.

In Anderson's synthesis, the key contribution led to the identification of the synthetic *pseudo*-rubriflordilactone B **33**, which match well with the isolated material. Their successful implementation of the key rhodium-catalysed cyclotrimerization strategy in the late-stage synthesis offered an appealing and viable protocol to obtain the related complex molecules. In their work, the ingenious reorganized synthetic strategy allowed for a more convergent synthesis.

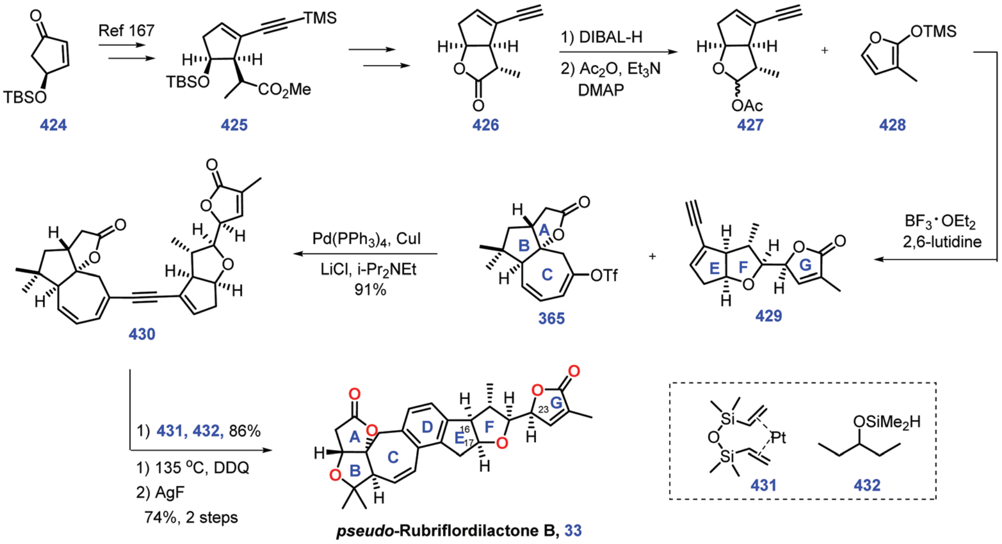
4.8 Li's synthesis of *pseudo*-rubriflordilactone B (2020)

In 2016, Li and co-workers disclosed the first total synthesis of *pseudo*-rubriflordilactone B **33**, involving 6π-electrocyclization/aromatization as the key step.[147] Unfortunately, the synthetic material did not match the natural material. The authors reasoned that the isolated sample of "rubriflordilactone B" may contain two components, that is **33** and its congener "*pseudo*-rubriflordilactone B". In 2019, Anderson's synthetic efforts resulted in the elucidation of the true structure of *pseudo*-rubriflordilactone B **33**.[145] Soon after, Li's group also successfully documented their detailed investigation aimed at elucidating the complete structure of *pseudo*-rubriflordilactone B **33** (Scheme 19).[166]

To pursue the real structure of **33**, Li and co-workers carefully prepared **33** and its fifteen stereoisomers. Considering that these stereoisomers share similar synthetic pathways, we will comment on the route shown in Scheme 20 since the obtained product was identical to that of the authentic *pseudo*-rubriflordilactone B.

Their synthetic endeavours commenced with chiral enone **424**,[167] which was processed through a four-step sequence involving α-iodination, Sonogashira coupling, Luche reduction, and Johnson–Claisen rearrangement to enyne **425**. Then, the TBAF-mediated deprotection of silyl ether followed by lactonization provided lactone **426**. **426** was converted into **427** *via* a two-step manipulation, including reduction of lactone and protection of the resulting semi-acetal. Treatment of **427** with 1-siloxyfuran **428**[168] *via* $BF_3 \cdot OEt_2$-mediated vinylogous Mukaiyama aldol reaction furnished **429**. Notably, 2,6-lutidine was crucial for securing the good efficiency of this transformation. Then, key fragments **429** and known **365** were then merged *via* a Pd-catalysed Sonogashira coupling reaction. Using this method, **430** was accessible in 91% yield.

