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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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Introduction

Limonoids are widely distributed in nature and have diverse biological activities. 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

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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, with the discovery of new chemistry, thus encouraging more challenging



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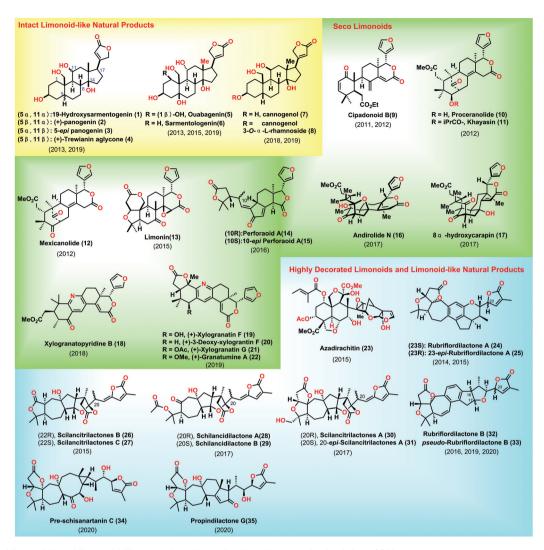


Fig. 1 Selected limonoids and limonoid-like natural products that have been synthesized since 2011.

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).

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. 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 379 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 C3acetylated 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 displacement11 to furnish acetal 51. Treating bromide 51 with BEt₃/(TMS)₃SiH¹² 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 acidmediated 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 regioand 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(PPh₃)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 a 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 functionalization¹⁸ 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, TiCl₄-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, H2O2 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 amalgammediated reductive opening of 73 smoothly achieved the desired triol 74 under "on-water" conditions²² (aqueous suspension). The selective protection of 74 to an acetonide followed by LiBEt₃H-induced reduction of the C3 ketone furnished 75, where the hydroxyl at C1 and C5 was protected as an ethyl boronic ester. Li/NH3 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 isomerization²³ 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 hydration²⁴ 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 Pdcatalysed 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 Co₂B²⁵ generated an intermediate, tetrasubstituted olefin 80, which was further treated with Barton's base²⁶ 81 under heat. The resulting enolate 82 was obtained with the desired stereochemistry at C17 (dr = 3:1) favored. Finally, deprotection of all

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 impor-

the hydroxyl groups in 82 completed ouabagenin (5).

tantly, 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. LiAlH4-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 reaction²⁸ 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 8429 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 cishydroxyl groups, dehydration of the tertiary alcohol and ozonolysis of the tetra-substituted olefin furnished orthoester 91. Pdcatalysed dehydrogenation31 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, 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 (Et₃B/n-Bu₃SnH/O₂) 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/NH3) 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 reaction³⁴ 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).

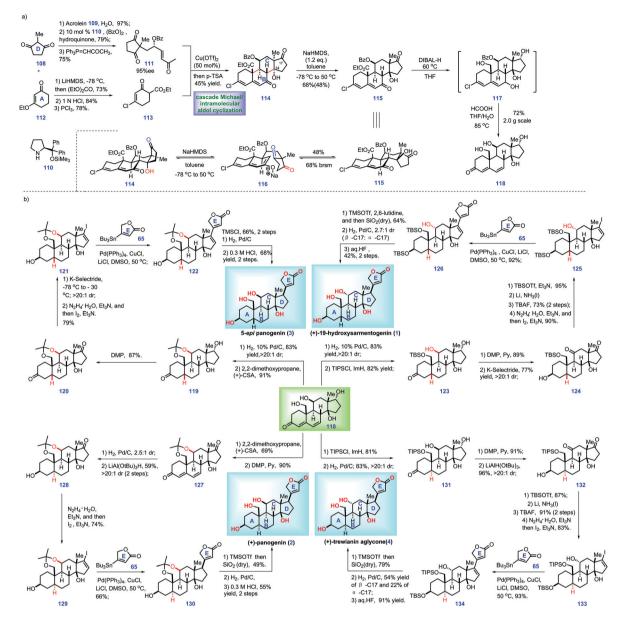
In Inoue's synthesis, the core strategy of ring formation was similar with their aforementioned work in the total synthesis of 19-hydroxysarmentogenin 1,8 both of which involved the Diels-Alder reaction to construct the ring AB system, a tactful SN2 bromine displacement to connect ring AB and ring D, 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. 46 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 addition³⁸ with acrolein 109, an organocatalyst 110 catalysed enantioselective oxidation reaction³⁹ 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 ${\rm LiAlH_4}$ led to complex results, while the reduction of C19 ester proceeded slowly with the use of LiBH₄ 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 2,2dimethoxypropane afforded acetonide 119 with a β-C5 stereocentre 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 crosscoupling 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. 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 C3ketone gave rise to 124. Treating 124 with TBSOTf induced selective protection of C17 ketone, thus generating a TBS ether product. Li/NH3 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)₃H-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. NaHCO₃ 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 H₂O₂-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 (H2O2) 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 C3and C17-silylated enol ether 151. Following a similar protocol, 151 was processed through a five-step sequence, including stereoselective reduction of ketone, desilvlation 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-Lrhamnoside (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

