

REVIEW

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## Recent progress in the total synthesis of pyrrole-containing natural products (2011–2020)†

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Natural products have long served as a rich resource for drug discovery in the treatment of illnesses and chronic diseases. Among many families exhibiting fascinating structural complexity and impressive bioactivity, pyrrole-containing natural products frequently present a significant challenge to practitioners of organic synthesis. As a result, synthetic chemists have paid intense attention to the construction of such frameworks, not least as the amounts of natural product isolated from their natural source is often far less than that needed for biological testing. This review discusses total syntheses of pyrrole-containing natural products over the last ten years, highlighting recent advances in the chemistry of pyrroles both in the context of their innate reactivity, and their preparation in complex settings.

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### 1. Introduction

The diverse structures and biological properties of natural products render them prime candidates for the discovery of novel lead compounds against human diseases. Among nitrogen-containing aromatic heterocycles, which are of high importance in medicinal chemistry research, the parent 5-membered heterocycle pyrrole was first extracted through the distillation of bone oil,<sup>1</sup> and first identified in 1834 by F. F. Runge as a constituent of coal tar.<sup>2</sup> It is a volatile, colourless liquid that darkens upon exposure to air, and has lower basicity than other nitrogen-containing compounds such as amines and pyridines due to the incorporation of its lone pair into its aromatic system. Pyrroles are well-known as biologically active scaffolds that possess a wide range of activities, and are found in an equally large number of natural products. Some of the most common natural molecules containing the pyrrole nucleus include bile pigments such as bilirubin, porphyrins of heme, porphyrinogens, chlorophyll and Vitamin B12.

Marketed drugs incorporating a pyrrole ring system exhibit diverse biological activities such as anticancer, antibacterial, anti-inflammatory, antimalarial and antipsychotic properties, among others. Prime examples include the multi-billion dollar

drugs atorvastatin, zomigpirac, and tolmetin.<sup>5</sup> Owing to this importance of the pyrrole nucleus in medicinal chemistry, the research community has extensively explored biological applications of naturally occurring pyrroles. Examples include the lamellarins,<sup>3</sup> isolated from marine invertebrates, which have been found to possess anti-HIV and antitumor activities, and halitulin,<sup>4</sup> a marine sponge alkaloid isolated from *Haliclona tulearensis* which showed wide range of activity against several tumor cell lines. Hundreds of marine natural products belong to the pyrrole-imidazole alkaloid family, the parent member of which is oroidin.<sup>5</sup> The marinopyrroles<sup>6</sup> are another important class of marine alkaloids which have gained significance due to their potent activity against methicillin-resistant bacteria. The tripyrrolic prodiginine alkaloids have been isolated from various bacteria (e.g. *Hahella chejuensis* KCTC 2396 and *Pseudoalteromonas denitrificans*) and found to display antifungal, antibacterial, antiprotozoal and antimalarial bioactivities.<sup>7,8</sup> In other cases, the amounts of natural products obtained through isolation is not enough to carry out extensive biological studies, and here total synthesis can provide a solution to the supply problem, facilitating biological research. The well known tendency of pyrrole to polymerize, especially under acidic conditions, means that its synthetic chemistry carries an intrinsic challenge – one that in many ways serves to heighten the interest of organic chemists in this fascinating class of molecule. The development of strategies for the assembly of pyrroles has been reviewed a number of times over recent years.<sup>9–14</sup> The last review on the synthesis of pyrrole containing natural products was reported in 2010.<sup>15</sup> This review offers a comprehensive coverage of endeavours towards total syntheses of natural products containing pyrroles over the last ten years. It is divided into two main sections: firstly,

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strategies employing premade pyrrolic moieties, and secondly those that feature *en route* construction of the pyrrole motif. Within each section, syntheses involving simple (monocyclic) pyrrolic moieties are presented first, followed by syntheses of natural products containing fused (polycyclic) pyrroles. This distinction is further divided into non-asymmetric and asymmetric syntheses, while within the category of fused pyrroles, we have included only those target compounds where the pyrrole heterocycle is fused with another ring in such a way that the fusion does not lead to the formation of another common category of heterocycle (*e.g.* indoles). Due to the space limitations of this treatise, we have focussed mainly on key transformations and strategies within the syntheses, and have also omitted synthetic work that generates only a pyrrole core rather than a complete natural product.

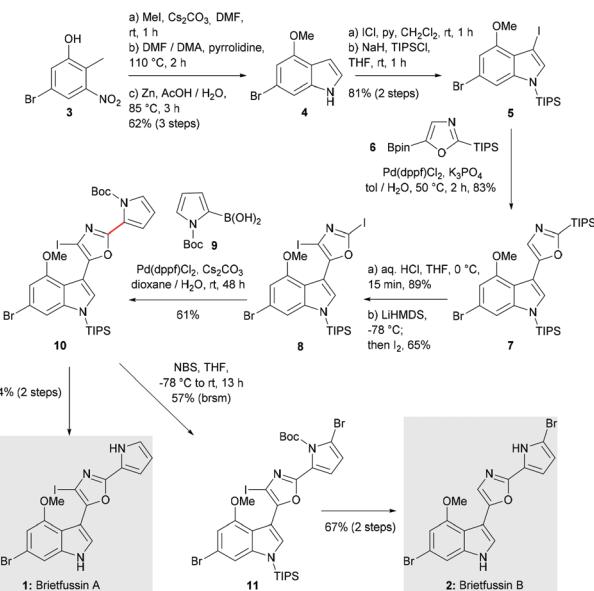
## 2. Total syntheses of natural products utilizing premade pyrrole motifs

This section discusses synthetic routes that employ a ‘premade’ pyrrole motif in the synthetic sequence. Initially we discuss total syntheses of natural products containing simple pyrrolic moieties, followed by natural products incorporating a fused pyrrole. As noted above, within each category the syntheses of achiral/racemic natural products are presented initially, followed by asymmetric syntheses.

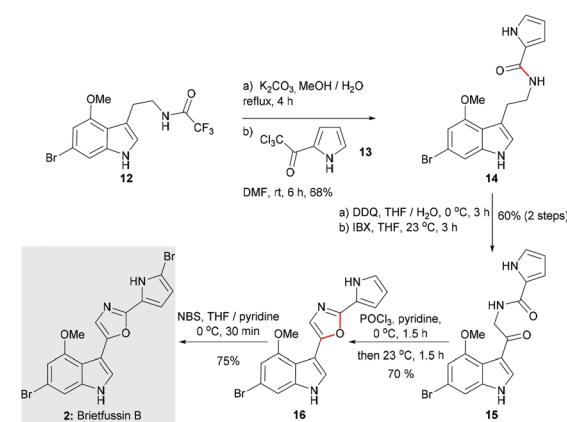
### 2.1. Premade pyrrole motifs in syntheses of natural products containing a simple pyrrolic moiety

**2.1.1 Brieffussins A and B.** The halogenated natural products brieffussin A **1** and B **2** were isolated from Arctic hydrozoan *Thuiaria brieffussi*.<sup>16</sup> In 2015, Bayer *et al.*<sup>17</sup> described their first total syntheses (Scheme 1). The synthetic approach commenced with the reaction of readily available phenol derivative **3** with iodomethane and caesium carbonate in DMF. Subsequent treatment with DMF:DMA and pyrrolidine, and then Zn powder, afforded **4** in moderate yield. Iodination at the C3 position of indole **4** and TIPS protection furnished **5**, which on Suzuki coupling with boronic ester **6** gave **7** in good yield. **7** was treated with aqueous HCl to selectively remove the TIPS protection at C2; metalation of this position and iodination resulted in the intermediate diiodooxazole **8**.<sup>17</sup> This underwent a further Suzuki coupling with *N*-Boc-2-pyrroleboronic acid **9** to give **10** in moderate yield; Boc removal followed by desilylation afforded brieffussin A **1**. Alternatively, bromination at the C2 position of the pyrrole in compound **10** afforded product **11**, which provided brieffussin B **2** in two further steps.

Sperry *et al.*<sup>18</sup> developed an iridium-catalyzed indole triborylation/alkoxylation process to install the C4 methoxy substituent in a formal synthesis of brieffussin B **2** (Scheme 2). Hydrolysis of the resulting protected tryptamine **12**, followed by amide coupling with 2-(chloroacetyl)pyrrole **13**, provided amide intermediate **14**, which intercepts with a previous syn-



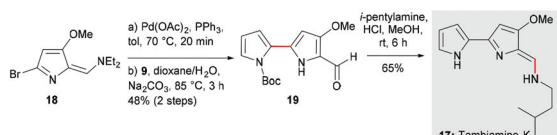
Scheme 1 Synthesis of brieffussin A **1** and B **2** (Bayer *et al.*, 2015).<sup>17</sup>



Scheme 2 Synthesis of brieffussin B **2** (Sperry *et al.*, 2018; Khan and Chen, 2015).<sup>18,19</sup>

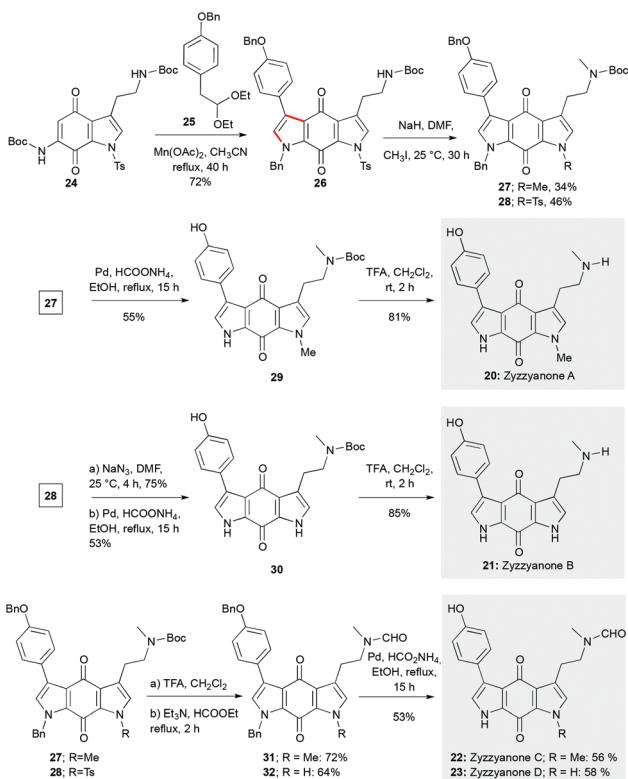
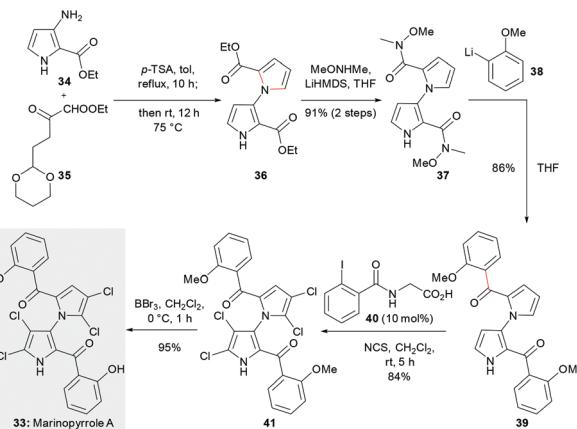
thesis of brieffussin B **2** by Khan and Chen.<sup>19</sup> In Chen’s work, this was converted to **15** in two steps using DDQ and IBX, which underwent Robinson–Gabriel cyclisation ion treatment with POCl<sub>3</sub> to obtain **16**. This compound could be converted to the natural product *via* bromination. Sperry *et al.*<sup>18</sup> synthesized the intermediate **14** in fewer steps compared to the synthesis of Chen and coworkers.<sup>19</sup>