With **430** in hand, the final step was the installation of the benzene ring of the target. According to their previous work,[147] **430** was then processed through a four-step sequence,



Scheme 19 Li's synthesis of *pseudo*-rubriflordilactone B (2020).

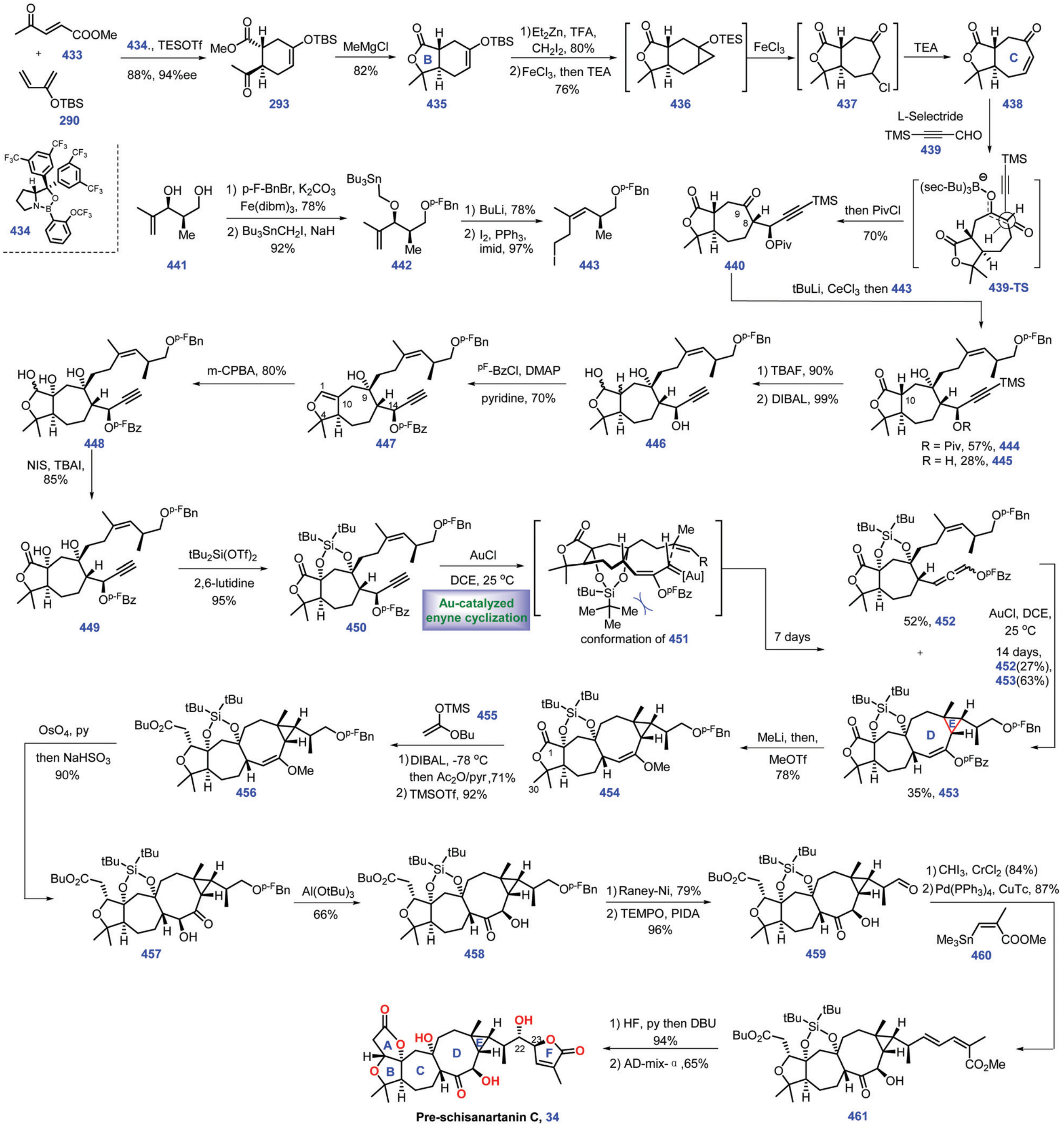
involving platinum-catalysed *cis*-hydrosilylation,[169,170] 6π-electrocyclization, DDQ-promoted oxidative aromatization, and AgF-mediated desilylation to provide synthetic rubriflordilactone B. Pleasingly, the NMR spectra of the above synthetic material matched well with that of the authentic *pseudo*-rubriflordilactone B. Notably, they found that the synthetic material demonstrated good inhibiting activity toward HIV infection (EC_{50} = 0.288 μM).