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 epoxide⁵⁰ 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-17furyl-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, propargyla-

tion and Ti(III)-mediated epoxide opening reaction generated allylic alcohol 175. Exposure of 175 to SOCl2 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)3·2H2O] 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 fivestep manipulation including reduction of the ester and C3ketone, separate protection of the diol, epoxidation of the exo methylene and NaCN-mediated ring opening of the epoxide followed by elimination of CH₃CN 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(OtBu)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, Tf₂O) followed by a Pd-catalysed Stille coupling reaction with butenolide 65gave 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 (¹O₂), 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 [(Ph₃P)₃RuCl₂] initiated isomerization of the endo-peroxide moiety,⁵⁸ affording bis-(epoxide) 191, which is in situ quenched by silica gel, inducing a 1,2hydride 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 $[PhI(OAc)_2/I_2/O_2(10 \text{ atm})/hv]$, 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 oxidation60 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 O2-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 \rightarrow 190 and 194 \rightarrow 196) were also vital to the overwhelming success of their work.

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 Zrmediated 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 conditions⁶⁷ could furnish the target olefin, which subsequently underwent Jones oxidation to deliver y-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 1,4addition 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, AlMe₃-mediated amidation with Me₂NH·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 IC50 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 coworkers 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 Rawaltype 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

Newhouse's synthesis of (\pm)-andirolide N and 8 α -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, Et₃SiH).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/O₂] 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 strategy⁷⁵ minimized the retro-aldol and aldol condensation side reactions. Furthermore, it was found that the blocked α -position of the 1,3-diketone⁷⁶ 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 isomerization⁷⁷ followed by oxidative cleavage78 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 \rightarrow 225 and 17 \rightarrow 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 (AgNO₂/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 fragmentation⁷² of 235 followed by Pd-catalysed oxidative stannylation82 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 conditions83,84 proved challenging since oxime 234 and stannane 239 decomposed during the reaction. Fortunately, it was discovered that when the aforementioned amine additives85 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) complex⁸⁷ 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 ZnEt2/CH2I2 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, [PtCl₂(C₂H₄)]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 Pdketone α,β-dehydrogenation and convergent catalysed 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 (+)-tetramisole⁸⁹ 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 siteselective 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 (\pm) - 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 hydrosilylation94 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 H₂O₂, 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 reaction⁹⁵ 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 $oxa-6\pi$ electrocyclization97 under thermal conditions to install 2Hpyran 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 siteselective Luche reduction. Notably, the utilization of less nucleophilic solvents, such as CF₃CH₂OH, 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 SOCl₂-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 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.

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 Ac₂O 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 (nBu₃SnH, 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

azadirachitin. 23

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/Ag₂O 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 researchers¹⁰⁹ 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 rubriflor-dilactones 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-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). According to their successful experience 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 conditions¹¹⁸ [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 iodolactonization¹¹⁹ 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 reaction¹²¹ with Me₂Zn 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 twostep 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, H2) 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. BF₃·OEt₂/Et₃SiH-mediated¹²² deoxygenation of the resultant hemi-ketal species gave 298. With access to 298, Pdcatalysed Stille cross-coupling reaction¹²³ with Me₃SnSnMe₃ 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)/CuTC124 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(Ot-Bu)₃ mediated the regionselective 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 6,5,6tricyclic system in conjunction with the easily dissociated tendency of the phenoxide moiety accounted for this outcome. Here, they added DAST¹²⁶ 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 BF₃·OEt₂-mediated¹²⁸ 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)2POCH2CO2Et, 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 TFAmediated 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 divne 309 to nBuLi 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 cobaltcatalysed 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 SOCl2/ZnCl2, 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) chloride¹³⁶ 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*. 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