**2.1.2 Tambjamine K.** Tambjamines A–J are members of a 2,2-bipyrrole family of alkaloids which differ in their aliphatic termini.<sup>20–24</sup> The tambjamines show a broad range of bioactivities including anti-cancer, antimicrobial, and immunosuppressive properties. Tambjamine K **17** (Scheme 3), isolated from the Azorean nudibranch *Tambja Ceutae* and the subject of this section,<sup>25</sup> showed antiproliferative activity and cytotoxicity against various cancer and noncancer cell lines. Lindsley *et al.*<sup>26</sup> disclosed the first total synthesis of tambja-

Scheme 3 Synthesis of tamjamine K 17 (Lindsley *et al.*, 2010).<sup>26</sup>

mine K, starting from bromoenamine **18**. This underwent Suzuki coupling with Boc-1*H*-pyrrol-2-yl boronic acid **9** to deliver the Boc-protected product **19**. Acid-catalyzed condensation between **19** and iso-pentylamine provided tambjamine K **17** in good yield.

**2.1.3 Zyzzyanones A–D.** Zyzzyanones A–D (20–23, Scheme 4) are tetracyclic bis-pyrroloquinone alkaloids isolated from *Zyzzya fuliginosa*,<sup>27–29</sup> the first total syntheses of which were reported by Velu *et al.*<sup>29</sup> in 2013 (Scheme 4). The zyzzyanone framework was prepared from pyrroloquinone **24**, which first underwent Mn(OAc)<sub>3</sub>-mediated oxidative coupling with acetal **25** at 80 °C to give bis-pyrroloquinone **26**. This was further treated with iodomethane under basic conditions to afford the methylated products **27** and **28**, in 34% and 46% yield respectively. Compound **27** was treated with Pd black and ammonium formate to provide **29** in moderate yield, which upon Boc removal using TFA afforded zyzzyanone A **20** as its TFA salt. Alternatively, removal of the *N*-benzyl, *N*-tosyl, *N*-Boc and *O*-benzyl protecting groups from **28** afforded zyzzyanone B **21**.

Scheme 4 Synthesis of zyzzyanone (A–D) 20–23 (Velu *et al.*, 2013).<sup>29</sup>Scheme 5 Synthesis of marinopyrrole A 33 (Gulder *et al.*, 2016).<sup>35</sup>

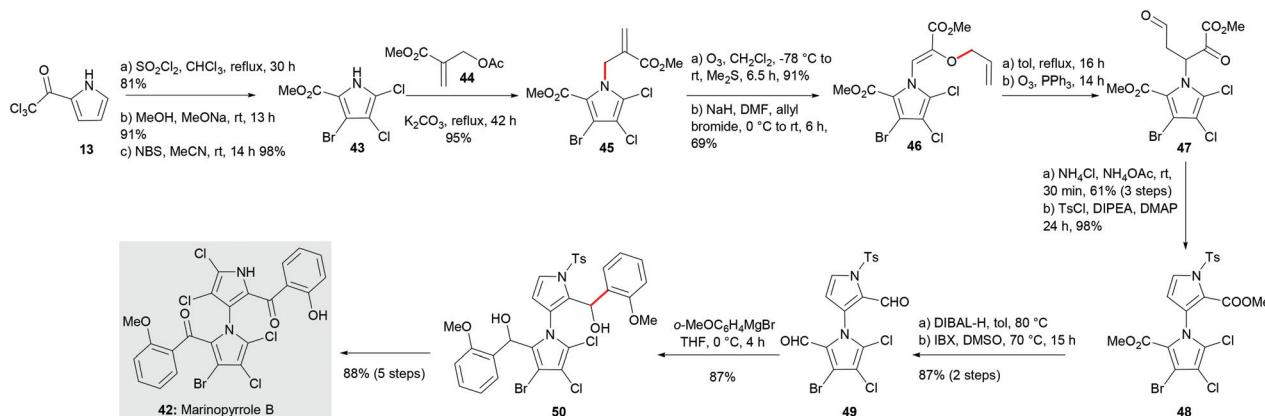
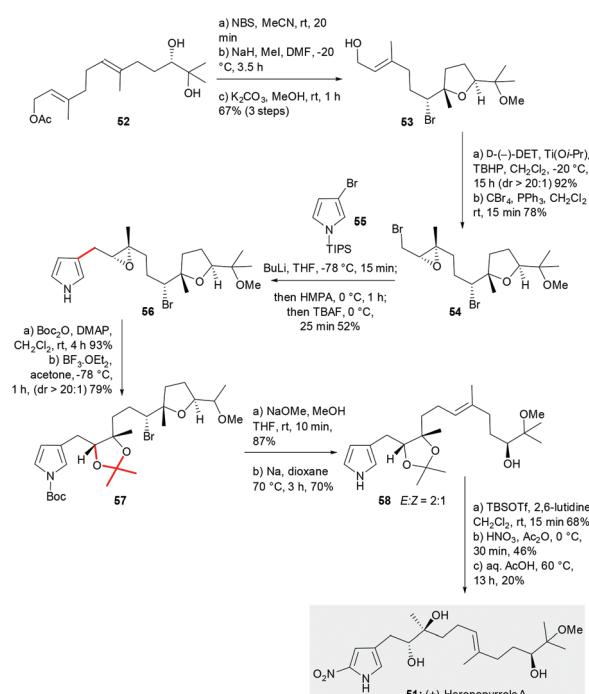
**21.** Selective Boc deprotection of **27** and **28**, followed by *N*-formylation and debenzylation afforded zyzzyanones C and D (22, 23) respectively.

**2.1.4 Marinopyrroles A and B.** The antimicrobial marinopyrroles A and B were first isolated by Fenical *et al.*<sup>30,31</sup> in 2008 from the marine *Streptomyces* strain CNQ-418. Their promising biological activity against MRSA strains and colon cancer cell lines make them attractive targets for drug development.<sup>32–34</sup> Gulder *et al.*<sup>35</sup> reported a synthesis of marinopyrrole A **33** in 2016 (Scheme 5), which began with preparation of bipyrrole **36** via condensation of aminopyrrole **34** with  $\delta$ -ketoaldehyde **35**. The ester groups were converted to bis-Weinreb amide **37**, which was reacted with *ortho*-lithiated anisole **38** to give diketone **39** in 86% yield. Perchlorination of the pyrrole rings was accomplished using NCS with a catalytic amount of iodobenzamide **40** (10 mol%), which provided *O,O*-dimethylmarinopyrrole **41** in 84% yield. Cleavage of the *O*-methyl groups under Lewis acidic conditions afforded **33**.

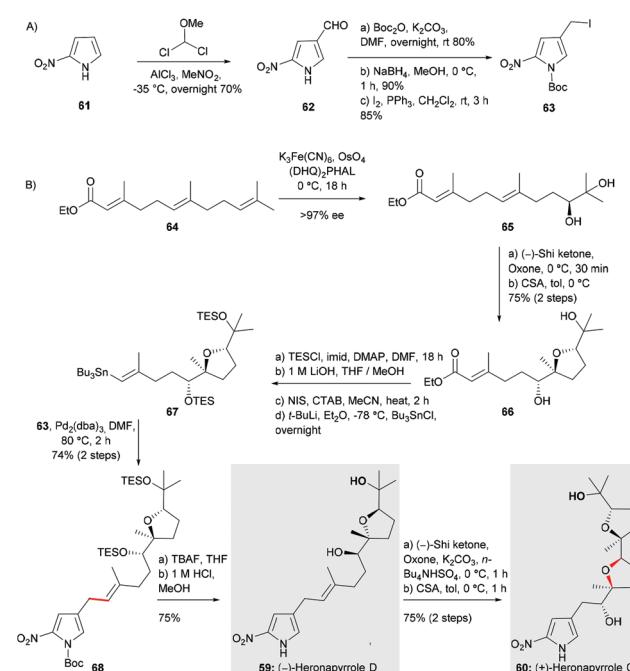
Clive *et al.*<sup>36</sup> described the first synthesis of marinopyrrole B (**42**, Scheme 6). Their route commenced with the commercially available trichloromethylketone **13**, which *via* a sequence of chlorination and bromination steps afforded bromodichloropyrrole **43**. Reaction of **43** with allylic acetate **44** gave pyrrole **45** in 95% yield, ozonolysis of which, followed by alkylation with allyl bromide, provided *O*-allyl enol ether **46**. An elegant Claisen rearrangement/ozonolysis sequence gave dicarbonyl **47**, which underwent Paal-Knorr pyrrole cyclization giving **48** and oxidation state adjustment to give the dialdehyde **49**. Double addition of *o*-methoxyphenylmagnesium bromide to this compound afforded diol **50**, which was then converted to marinopyrrole B **42** in a further five steps.

## 2.2 Premade pyrrole motifs in asymmetric syntheses of natural products containing a simple pyrrolic moiety

**2.2.1 Heronapyrroles A, C and D.** The heronapyrroles are a family of antibiotic natural products that were first isolated in 2010 from *Streptomyces* sp.<sup>37</sup>

Scheme 6 Synthesis of  $(\pm)$ -marinopyrrole B 42 (Clive *et al.*, 2013).<sup>36</sup>Scheme 7 Synthesis of  $(+)$ -heronapyrrole A 51 (Morimoto *et al.*, 2015).<sup>38</sup>

Morimoto *et al.*<sup>38</sup> described a total synthesis of  $(+)$ -heronapyrrole A 51 in 2015 (Scheme 7). Their strategy commenced with the preparation of epoxy bromide 54 from known  $(1S)$ -diol 52<sup>38</sup> through a five step sequence, including a chemoselective bromoetherification to form the tetrahydrofuran ring as a protecting group for the central trisubstituted alkene. The bromopyrrole 55 was alkylated with 54 following lithiation in THF/HMPA, and upon desilylation afforded pyrrole 56. After Boc protection of the pyrrole nitrogen atom, treatment with acetone/ $\text{BF}_3\cdot\text{OEt}_2$  effected epoxide ring opening/acetalization to give acetonide 57. Boc deprotection, and bromoether elimination using sodium metal generated the C11–C12 trisubstituted double bond in 58. Temporary silylation of the resulting

Scheme 8 Synthesis of  $(+)$ -heronapyrrole C 60 and  $(-)$ -heronapyrrole D 59 (Brimble *et al.*, 2016).<sup>39</sup>

hydroxyl group enabled pyrrole nitration; finally removal of the protecting groups yielded  $(+)$ -heronapyrrole A 51.