In Li's work, the comprehensive synthesis of a series of *pseudo*-rubriflordilactone B **33** and its 15 stereoisomers was vital to its overwhelming success. Obviously, this effort qualifies as a landmark in identifying the complete structure of *pseudo*-rubriflordilactone B **33**. Also, the confirmed structure of *pseudo*-rubriflordilactone B **33** is crucial for further investigation of its structure–activity relationship.

4.9 Yang's synthesis of pre-schisanartanin C (2020)

In 2010, Sun's group reported the isolation of a new *Schisandra* nortriterpenoid, called pre-schisanartanin C **34**,[108] from *Schisandra propinqua* var. *propinqua*. Structurally, it contained a bicyclo[6.1.0]nonane framework, a quaternary stereogenic center at C13 and a labile α-hydroxyl ketone, which posed a considerable challenge for its total synthesis. Notably, its absolute configuration was still not determined. The biological investigation showed that it exhibited promising anti-cancer, anti-HIV and anti-hepatitis activities.[171] Recently, Yang and Chen reported the completion of their synthetic efforts toward pre-schisanartanin C.[172] In 2017, the authors accomplished the synthesis of one of the *Schisandra* nortriterpenoids, arisandilactone A,[112] where an ideal aldehyde intermediate was achieved *via* somewhat lengthy routes (31 steps) from (*R*)-carvone. Considering that the authors had gained sufficient experiences from Au-catalysis in total synthesis,[173,174] they envisioned Au-catalysed enyne cyclization as the core step to provide a more concise platform to the bicyclo[6.1.0]nonane skeleton,[175] thus allowing efficient completion of pre-schisanartanin C **34** (Scheme 20). Their project commenced with the construction of fragment ketone **440** and iodide **441**. Initially, the authors planned to treat diene **290** with dienophile **433** *via* an enantioselective Diels–Alder reaction. Using this method, ketoester **293** was obtained. However, utilizing **433** as a precursor was challenging since both the ketone and ester groups in **433** may coordinate to the chiral catalyst, thus leading to regioselectivtiy issue.[176] Hence, the authors anticipated the meticulous evaluation of various chiral Lewis acids could enable the Diels–Alder reaction. Fortunately, chiral Lewis acid **434** was identified to catalyse the enantioselective Diels–Alder reaction, generating chiral ketoester **293** in 88% yield with 94% ee. Treatment of **293** with MeMgCl initiated a cascade Grignard addition/lactonization, giving lactone **435**. Simmon–Smith cyclopropanation of the silyl enol ether in **435** afforded **436**, which upon *in situ* treatment with $FeCl_3$, cyclopropanol oxidative fragmentation/elimination[177] ensued, thus giving enone **438**. L-Selectride-mediated[178] 1,4-reduction of **438** followed by an aldol reaction[179] with aldehyde **439** and Piv protection of the resultant alcohol generated **440**. In this work, the author reasoned that the formation of the less steric-demand complex **439-TS**[180] accounted for the observed diastereoselectivity of aldol condensation.

Subsequently, their next task was to construct iodide **443**. Initially, the authors anticipated to protect diol **441** *via* treatment with *p*-F-BnBr in the presence of $Fe(dibm)_3$[181] to yield the benzyl ether product, which was followed by exposure to Bu_3SnCH_2I/NaI. The desired stannane **442** was secured. Exposing **442** to *n*BuLi induced a Wittig–Still[182] rearrangement, and the resultant alcohol was then processed through Appel iodination[183] to provide iodide **443**. Moving forward, key fragments **443** and **440** were then connected *via* a stereo-selective alkylation reaction, which delivered **444** (57%) together with **445** (28%) without the Piv group. The authors guessed that the observed diastereoselectivity was attributed to the



Scheme 20 Yang's synthesis of pre-schisanartanin C (2020).

approach of the alkylating agent to the carbonyl C9 of **443** from the less hindered face.