23-epi-rubriflordilactone A, 25

rubriflordilactone A, 24 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/Bu₃SnH. 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 stannylation¹⁴¹ of 336 with (Bu₃Sn)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/ CH₃I, inducing C23 methylation, then followed by an NaBrtriggered 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 CuCl₂-mediated dehydration¹⁴³ 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/nBu₃SnH only resulted in the decomposition of 348. Besides, photoredox catalysis 144 was also found to be unfeasible. Ultimately, they discovered that Luche's condition¹⁴⁵ (CuI, Zn under ultrasound) was capable of being converted 348 into the desired cyclized product 349 with the formation of ring B. m-CPBAmediated epoxidation of 349 resulted in 350, which served as precursor for a cascade ring opening reaction/reduction (NaOMe, NiCl₂·6H₂O/NaBH₄), thus constructing alcohol 352. In the final stage of the synthesis, the authors focused on

appending a lactone motif onto the advanced core 352. IClmediated iodination¹⁴⁶ at C20 in 352 provided iodo 353, which was further treated with stannane 337 under AIBN/Bu₃SnH 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

their endeavour was the strategic use 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 dehydrogenation¹⁴⁸ 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 Et2AlCN 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 silvlation 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, PhNTf₂) of 363 followed by displacement of silvl ether with an acetate group gave 297. LiHMDS-mediated intramolecular Dieckmann condensation of 297 followed by BF₃·OEt₂-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 desilvlation/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 catalyst¹⁵¹ 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 O₂/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. SmI₂-induced reductive ring opening¹⁵³ of 383 afforded 384, which served as a substrate for the PyHBr₃-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 catalysis144 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-epischilancitrilactone 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 dehydration¹⁴³ of 394 furnished enone 395. L-Selectride-induced selective reduction of 395 produced 396. Exposing 396 to Mukaiyama conditions [Co(acac)₂, PhSiH₃, and O₂]²⁴ installed a tertiary alcohol in C9. PyHBr₃-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 latestage 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).

422b

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]

cycloaddition¹⁶⁰ 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 divne 406 led to the acetal product, which was then treated with I₂/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 408161 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 Novori'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 CH3I 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) 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 (CrCl2) followed by TBAFmediated 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 protocol¹⁶⁵ 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

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 pseudorubriflordilactone B.

Their synthetic endeavours commenced with chiral enone 424, 167 which was processed through a four-step sequence involving α -iodination, Sonogashira coupling, 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 BF3·OEt2-mediated vinylogous Mukaiyama aldol reaction furnished 429. Notably, 2,6lutidine 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 $(EC_{50} = 0.288 \mu M).$

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 Schisandra propingua var. propingua. 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 preschisanartanin 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 Aucatalysed 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 FeCl₃, cyclopropanol oxidative fragmentation/elimination¹⁷⁷ ensued, thus giving enone 438. L-Selectride-mediated¹⁷⁸ 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 Bu₃SnCH₂I/NaI. The desired stannane 442 was secured. Exposing 442 to nBuLi induced a Wittig-Still¹⁸² rearrangement, and the resultant alcohol was then processed through Appel iodination¹⁸³ 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

Pre-schisanartanin C. 34

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 conformation¹⁸⁴ 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.

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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% vield, 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, hemiaprotection 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 condition¹⁸⁸ produced 457, thus allowing the key Al (OtBu)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 Aucatalysed enyne cyclization strategy proceeded in an efficient and stereo-selective manner to establish the critical bicyclo [6.1.0]nonane core. An Al(OtBu)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 oxygencontaining 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). 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 Ac₂O/NEt₃ followed by treatment with trichloroisocyanuric acid¹⁹⁶ gave chlorohydrin **465** with the desired β -OH at C11 installed.¹⁹⁷ Exposing **465** to Suárez's conditions (DIB/I₂, hv) followed by reduction with Zn and aq. NH₄Cl 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/H₂O 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/H₂O. 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 hydroperoxysilylation²⁰¹ of 469 to provide peroxysilyl alcohol 470, which was induced by BF₃·Et₂O 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 LiAlH₄-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 C3hydroxyl 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 C16enone moiety. Accordingly, exposure of alcohol 476 to Swern oxidation conditions followed by a homologation²⁰³ reaction with 477 transformed it into 478. The Z-selective Horner-Wadsworth-Emmons reaction²⁰⁴ 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 alcoholmediated BF₃·OEt₂ 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 nickelcatalysed 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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