Subsequent to this work, Brimble *et al.*<sup>39</sup> reported total syntheses of  $(+)$ -heronapyrrole C 60 and  $(-)$ -heronapyrrole D 59 (Scheme 8). Their strategy focused on  $\text{sp}^2$ – $\text{sp}^3$  Stille coupling to attach the pyrrole motif to the tetrahydrofuran-containing side chain, and involved an early stage nitration. Iodomethyl nitropyrrole 63 was first efficiently obtained *via* a formylation/reduction/iodination sequence from 2-nitropyrrole 61. The stannane partner for the planned coupling was prepared from triene 64, which underwent a chemoselective asymmetric dihydroxylation of the terminal trisubstituted alkene of 65, followed by Shi epoxidation of the C7–C8 olefin of 65 and

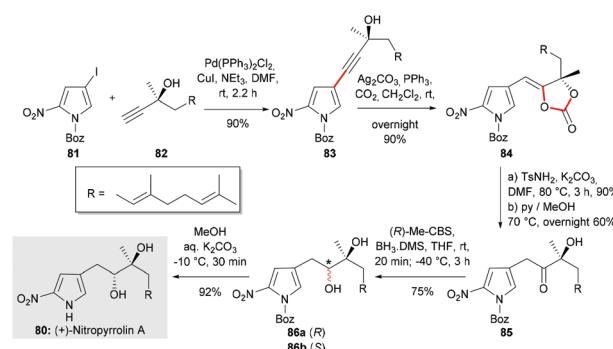
acid-catalyzed cyclization to tetrahydrofuran **66**. This was converted to stannane **67** using a Hunsdiecker decarboxylation to transform the carboxyl group into an alkenyl iodide, and subsequent lithiation/stannylation. The key cross-coupling of alkenyl stannane **67** with iodomethylpyrrole **63** afforded compound **68**, deprotection of which gave (−)-heronapyrrole D **59**. A further asymmetric epoxidation/CSA-catalyzed epoxide ring-opening/cyclization afforded diastereomerically pure (+)-heronapyrrole C **60**.

**2.2.2 Roseophilin.** Ansa-bridged prodiginines are lipochromophores which are produced by marine and terrestrial bacteria.<sup>40–42</sup> Roseophilin (**69**, Scheme 9) is a relatively new addition to this family; its structure contains two C–C σ bonds connecting its hydrocarbon core to its bis-heterocyclic tail. Harran *et al.*<sup>43</sup> reported an asymmetric synthesis of (+)-roseophilin **69** in 2013 (Scheme 9). This began with linked pyrrole-furan **70**, which was obtained by lithiation of the corresponding 3-methoxyfuran at the 2-position, followed by treatment with ZnBr<sub>2</sub> and Pd-catalyzed carboxylation. Activation of the carboxylic acid with benzotriazole **71** provided an intermediate benzotriazole amide, which underwent TiCl<sub>4</sub>-mediated acylation with 2-(8-nonenyl)pyrrole **72** to give the bis-heteroarylketone **73** in good yield. This pyrrole was protected by treatment with diethylchlorophosphite to provide the phosphoramidate **74**, presumably *via* aerobic oxidation of the intermediate *N*-phosphinyl derivative. Cross metathesis of **74** with ketone **75** using Grubbs II catalyst (5 mol%), followed by *in situ* reduction of the resultant enone through Pd-catalyzed hydrosilylation, yielded diketone **76**. The macrocycle **77** was then obtained in good yield (66%) by aldol condensation on treatment of **76** with KHMDS/18-crown-6. At this point, prochiral pyrrolophane **77** was subjected to hydrogenation using Rh(cod)<sub>2</sub>OTf (5 mol%)/Josiphos ligand **78** (5 mol%) as catalyst, to produce **79** in 67% *ee* and excellent diastereoselectivity.

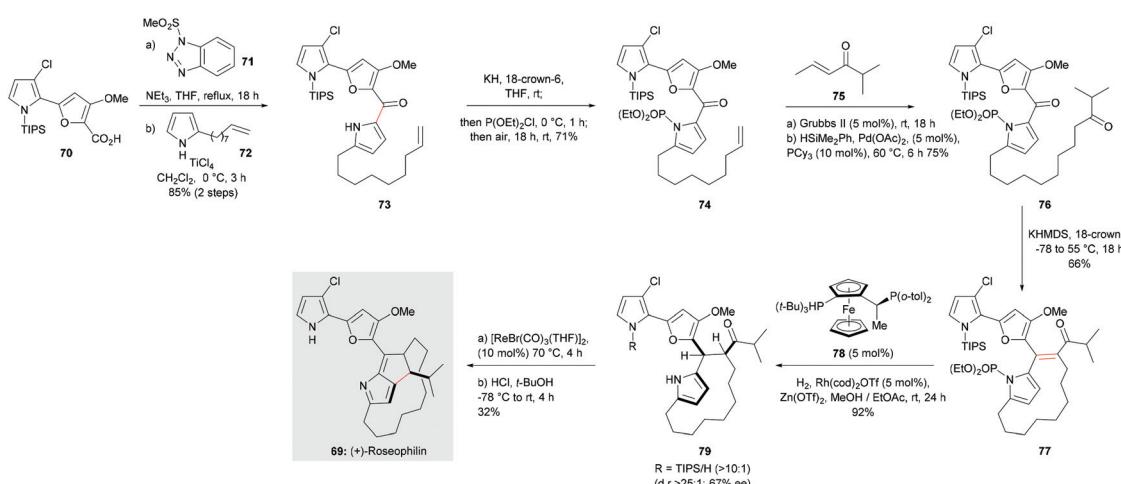
This was treated with 10 mol% of a rhenium tricarbonyl Lewis acid, which triggered a nucleophilic cyclization by the pyrrole onto the proximal ketone to produce an unstable 2-aza-

fulvene intermediate. Protonation of this product with dry HCl/t-BuOH (25 mol%) afforded (+)-roseophilin hydrochloride salt **69**.

**2.2.3 Nitropyrrolin A.** Fenical and coworkers isolated nitropyrrolins A–E from a marine sediment collected from La Jolla, California in 2010.<sup>44</sup> Produced by the MAR4 strain CNQ-509,<sup>44</sup> nitropyrrolins A, B and D showed cytotoxicity towards human colon carcinoma cells. Morimoto *et al.*<sup>45</sup> reported the first total synthesis of these nitropyrrolins in 2016 using a strategy similar to that of their heronapyrrole syntheses described previously (Scheme 7). Brimble *et al.*<sup>46</sup> later described the total synthesis of (+)-nitropyrrolin A **80**, which is shown in Scheme 10. This involved a Sonagashira coupling between iodopyrrole **81** and terminal alkyne **82** to install the pyrrole C3 side chain; the key hydroxyketone motif was then constructed by a high-yielding silver-catalyzed carboxylative cyclization of **83** to give enol carbonate **84**. Cleavage of this cyclic carbonate was achieved by formation of a sulfonyl carbamate on treatment with TsNH<sub>2</sub>, then pyridine-promoted methanolysis to give **85**. Diastereoselective reduction of **85** gave a 6:1 mixture of alcohols **86a** and **86b**, with methanolysis of the *N*-Boz (*N*-benzyloxymethyl) group delivering (+)-nitropyrrolin A **80**.



Scheme 10 Synthesis of (+)-nitropyrrolin A **80** (Brimble *et al.*, 2017).<sup>46</sup>

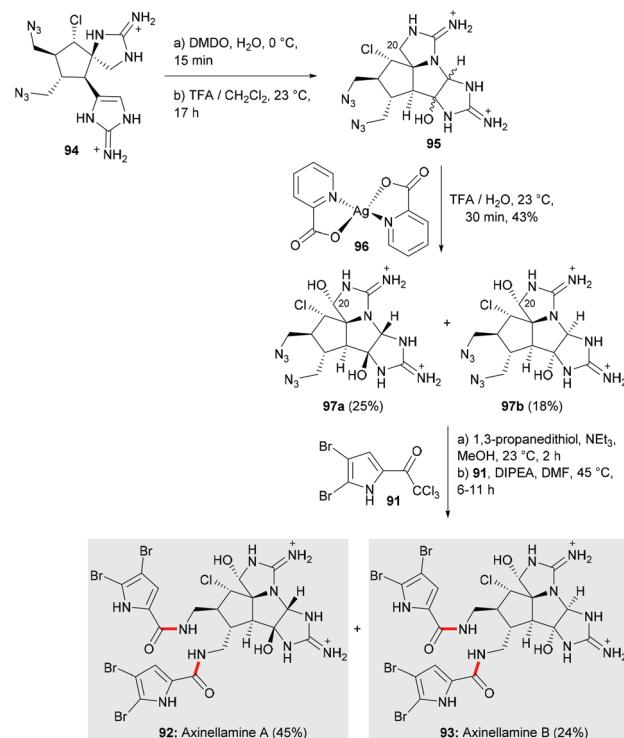


Scheme 9 Asymmetric synthesis of (+)-roseophilin **69** (Harran *et al.*, 2013).<sup>43</sup>

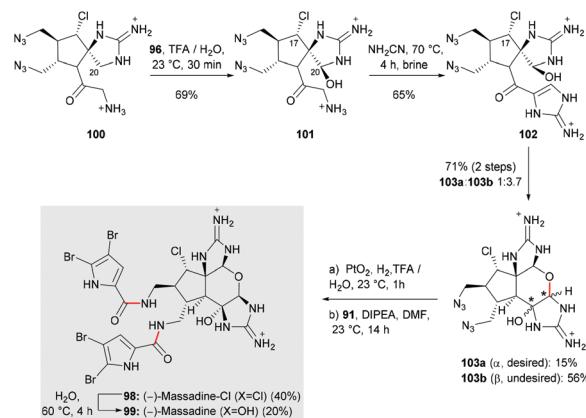
**2.2.4 Mukanadin F.** Numerous linear C9-substituted bromopyrrole alkaloids have been isolated from sponges of the *Agelasida* and *Axinellida* genera. Barker *et al.*<sup>47</sup> reported an enantioselective synthesis of (*S*)-mukanadin F **87** (Scheme 11), which began with alcohol (*R*)-**88**.<sup>47</sup> This was subjected to Swern oxidation, followed by Horner–Wadsworth–Emmons reaction with phosphonate **89** to afford a diastereomeric mixture of enamides (*S*)-**90** (*E/Z* 1 : 2). The PMB and Boc groups in **90** were deprotected under acidic conditions to give an amine salt, which underwent coupling with trichloromethyl ketopyrrole **91** to afford the natural product **87**.