Then, the authors sought to install the C10 hydroxyl with the requisite stereochemistry. The mixture of **444** and **445** was advanced to **446** *via* lactone reduction, alkyne desilylation and secondary alcohol deacylation. Chemoselective protection of C1 alcohol followed by elimination resulted in vinyl ether **447**. Epoxidation of **447** followed by hydration afforded diol **448** with C10 hydroxyl installed. Notably, the methyl group at C4 masked the top face of the double bond (C1–C10), thus allowing epoxidation of the vinyl ether with the desired stereoselectivity. The C1 hydroxyl group in diol **448** was then oxidized to lactone **449**. Here, the authors envisioned that a strongly biased conformation[184] would be crucial to the key Au-catalysed annulation reaction. Hence, the *cis*-diol was capped as cyclic silylidene **450**,[185] which was confirmed by X-ray crystallography. Pleasingly, the X-ray structure demonstrated that the enyne components approached each other, thus feasibly allowing the next Au-catalysed cyclization reaction.

With access to **450**, the crucial cyclization was then explored. In this experiment, the authors speculated that the benzoyl group in **450** would first undergo a 1,2-migration[186] to give gold carbene **451**, which served as an intermediate for the key Au-catalysed intramolecular cyclopropanation to construct **453** with the challenging ring DE system installed. In practice, exposure of **450** to AuCl under strict anhydrous conditions for one week installed pentacycle **453** (35%) together with allenyl ester **452**. It is worth noting that exposing **452** to AuCl for a prolonged reaction time (14 days) gave rise to **453** in 27% yield, albeit with the recovered allenyl ester **452** (63%). The author discovered that when the hydroxyl group was protected with benzyl ether, the reaction was complicated, which was attributed to the migration of the benzylic hydrogen to form vinyl gold carbene complexes.[187] Instead, installation of pF-Bz as a protecting group prevented the undesirable benzylic hydrogen-shift process. Removal of the pF-Bz protecting group followed by treatment with MeOTf formed methyl ether **399**, which was advanced to **456** through three additional manipulations, involving DIBAL-H mediated lactone reduction, hemiacetal protection and TMSOTf-promoted stereoselective Mukaiyama aldol reaction with enol silyl ether **455**. The authors proposed that the axial methyl group at C30 in **454** guided the enol silyl ether **455** to access an *in situ* oxonium ion from the opposite orientation, which elucidated the newly installed C1 stereogenic center. Subjecting **456** to dihydroxylation condition[188] produced **457**, thus allowing the key Al(O*t*Bu)$_3$-mediated[189] hydroxyl ketone isomerization to obtain the thermodynamically more stable **458**. Then **458** was converted into aldehyde **459** *via* RANEY® Ni catalysed deprotection of the pFBn group and TEMPO/PIDA-mediated alcohol oxidation.[190] Takai–Utimoto olefination[191] of aldehyde **459** afforded a vinyl iodide, which served as an intermediate for the Pd-catalysed Stille cross-coupling reaction with stannane **460**, yielding diene **461**. To complete the synthesis, the conditions for the requisite ring A and F needed to be established. Treatment of **461** with HF/py followed by DBU-promoted lactonization furnished the lactone product with ring A formed, which was subsequently subjected to Sharpless asymmetric dihydroxylation conditions (AD mix-α) to achieve the synthesis of pre-schisanartanin C **34**.

In this synthetic campaign, the novel and impressive Au-catalysed enyne cyclization strategy proceeded in an efficient and stereo-selective manner to establish the critical bicyclo[6.1.0]nonane core. An Al(O*t*Bu)$_3$-mediated isomerization strategy tactfully formed the desired core hydroxy ketone structure in ring D. An elegant Sharpless asymmetric dihydroxylation nicely constructed the desired ring F albeit with the desired stereocentres at C22 and C23. Definitely, the successful implementation of creative strategies in this synthesis will encourage further synthetic endeavours toward other total syntheses involving bicyclo[6.1.0]nonane cores.

4.10 Gui's synthesis of propindilactone G (2020)

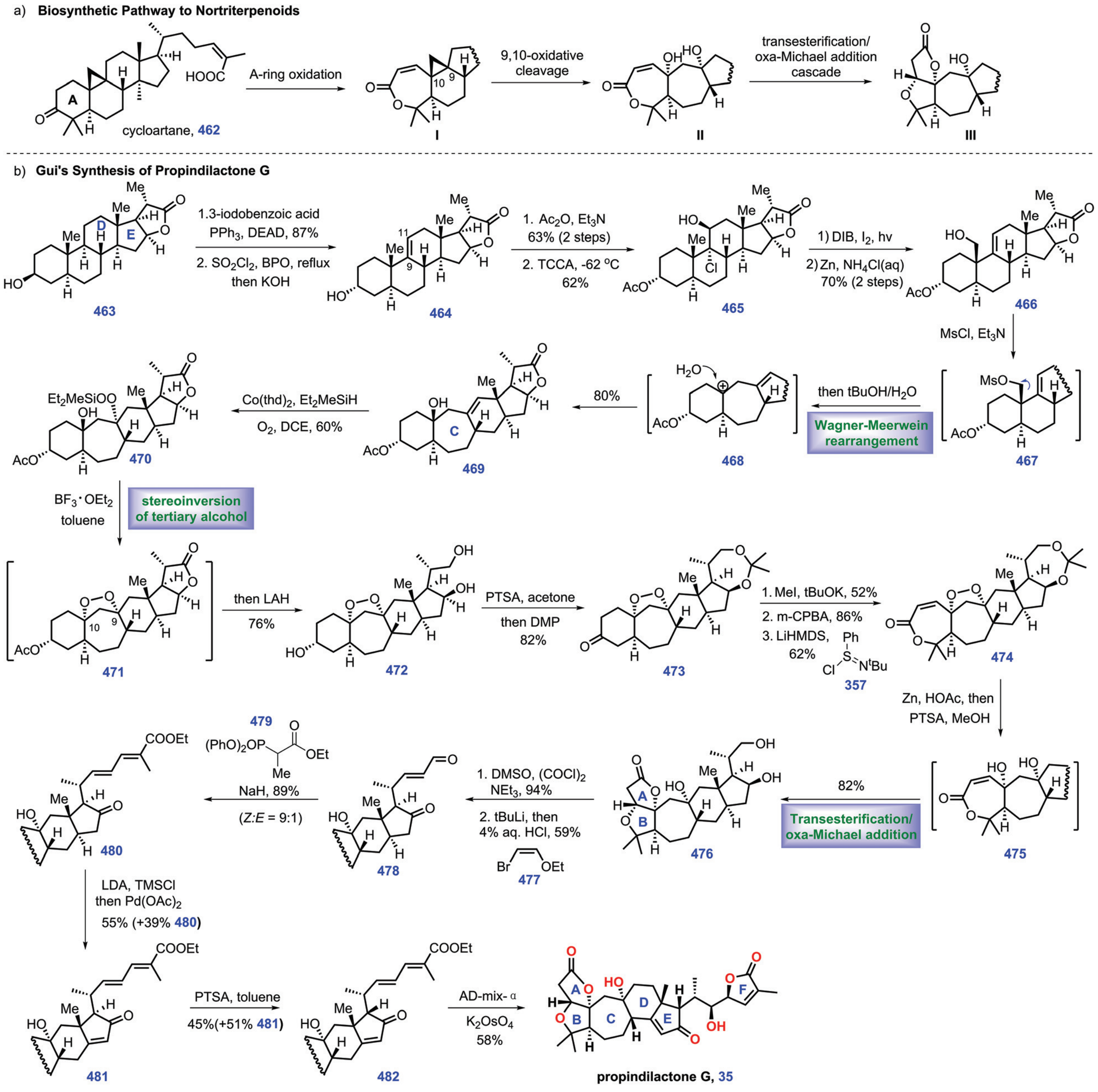
In 2008, propindilactone G, a C29 schinortriterpenoid, was isolated by Sun's group from the stems of *Schisandra propinqua* var. *propinqua*.[192] Structurally, propindilactone G bears a 5/5/7/6/5-pentacyclic skeleton, 10 stereocentres and multiple oxygen-containing functional groups. In 2015, Yang and co-workers disclosed an excellent synthesis of propindilactone G **35**. Key to their success was an asymmetric Diels–Alder reaction, Pauson–Khand reaction and an oxidative hetero-coupling reaction to append the side motif.[111] Notably, Yang's synthesis corrected the originally proposed synthetic compound to be C17-*epi*- propindilactone G. Recently, Gui and co-workers reported the beautiful bioinspired synthesis of nortriterpenoid propindilactone G **35**.[193]