**2.2.5 Axinellamines A and B and massadine.** Dimeric pyrrole-imidazole alkaloids represent a topologically rich class of bromopyrrole alkaloids.<sup>48</sup> In 1999, Quinn *et al.*<sup>49</sup> reported the first members of this family, namely axinellamines A and B (**92** and **93**). A few years later, Fusetani *et al.*<sup>50</sup> isolated the tetracyclic pyrrole-imidazole alkaloid massadine **98**, which features a different heterocycle connectivity to the axinellamines. The densely functionalized cores display a high nitrogen content, and eight contiguous stereocenters, as well as sensitive functional groups such as halogens and hemiaminals.

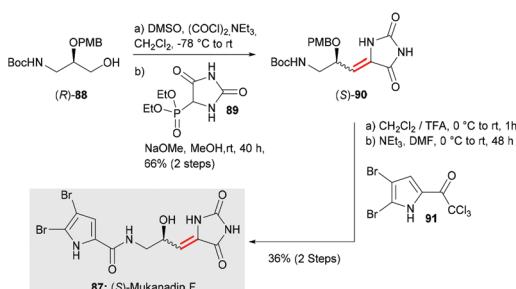
Baran *et al.*<sup>51</sup> reported enantioselective total syntheses of axinellamines A and B, and massadine, in 2011 (Schemes 12 and 13 respectively). Among many challenges, the synthesis of the axinellamines presents two significant problems: formation of the polycyclic core, and oxidative installation of the C20 hemiaminal. The former challenge was solved by an oxidative cyclization of the aminoimidazole **94**, the cyclopentane ring of which was originally derived from a Pauson–Khand synthesis. Introduction of the hemiaminal was achieved after a thorough screen of oxidants (*e.g.* halogenating agents, hyper-va lent iodine, potassium persulfate, potassium ferrate), with the most satisfactory results obtained by employing silver(II) picolinate **96** in aqueous trifluoroacetic acid, which delivered **97a** and **97b** in modest yield. The reduction of the azides in these compounds required conditions that could accommodate the highly polar and sensitive nature of the substrate, a challenge that was overcome by using propanedithiol and triethylamine. This provided the corresponding diamines in sufficient purity to undergo double acylation with (trichloroacetyl)pyrrole **91**, to give (–)-axinellamine A **92** and (–)-axinellamine B **93**.



**Scheme 12** Enantioselective synthesis of (–)-axinellamine A **92** and (–)-axinellamine B **93** (Baran *et al.*, 2011).<sup>51</sup>



**Scheme 13** Enantioselective synthesis of (–)-massadine **99** (Baran *et al.*, 2011).<sup>51</sup>



**Scheme 11** Enantioselective synthesis of (*S*)-mukanadin F **87** (Barker *et al.*, 2018).<sup>47</sup>

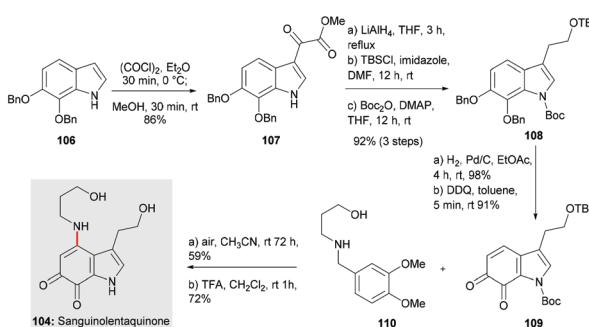
The main challenge in the approach to massadine **99** (Scheme 13) is control over the C20 oxidation state of the massadine skeleton. Use of the silver(II) picolinate salt **96** again provided the solution, enabling oxidation of **100** to **101**. Interestingly, the optimal conditions for the synthesis of the 2-aminoimidazole ring employing brine as the solvent, which reduced the extent of Cl/OH exchange at C17, and provided **102** in good yield. Oxidation of **102** to a transient epoxide with DMDO, followed by acid-promoted cyclization, gave the desired epimer **103a** in low yield. Azide hydrogenolysis, fol-

loured by acylation of the resulting amines with pyrrole **91**, provided the natural product **98** and **99** in a 2 : 1 ratio.

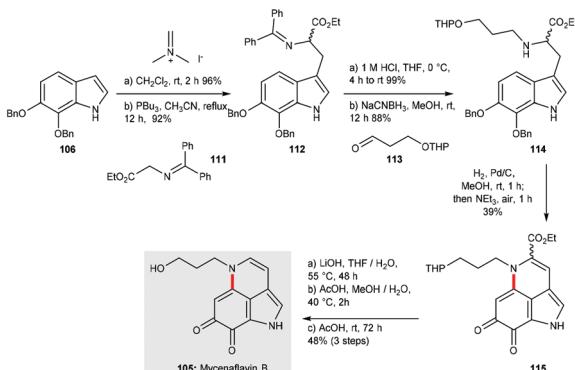
### 2.3. Premade pyrrole motifs in syntheses of natural products containing a fused pyrrolic moiety

**2.3.1 Sanguinolentaquinone and mycenaflavin B.** Sanguinolentaquinone **104** (Scheme 14), isolated from *Mycena sanguinolenta*,<sup>52</sup> and mycenaflavins A and B **105** (Scheme 15), isolated from *Mycena haematopus*,<sup>53</sup> feature interesting pyrrole-*ortho*-quinone cores. Spiteller *et al.*<sup>54</sup> reported the first total synthesis of sanguinolentaquinone and mycenaflavin B in 2018. The approach to **104** (Scheme 14) started with bis-benzylloxyindole **106**, which was converted to quinone **109** in 6 steps. This underwent Michael addition with 3,4-dimethoxybenzyl (DMB) protected 3-aminopropanol **110**, followed by aerobic oxidation to give protected sanguinolentaquinone. The Boc group was removed under standard acidic conditions to provide the natural product **104**.

The synthesis of **105** used the same indole starting material **106**, which in this case underwent C3-alkylation with Eschenmoser's salt, and then Somei-Kametani substitution of the dimethylamino group with imine **111** to give **112**. Treatment with aqueous HCl liberated the amine group, and the side chain was introduced by reductive amination with aldehyde **113** to afford amine **114**. Hydrogenolysis of the



Scheme 14 Synthesis of sanguinolentaquinone **104** (Spiteller *et al.*, 2018).<sup>54</sup>



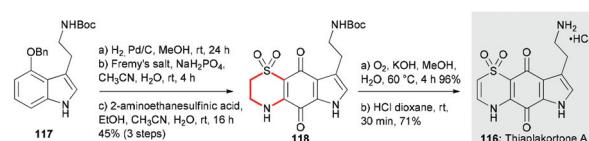
Scheme 15 Synthesis of mycenaflavin B **105** (Spiteller *et al.*, 2018).<sup>54</sup>

benzyl groups, and then aerobic oxidation gave the corresponding quinone **115**. Saponification of the ethyl ester group in **115**, followed by decarboxylation under acidic conditions and THP deprotection, afforded mycenaflavin B **105**.

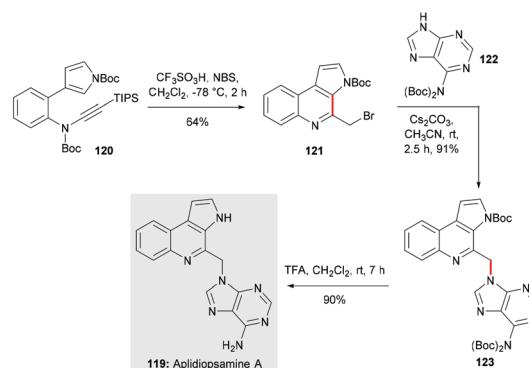
**2.3.2 Thiaplakortone A.** Thiaplakortone A **116** (Scheme 16) was isolated from the marine sponge *Plakortis lita*.<sup>55</sup> Quinn *et al.*<sup>56</sup> described a total synthesis of this potent antimalarial natural product in 2013. From indole **117**, hydrogenolysis of the benzyl protecting group was followed by oxidation of the unstable intermediate phenol with Fremy's salt. The resulting quinone then underwent a double conjugate addition/oxidation sequence on reaction with 2-aminoethanesulfinic acid to give dihydrothiazine dioxide **118**. The dihydrothiazine ring was then oxidized, with Boc deprotection affording the HCl salt of thiaplakortone A **116**.

**2.3.3 Aplidiopsamine A.** The alkaloid aplidiopsamine A **119** (Scheme 17), obtained from the Australian ascidian, *Aplidiopsis confluata*,<sup>57</sup> exhibited significant growth inhibition of drug-resistant strains of *Plasmodium falciparum*. Takasu *et al.*<sup>57</sup> described a synthetic strategy to aplidiopsamine A beginning with ynamide **120**, treatment of which with triflic acid at -78 °C triggered cyclization and NBS-mediated bromination to give **121**. Reaction of bromide **121** with di-Boc-protected adenine **122**<sup>58</sup> in the presence of caesium carbonate gave **123**, which on acidic deprotection afforded aplidiopsamine A **119** in high yield.