Gui's synthesis was inspired by the biosynthetic mechanism proposed by Sun and co-workers. Sun supposed that the core framework of schinortriterpenoid **III** may be derived from **II** *via* a smart transesterification/oxa-Michael addition (Scheme 21a).[108] **II** could be traced back to **I** *via* 1,10-oxidative cleavage. **I** was obtained from cycloartane **462** *via* dehydrogenation and Baeyer–Villiger oxidation. Notably, the authors found that propindilactone G **35** and steroidal lactone **463** possessed the same stereo-centres at C5, C8, C13, and C20 and similar C/D-ring systems. Moreover, steroidal lactone **463** could be feasibly acquired from the degradation of tigogenin.

To experimentally confirm this speculated biosynthetic pathway, their synthetic efforts began with installation of the C9–C11 alkene from steroidal lactone **463** (Scheme 21b). Taking inspiration from Breslow's remote functionalization strategy,[194] treatment of **463** with 3-iodobenzoic acid under Mitsunobu reaction conditions provided a C3 α-iodobenzoate, which was employed as a precursor for selective chlorination at C9 followed by E2 elimination,[195] thus providing the desired olefin **464**.

Moving forward, the authors attempted the functionalization of the C19-Me group. They considered Suárez's remote radical functionalization strategy directed by the β-OH group at C11, which was capable of the site-selective oxidation of the C19-Me group. In practice, subjecting **464** to Ac$_2$O/NEt$_3$ followed by treatment with trichloroisocyanuric acid[196] gave chlorohydrin **465** with the desired β-OH at C11 installed.[197] Exposing **465** to Suárez's conditions (DIB/I$_2$, *hν*) followed by reduction with Zn and aq. NH$_4$Cl furnished C19-alcohol **466**.

Equipped with **466**, the authors turned their attention toward the construction of ring C *via* a ring expansion reaction. According to the modified work by Barton *et al.*,[198] the authors expected to introduce a good leaving group to facilitate Wagner–Meerwein rearrangement. After extensive screenings, they eventually identified mesylation of **466** followed by treatment with THF/H$_2$O at 80 °C triggered Wagner–Meerwein rearrangement *via* the proposed tertiary cation **468**. The desired C10-alcohol **469** was obtained in 60% yield. Pleasingly, the authors discovered that this ring expansion reaction could be scaled up (4 g) with a higher yield (80%) using a mixed solvent of *t*BuOH/H$_2$O. Then **469** was subjected to Mukaiyama hydration conditions. The resulting diol was generated. However, the stereochemistry of the formed hydroxyl group at C10 was opposite to that of propindilactone G. Initially, the



Scheme 21 Gui's synthesis of propindilactone G (2020).

authors attempted to invert the stereocenter of C10, which was found to be unfeasible.[199] Dussault *et al.* reported[200] that the opening of oxetanes by alkyl hydroperoxides could be achieved by Lewis acids. Inspired by Dussault's work, the authors then conducted Co(thd)$_2$-catalysed Mukaiyama hydroperoxysilylation[201] of **469** to provide peroxysilyl alcohol **470**, which was induced by $BF_3 \cdot Et_2O$ *via* intramolecular cyclization.[202] Pleasingly, endoperoxide **471** was generated with the desired α-configuration of C10 established. Interestingly, the endoperoxide moiety here could be utilized as a temporary protecting group of C9,C10-diol in the following transformations. The $LiAlH_4$-mediated reduction of both the ester and lactone in **471** gave rise to triol **472**.

Moving forward, the authors then sought to develop conditions for the installation of the key 5/5-fused bicyclic lactone *via* a key biomimetic transesterification/oxa-Michael addition cascade. Initially, the hydroxyl groups at C16 and C22 in **472** were protected to form an acetonide, which served as a substrate for the following Dess–Martin oxidation of the C3-hydroxyl group. The resulting ketone **473** was produced in 82% yield. Then **473** was converted to **474** *via* a three-step manipulation, involving selective α-dimethylation, Baeyer–Villiger oxidation, and Mukaiyama dehydrogenation.[148] The authors speculated that **474** would be reduced to diol **475**, thus setting the stage for the proposed biomimetic cascade. In the real experiment, the Zn/HOAc-mediated reductive opening of endoperoxide **474** afforded diol **476**. Interestingly, the authors discovered that **475** partially underwent the cascade transesterification/oxa-Michael addition to form the desired 5/5-fused bicyclic lactone skeleton (AB ring system). Fortunately, they identified that the addition of *p*-toluenesulfonic acid and MeOH to the above conditions secured the reaction, thus leading to diol **476** in 82% yield from **474**.

To complete the synthesis of propindilactone G, the final step was to attach the challenging side moiety onto core **476**. The authors anticipated to employ the C16 and C22 hydroxyl groups to introduce the butenolide side chain and the C16-enone moiety. Accordingly, exposure of alcohol **476** to Swern oxidation conditions followed by a homologation[203] reaction with **477** transformed it into **478**. The Z-selective Horner–Wadsworth–Emmons reaction[204] of **478** with **479** generated diene **480**, which was subjected to Saegusa oxidation,[28] thus affording enone **481**. However, initial screenings to achieve dihydroxylation of the C22–C23 olefin of **481** suffered from low efficiency. According to the work from Yang's group,[111] the authors found that the configuration at C17 of **481** was essential to this reaction. Accordingly, the configuration at C17 was epimerized as a 1 : 1 ratio *via* catalytic TsOH. Pleasingly, subjecting the desired **482** to Sharpless asymmetric dihydroxylation conditions successfully completed the synthesis of propindilactone G.

In general, this beautiful work showcased the experimental evidence of the proposed biosynthesis pathway of propindilactone G **35**. The clever use of stereoinversion of tertiary alcohol-mediated $BF_3{\cdot}OEt_2$ nicely constructed the desired stereocentre at C10. The impressive biomimetic transesterification/oxa-Michael addition cascade efficiently installed the 5/5-fused bicyclic lactone moiety. It is worthy of praise that the entire propindilactone G synthetic campaign only required 20 steps and some sequences could be scaled up. It is believed that the Wagner–Meerwein rearrangement, Suárez remote radical functionalization, in conjunction with the transesterification/oxa-Michael addition cascade, may have broader heuristic value for the synthesis of related natural product.

5. Conclusions

We summarized the recent advancements in the synthesis of limonoids and limonoid-like natural products, where novel and elegant synthetic methodologies, including copper-catalysed cascade Michael addition/cyclization,[35–37] metal catalysed cycloisomerization,[109,159] Au-catalysed enyne cyclization,[172] metal-mediated radical cascade cyclization,[53] 6π-electro-cyclization,[90,116] Pauson–Khand reaction,[63] nickel-catalysed sp2–sp3 cross-coupling, and biomimetic transesterification/oxa-Michael cascades, have been successfully employed to conquer the challenging target molecules. Considering the diverse structure of limonoids, particularly the highly decorated limonoid-related molecules, sometimes novel and unique synthetic strategies are desirable, such as Watanabe's installation of the C8–C14 bond of azadirachtin *via* an ingenious radical cascade cyclization strategy.[53] Several limonoids share a common core structure, thus the rational design of synthetic strategies to establish a common intermediate will allow the convergent syntheses of limonoids and limonoid-like natural products with higher efficiency. The carbocation-mediated polyene cyclization is common in biosynthesis; however, it is seldom utilized in the total syntheses of limonoid-related molecules. In addition, scalability poses a challenge for most synthetic limonoid-related compounds, which is a key limitation for molecules with clinical potential. Protecting-group-free synthesis is also a challenge in the syntheses of limonoids. Definitely, excess protecting groups and redox operations involved will reduce the step economy. Hence, efficient syntheses are possible when powerful synthetic methodologies are leveraged on judiciously chosen reactants in conjunction with optimal reaction conditions. We believe that researchers can draw enough experiences from emerging limonoids and limonoid-like total syntheses, thus guiding their future endeavours towards the total syntheses of these compounds.

Conflicts of interest

There are no conflicts to declare.

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