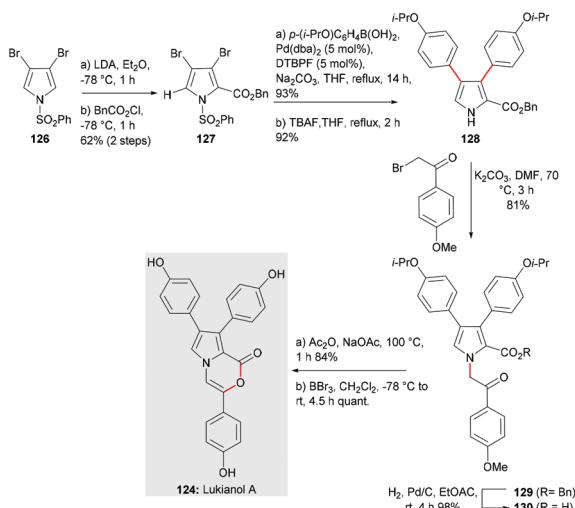
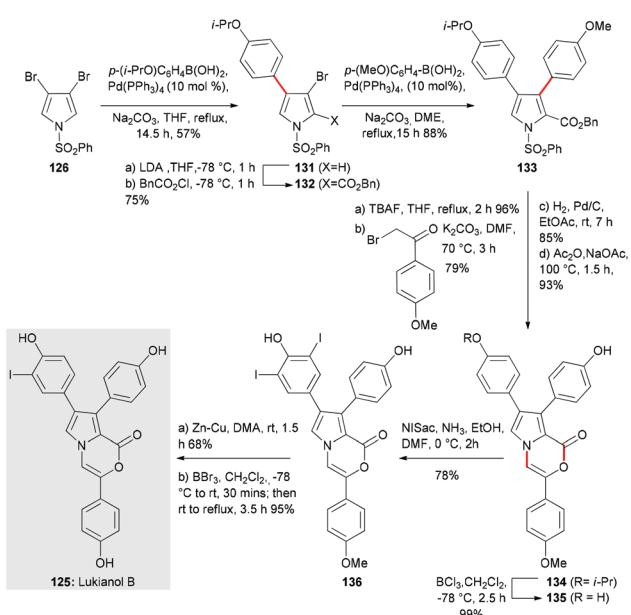
**2.3.4 Lukianols A and B.** Scheuer *et al.*<sup>59</sup> isolated lukianols A **124** (Scheme 18) and B **125** (Scheme 19) from a tunicate collected from a lagoon of the Palmyra atoll. Lukianol B **125** exhibited high h-ALR2 inhibitory activity. Iwao *et al.*<sup>60</sup> developed approaches to lukianol A **124** and lukianol B **125**; the key steps in the total syntheses are pyrrole lithiation, and Pd-cata-



Scheme 16 Synthesis of thiaplakortone A **116** (Quinn *et al.*, 2013).<sup>56</sup>



Scheme 17 Synthesis of aplidiopsamine A **119** (Takasu *et al.*, 2014).<sup>57</sup>

Scheme 18 Synthesis of lukianol A 124 (Iwao et al., 2013).<sup>60</sup>Scheme 19 Total Synthesis of Lukianol B 125 (Iwao et al., 2013).<sup>60</sup>

lyzed cross-coupling to install the phenol side chains. Thus, lithiation of **126**<sup>61</sup> at  $-78^{\circ}\text{C}$  (Scheme 18) followed by trapping with benzylchloroformate gave 2-benzyloxycarbonylpyrrole **127**.

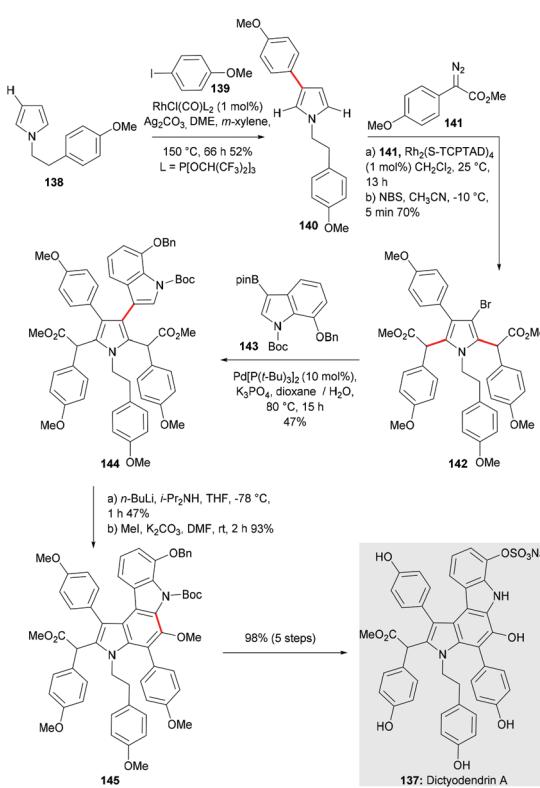
This was subjected to Suzuki coupling with *p*-isopropoxybenzylboronic acid, followed by removal of the sulfonyl protecting group to afford **128**. Alkylation of **128** with *p*-methoxyphenacyl bromide afforded **129**, and hydrogenolysis of the benzyl ester resulted in **130**. Finally, heating in  $\text{Ac}_2\text{O}$  followed by deprotection of the aryl isopropyl and methyl ethers with  $\text{BBr}_3$  afforded Lukianol A **124**.

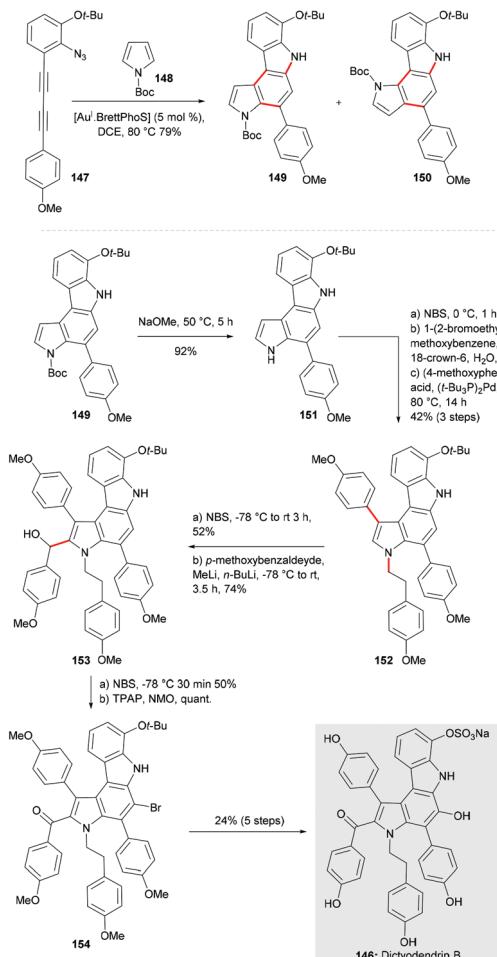
The synthesis of Lukianol B **125** requires differentiation of the phenol side chains and commenced with a Pd-catalyzed

coupling of **126** with *p*-isopropoxyphenylboronic acid. The mono coupling product **131** was treated with LDA/benzyl chloroformate to give **132**, which underwent a second cross-coupling with *p*-methoxyphenylboronic acid to produce **133**. The resultant bis-arylated compound **133** was transformed into pyrrolooxazinone **134** in the same manner as described for the synthesis of Lukianol A **124**. **134** was treated with  $\text{BCl}_3$  to selectively deprotect the isopropyl ether, followed by double iodination of the resultant phenol with *N*-iodosaccharin (NISac) to give diiodide **136**. Finally, reaction of **136** with Zn–Cu couple, followed by demethylation with  $\text{BBr}_3$ , afforded Lukianol B **125**.

**3.3.5 Dictyodendrins A and B.** Dictyodendrin A **137** (Scheme 20) exhibits anticancer activity by telomerase inhibition.<sup>62–64</sup> Davies *et al.*<sup>62</sup> reported a synthetic strategy to dictyodendrin A which commenced with C–H arylation of pyrrole **138**, followed by C–H insertion using aryl diazoacetate **141**. Product **142** underwent Suzuki–Miyaura coupling with indole-3-boronic ester **143** to give **144**, which underwent  $6\pi$ -electrocyclization of the corresponding dianion intermediate, and methylation of the phenol, to give **145**. This intermediate was transformed into dictyodendrin A **137** in a further five steps with a remarkable 98% yield.

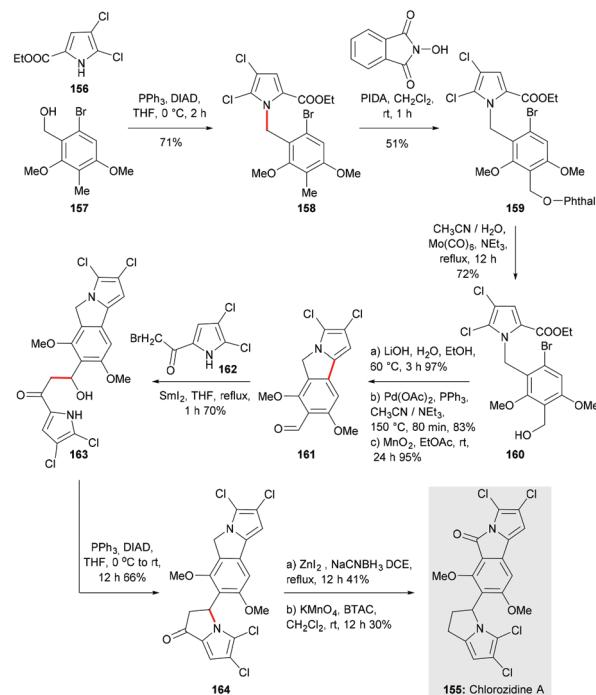
Ohno *et al.*<sup>65</sup> developed a route to dictyodendrin B **146** (Scheme 21) using a gold-catalyzed cascade cyclization of a conjugated diaryl aryl azide with pyrrole to generate three bonds and two aromatic rings in a single step. Thus, treatment of azido diarye **147**<sup>65</sup> with Boc protected pyrrole **148** led to the

Scheme 20 Synthesis of dictyodendrin A **137** employing sequential C–H functionalizations (Davies *et al.*, 2014).<sup>62</sup>

Scheme 21 Synthesis of dictyodendrin B 146 (Ohno et al., 2017).<sup>65</sup>

formation of two possible annulation products **149** and **150**. The desired product **149** was treated with NaOMe to deprotect the pyrrole Boc group, and the resulting product **151** was subjected to a C3 bromination/N-alkylation sequence, followed by Suzuki coupling, to afford compound **152**. This underwent further C2 bromination, followed by bromine–lithium exchange and addition of *p*-methoxybenzaldehyde, to give alcohol **153**. Selective monobromination of the central aromatic ring, followed by Ley–Griffith oxidation, afforded compound **154**; this was transformed into dictyodendrin B **146** in five further steps.

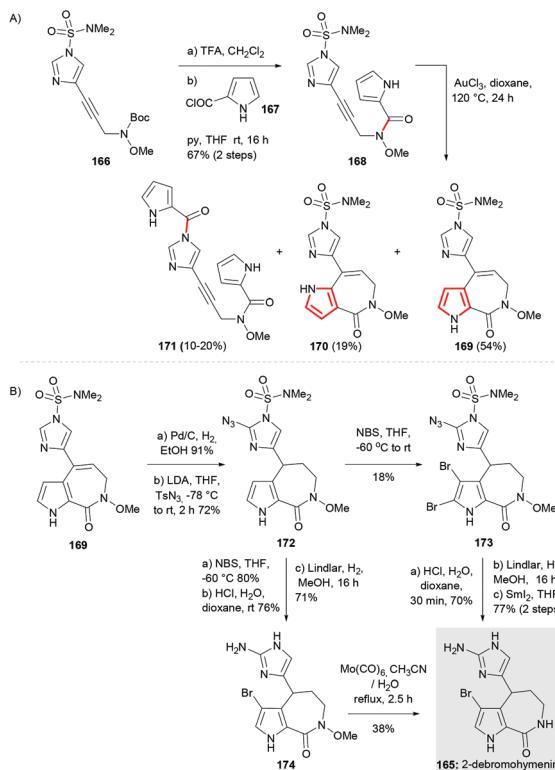
**2.3.6 Chlorizidine A dimethyl ether.** In 2013, Hughes *et al.*<sup>66</sup> isolated chlorozidine A from *Streptomyces* sp. strain CNH-287. This natural product exists as the (*S*)-atropisomer of a 2,3-dihydropyrrolizine ring system connected to a 5*H*-pyrrolo[2,1-*a*]isoindol-5-one. Mhaske *et al.*<sup>67</sup> reported the first synthesis of the dimethyl ether derivative of chlorozidine A (**155**, Scheme 22) in 2017. Pyrrole **156** was first coupled with alcohol **157** under Mitsunobu esterification conditions to give **158** in high yield. **158** was oxidized by treatment with *N*-hydroxyphthalimide to afford **159**, the N–O bond in which was cleaved using Mo(CO)<sub>6</sub> to afford alcohol **160**. The ester in

Scheme 22 Synthesis of chlorozidine A **155** (Mhaske *et al.*, 2017).<sup>67</sup>

**160** underwent hydrolysis with LiOH, and the resultant acid was treated with Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> to effect a decarboxylative cyclization of the aryl bromide onto the pyrrole ring, followed by benzylic oxidation with MnO<sub>2</sub> to afford aldehyde **161**. Reaction of this aldehyde with bromoketone **162**<sup>67</sup> under Reformatsky conditions led to  $\beta$ -hydroxy ketone **163** in moderate yield. The endgame consisted of a Mitsunobu cyclization to **164**, followed by reduction of the ketone, and oxidation of the upper pyrrolopyrrolidine ring using KMnO<sub>4</sub> to afford methyl-protected chlorozidine A **155**.

**2.3.7 2-Debromohymenin.** 2-Debromohymenin **165** (Scheme 23) was isolated from *Styliissa carteri* (syn. *Axinella carteri*).<sup>68</sup> Lovely *et al.*<sup>69</sup> reported a racemic synthesis of **165** in 2020 using an Au-catalyzed alkyne hydroarylation. Hydroxylamine derivative **166** (Scheme 23A) was first treated with TFA to remove the Boc group, and the resulting *N*-methoxyamine was acylated with pyrrolecarbonyl chloride **167** to afford pyrrole amide **168**. Treatment of **168** with AuCl<sub>3</sub> in dioxane led to cyclization to pyrroloazepinone **169** along with minor regioisomer **170**, and a small amount of trans acylated derivative **171**. The desired product **169** was then hydrogenated with Pd/C and H<sub>2</sub>; subsequent lithiation with LDA and reaction with TsN<sub>3</sub> resulted in the synthesis of azide **172**.

Low yielding dibromination was achieved upon treatment of **172** with NBS (to give **173**), treatment of which with HCl followed by Lindlar reduction, and N–O reduction with SmI<sub>2</sub> in THF, afforded 2-debromohymenin **165** in good yield. An alternative route from **172** to **165** involved reaction with NBS followed by HCl, and then Lindlar reduction to afford **174**;

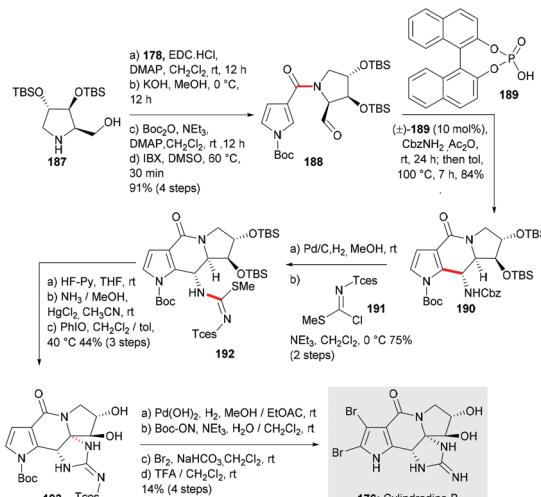
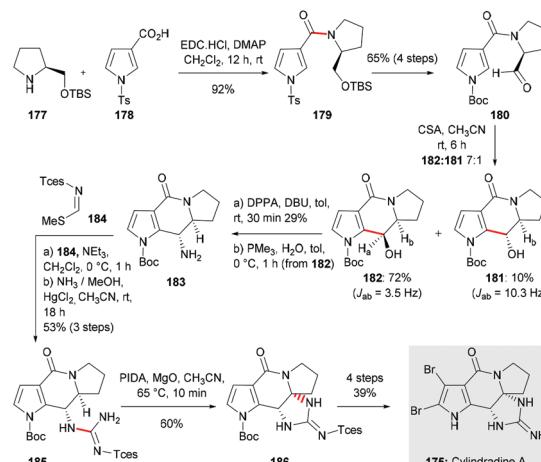


reduction of the N–O bond using  $\text{Mo}(\text{CO})_6$  in acetonitrile gave 2-debromohymenin **165**.

#### 2.4. Premade pyrrole motifs in asymmetric syntheses of natural products containing a fused pyrrolic moiety

**2.4.1 Cylindradines A and B.** Pyrrole-imidazole alkaloids (PIAs) are members of the wider oroidin-derived marine natural products,<sup>70–74</sup> and exhibit diverse biological activities including immunosuppressive, adrenoceptor agonistic and anticancer activities. Uno *et al.*<sup>75</sup> isolated cylindradine A **175** (Scheme 24) and B **176** (Scheme 25) from *Axinella cylindratus*. Unlike other PIAs which consist of a 2-carbamoylpyrrole unit, cylindradines A and B contain an unusual 3-carbamoylpyrrole.<sup>14</sup> As with other members of the family, cylindradine A **175** also features a characteristic *N,N'*-aminal in the cyclic guanidine moiety; the enantioselective construction of this aminal is the key challenge<sup>76,77</sup> in the construction of the cylindradine skeleton.

The first total synthesis of  $(+)$ -cylindradine A **175** (Scheme 24) was disclosed by Nagasawa *et al.*<sup>78</sup> Their synthesis is based on an intramolecular Friedel–Crafts cyclization followed by oxidative cyclization. The synthetic approach to cylindradine A commenced with amide bond formation between pyrrolidine **177** and acid **178**<sup>79</sup> using EDC·HCl and DMAP, which gave **179**. This was converted into pyrrole-aldehyde **180** in four steps. Friedel–Crafts cyclization was achieved in good yield on treatment of **180** with CSA to give **182** as the major



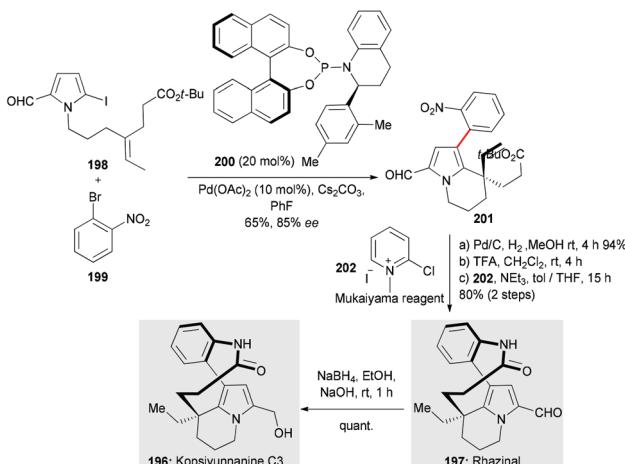
product isomer. Stereoselective azidation of **182** with DPPA and DBU, followed by reduction under Staudinger conditions gave amine **183**. Guanidine **185** was then synthesised by reaction with 2,2,2-trichloroethoxysulfonyl (Tces) protected imine **184**,<sup>80</sup> which on oxidation with PIDA in the presence of MgO gave tetracyclic guanidine **186**. This product was transformed into cylindradine A **175** in a further four steps with a 39% yield.

Cylindradine B **176** (Scheme 25) features an *anti*-1,2-diol on the pyrrolidine D ring. Nagasawa *et al.*<sup>81</sup> described the first total synthesis of  $(+)$ -cylindradine B **176**, based on an improved version of their synthesis of cylindradine A.<sup>78</sup> The strategy involves a diastereoselective Pictet–Spengler reaction for the synthesis of amine **190** from pyrrole **188**, employing phosphoric acid catalyst **189**. Amine **190** was treated with  $\text{H}_2$  and 10% Pd/C to deprotect the Cbz group, followed by reaction of the resultant pyrrolidine with **191** to give **192** in 75% yield. After

desilylation, the *S*-methylisothiourea was converted into the target guanidine motif by reaction with NH<sub>3</sub>/MeOH and mercury(II) chloride, followed by oxidative cyclization with PhIO. A four step sequence including dibromination of the pyrrole moiety afforded (+)-cylindradine B 176.

**2.4.2 Rhazinal and kopsiyunnanines C1–3.** Three rhazinolam derived alkaloids, kopsiyunnanines C1–C3, were isolated from *Yunnan Kopsia Arboria* in 2009.<sup>82</sup> Kopsiyunnanines C1 and C2 (194 and 195, Scheme 27) contain ethoxymethyl or methoxymethyl sidechains, while C3 (196, Scheme 26) features the corresponding free alcohol. Gu *et al.*<sup>83</sup> presented the first asymmetric total synthesis of kopsiyunnanines C1–C3 (Schemes 26 and 27), along with (+)-rhazinal (197, Scheme 26). The latter two natural products were formed from an asymmetric Heck reaction of pyrrole iodide 198 (Scheme 26) under the influence of ligand 200, and then Pd-catalyzed C3 arylation with 199, to give fused ring pyrrole 201. Both the nitro group and alkene of 201 were reduced with Pd/C and H<sub>2</sub>; the resulting intermediate was treated with TFA, followed by addition of the Mukaiyama reagent 202 to achieve cyclization leading to the formation of (+)-rhazinal 197. The aldehyde group in 197 was reduced with NaBH<sub>4</sub>/EtOH to afford (+)-kopsiyunnanine C3 196.

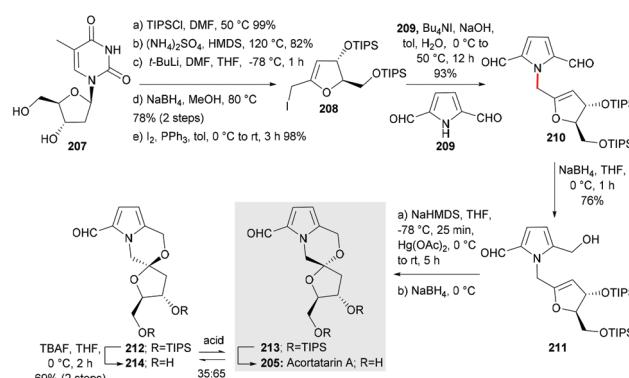
The same group pursued a number of strategies to synthesize (+)-kopsiyunnanines C1 and 2 from *t*-butyl ester 203



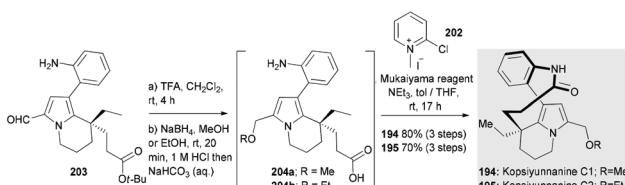
**Scheme 26** Synthesis of (+)-rhazinal 197 and (+)-kopsiyunnanine C3 196 (Gu *et al.*, 2016).<sup>83</sup>

(Scheme 27); eventually it was found that the *t*-butyl group could be hydrolyzed by TFA, followed by reduction of the aldehyde with NaBH<sub>4</sub> and acidification with HCl to give ethers 204a and 204b. These were treated with the Mukaiyama reagent 202 to afford (+)-kopsiyunnanines C1 194 and C2 195 in good yield.

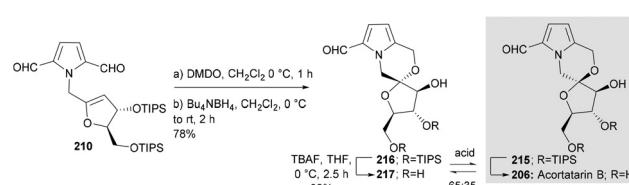
**2.4.3 Acortatarins A and B.** The acortatarins are spiroketal pyrrole alkaloids isolated from the roots of *Acorus tatarinowii*.<sup>84</sup> Tan *et al.*<sup>85</sup> reported an efficient synthesis of (+)-acortatarin A 205 (Scheme 28) and (−)-acortatarin B 206 (Scheme 29) through stereoselective glycal spirocyclizations. The synthesis commenced with D-thymidine 207, which underwent TIPS protection of hydroxyl groups, followed by hydrolysis of the N,O-acetal with ammonium sulfate to give the corresponding TIPS protected D-ribal. This intermediate underwent C1 formylation and reduction to give TIPS-protected C1-hydroxymethyl-D-ribal which was then converted to D-ribal iodide 208 upon treatment with iodine and PPh<sub>3</sub>. 208 was alkylated with pyrrole dicarboxyaldehyde 209 under biphasic conditions to give 210, which in turn was reduced to alcohol 211. Oxidative spirocyclisation promoted by Hg(II) acetate afforded the β-mercurial spiroketals, which were reduced by NaBH<sub>4</sub> to give spiroketals 212 and 213. Desilylation of the mixture of 212 and 213 afforded C1-*epi*-acortatarin A 214 and (+)-acortatarin A 205. In subsequent work, the same group applied an epoxidation-spirocyclisation approach for the synthesis of acortatarin B 206, in which pyrrolglycal 210 underwent epoxidation using DMDO; treatment with Bu<sub>4</sub>NBH<sub>4</sub> afforded the desired β-spiroketal 215 in good



**Scheme 28** Stereoselective synthesis of (+)-acortatarin A 205 (Tan *et al.*, 2012).<sup>85</sup>



**Scheme 27** Synthesis of (+)-kopsiyunnanine C1 194 and (+)-kopsiyunnanine C2 195 (Gu *et al.*, 2016).<sup>83</sup>



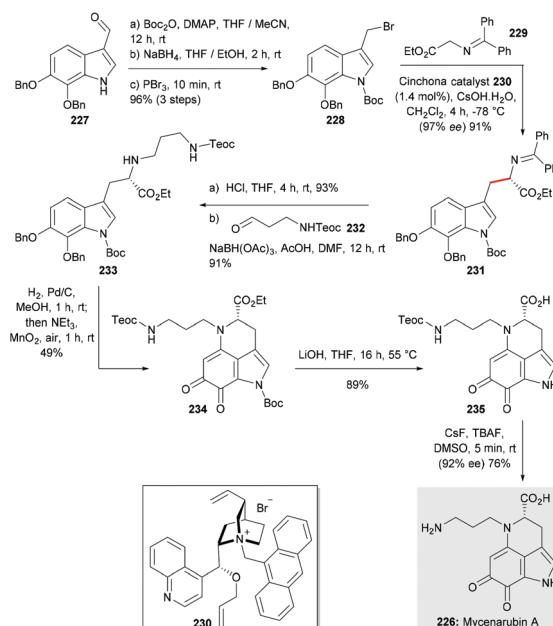
**Scheme 29** Stereoselective synthesis of (−)-acortatarin B 206 (Tan *et al.*, 2012).<sup>85</sup>

yield and diastereoselectivity at the C3 position. Desilylation provided (–)-acortatarin B 206 and its C1-epimer.

In 2017, Pale *et al.*<sup>86</sup> developed a different synthetic route to (+)-acortatarin A 205 using a variety of zeolite catalysts (Scheme 30), which provide an interesting alternative to solution-based catalysts in organic synthesis. Bromoalkyne 220 was first synthesized from 2-deoxy-D-ribose 218 in six steps, two of which (glycoside formation and hydrolysis) were acid-catalyzed using the protic zeolite H-ZSM5. The bromoalkyne itself was formed by Ramirez olefination of the intermediate 219, followed by protection of the resulting hydroxyl group, and E2 elimination from the dibromoalkene. Its coupling partner 221 was easily obtained from available ethyl pyrrole-2-carboxylate.<sup>87</sup> Ullmann coupling between 220 and 221 was achieved using a CuI-zeolite catalyst to give the aryl ynamine 222. Two-step spiroketalisation was achieved using three further zeolite-based catalysts to give 224; a further three steps yielded (+)-acortatarin A 205. Another asymmetric synthesis of acortatarin A has been reported by Brimble *et al.*<sup>88</sup> in 2014.

**2.4.4 Mycenarubin A.** The first total synthesis of (+)-mycenarubin A 226 (Scheme 31), isolated from *Mycena rosea*,<sup>89</sup> was reported by Spiteller *et al.* in 2018 (Scheme 31).<sup>54</sup> Their strategy commenced with the synthesis of bromomethyl indole 228 from known compound 227 in three steps. 228 was combined with *N*-(diphenylmethylene)glycine ethyl ester 229 in the presence of Corey's cinchona catalyst 230 (1.4 mol%) and CsOH·H<sub>2</sub>O to afford product 231 in high yield and enantioselective excess. Treatment of 231 with HCl, followed by reductive amination of the resultant aldehyde with amine 232 afforded the amine 233. Hydrogenolysis of the benzyl groups, followed by oxidation to the pyrroloquinoline 234 using MnO<sub>2</sub> allowed access to (+)-mycenarubin A 226 in two further steps.

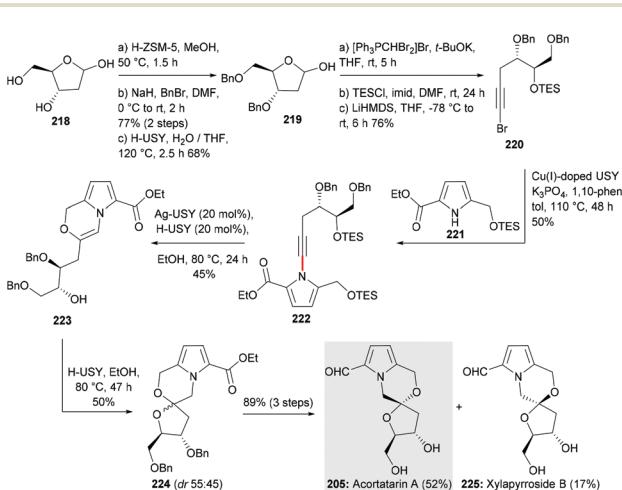
**2.4.5 Curvularamine.** Tan *et al.*<sup>90</sup> isolated the bispyrrole alkaloid curvularamine 236 (Scheme 32) from *Curvularia* sp. IFB Z10 in 2014. Marimone *et al.*<sup>91</sup> reported the first enantioselective synthesis of (–)-curvularamine and related alkaloids, which was completed in just ten steps. The synthesis commenced with



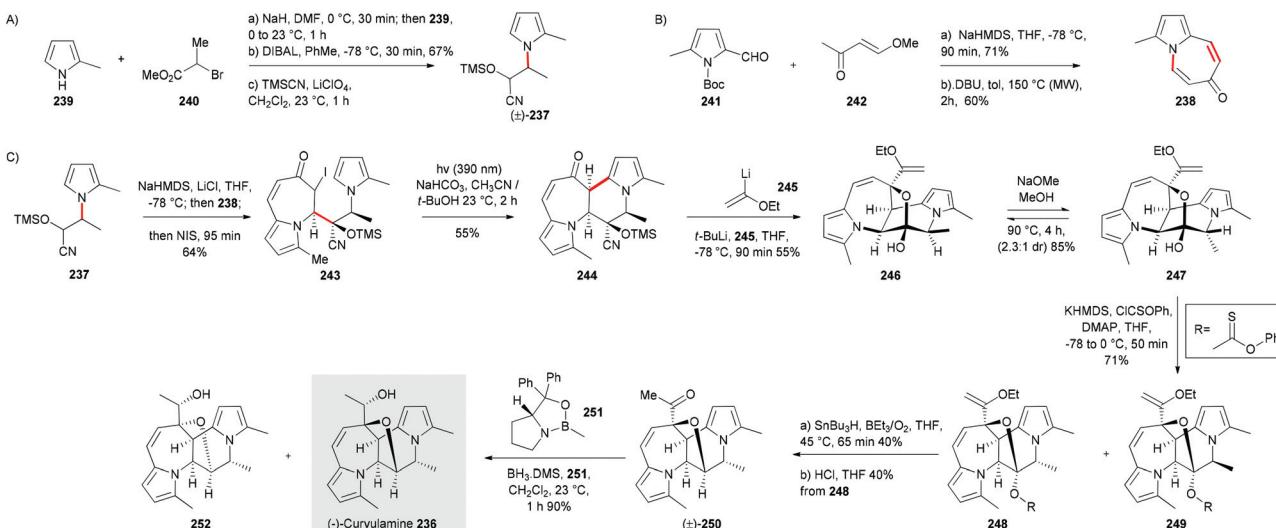
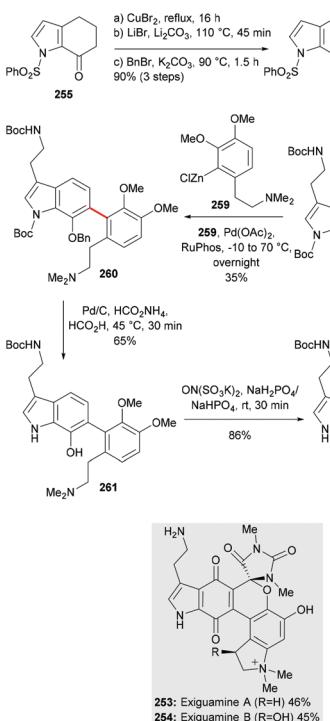
Scheme 31 Synthesis of (+)-mycenarubin A 226 (Spiteller *et al.*, 2018).<sup>54</sup>

the preparation of racemic cyanohydrin 237 and pyrrole 238. The former was assembled by S<sub>N</sub>2 reaction of the sodium salt of 2-methyl pyrrole 239 with methyl 2-bromopropanoate 240, followed by methyl ester reduction to yield an intermediate aldehyde, which was then transformed to cyanohydrin (±)-237. Aldol condensation of Boc-protected pyrrole 241 and (E)-4-methoxybut-3-en-2-one 242 afforded a dienone, which under microwave irradiation with 1,8-diazabicyclo[5.4.0]undec-7-ene cyclized to 238 in 60% yield. With these partners in hand, cyanohydrin 237 was treated with NaHMDS/LiCl followed by addition to heterocycle 238 to form a key congested C–C bond. The intermediate enolate was quenched with NIS to generate iodide 243. Irradiation of iodide 243 in *t*-BuOH triggered radical cyclization onto the pyrrole, affording product 244. This was treated with excess lithiated ethyl vinyl ether 245 in THF to afford hemiketal 246. Epimerization of this lactol was required to transform the methyl-bearing stereocentre into the desired configuration. As such, 246 was heated with NaOMe in methanol to form targeted epimer 247 in high yield. 247 was deprotonated with KHMDS, then reacted with ClCSOPh to afford the mixture of thiocarbamate epimers 248 and 249. Radical deoxygenation of 248, followed by hydrolysis of the enol ether afforded racemic methylketone 250. Treatment of 250 with (*R*)-2-methyl-CBS-oxazaborolidine 251 and BH<sub>3</sub>·DMS afforded the natural product (–)-236 and the epimer of its enantiomer, (+)-252.

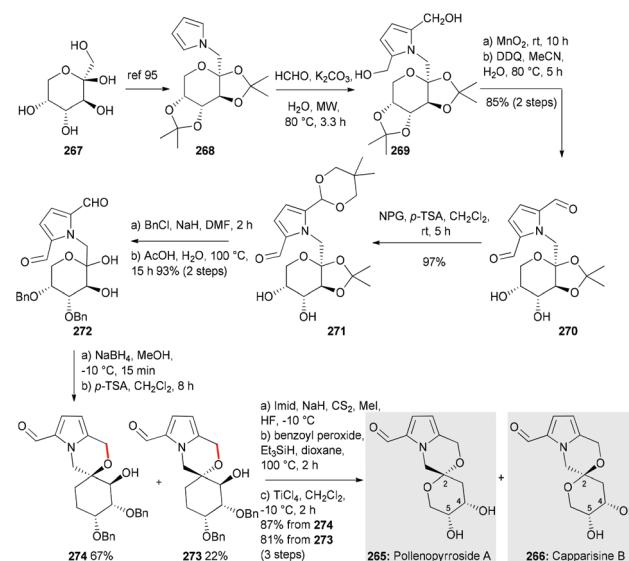
**2.4.6 Exiguamines A and B.** Exiguamine A 253 and B 254 (Scheme 33) were isolated from *Neopetrosia exigua*. Trauner *et al.*<sup>92</sup> reported the total syntheses of exiguamine A 253 and exiguamine B 254. Their strategy began with fused pyrrole cyclohexanone 255, which was doubly brominated adjacent to the ketone, aromatized *via* elimination of HBr, and finally pro-



Scheme 30 Zeolite catalyzed synthesis of (+)-acortatarin A 205 (Pale *et al.*, 2017).<sup>86</sup>

Scheme 32 Enantioselective synthesis of (*-*)-curvulamine 236 (Marimone *et al.*, 2020).<sup>91</sup>Scheme 33 Syntheses of exiguanines A 253 and B 254 (Trauner *et al.*, 2012).<sup>92</sup>

tected as its benzyl ether 256. Desulfonylation, formylation, and Henry reaction with nitromethane gave 257, treatment of which with borane in THF resulted in the reduction of the nitrovinyl moiety. After Boc protection, 258 underwent Negishi coupling with aryl zinc 259 to give biaryl 260, which was then deprotected to afford 7-hydroxyindole 261. Oxidation of 261 proceeded smoothly to yield indole *p*-quinone 262. This intermediate was treated with an excess of *N,N*-dimethylhydantoin 263, followed by BBr<sub>3</sub>, to afford 264. Reaction of this catechol

Scheme 34 Syntheses of (+)-pollenopyrroside A 265 and (+)-capparisine B 266 (Zhao *et al.*, 2015).<sup>94</sup>

with silver(II) oxide effected double cyclization to give exiguanine A 253 in moderate yield. In an attempt to improve the yield of 253, 264 was treated with a 20-fold excess of silver(II) oxide, which afforded exiguanine B 254 *via* further benzylic oxidation.

**2.4.7 Pollenopyrroside A and capparisine B.** The pyrrole spiroketal alkaloids (PSAs) capparisins A and B were isolated from powdered fruits of *Capparis spinosa*,<sup>93</sup> and pollenopyrroside A and B were collected from *Brassica campestris* pollen. The PSAs feature a pyrrole ring fused to a spiroketal. Pollenopyrroside A 265 and capparisine B 266 are closely related, being epimeric at the spiroketal carbon atom. Zhao *et al.*<sup>94</sup> also reported total syntheses of (+)-pollenopyrroside A 265 and (+)-capparisine B 266 (Scheme 34). The synthesis

began with the known preparation of pyrrole **268**<sup>95</sup> from D-fructose **267**. **268** was transformed into bis-hydroxymethyl pyrrole **269** under microwave irradiation with formaldehyde. **269** was oxidized using MnO<sub>2</sub>, followed by a series of protecting group manipulations to provide **272**. Reduction of one of the formyl groups in **272** with sodium borohydride, followed by PTSA-promoted spiroketalization, afforded compounds **273** and **274**. These underwent deoxygenation and two step debenzylation to deliver **265** and **266** respectively.

### 3. Total syntheses of natural products entailing *en route* construction of the pyrrole motif

This section of the review discusses synthetic strategies wherein the pyrrole motif is constructed as a key part of the synthesis. As before, the syntheses of natural products containing a simple pyrrolic moiety are discussed first, followed by syntheses of natural products incorporating a fused pyrrolic moiety. Within each category, the syntheses of achiral and racemic natural products are presented initially, followed by asymmetric syntheses of natural products.

#### 3.1. En route generation of a pyrrole in syntheses of natural products containing a simple pyrrole motif

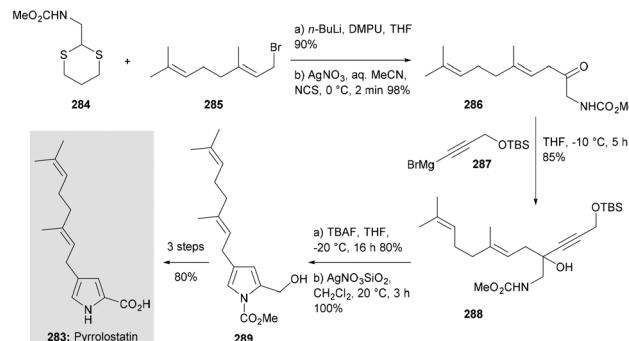
**3.1.1 Magnolamide and lobechine.** Magnolamide **275** and lobechine **276** (Scheme 35) were isolated from *Magnolia coco* and *Lobelia chinensis* respectively. Brimble *et al.*<sup>96</sup> disclosed the first synthetic approach to lobechine **276**, and a route to magnolamide **275**, which employed Maillard condensations to form the pyrrole rings of the natural products. The route to magnolamide **275** commenced with a condensation reaction between amine **277** and dihydropyranone **278**, prepared from furfuryl alcohol in four steps. The resulting amine salt **279** underwent coupling with succinimidyl ester **280** (which was prepared from ferulic acid) to afford magnolamide **275**. The synthesis of lobechine **276** followed an equivalent path, using aminoester **281** as the initial coupling partner. In this case,

the TBS-protected product **282** was desilylated using TFA, followed by saponification to afford lobechine **276**.

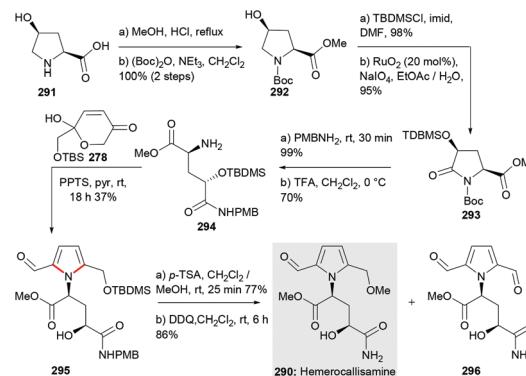
**3.1.2 Pyrrolostatin.** Pyrrolostatin **283** (Scheme 36) is another member of the relatively rare mono-pyrrole natural product class. Knight *et al.*<sup>97</sup> developed a novel approach to pyrrolostatin which improved on previous methods. Their route features construction of the pyrrole ring in the final step of the synthesis by a Ag(I)-catalyzed 5-*endo*-dig-cyclisation. The strategy commenced with double deprotection of dithiane-carbamate **284** using *n*-BuLi/DMPU, followed by alkylation with bromide **285**. Ketone **286** was then revealed using *N*-chlorosuccinimide/silver nitrate. Nucleophilic addition of O-TBS-propargyl alcohol **287** to **286** produced propargylic alcohol **288** in good yield. **288** was found to be inert to silver nitrate on silica gel, potentially due to steric crowding. However, after deprotection (TBAF), a quantitative cyclization reaction was observed to afford **289**. This was converted into pyrrolostatin **283** in three further steps with 80% yield.

#### 3.2. En route generation of a pyrrole in asymmetric syntheses of natural products containing a simple pyrrole motif

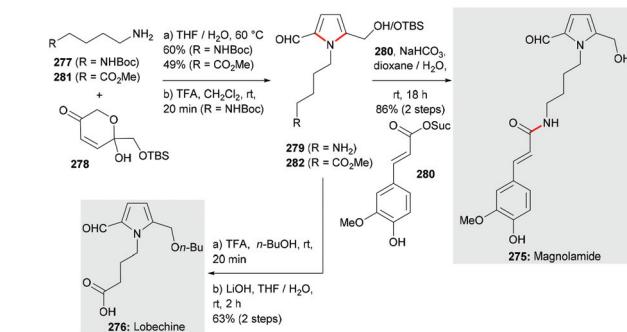
**3.2.1 Hemerocallisamine.** Hemerocallisamine **290** (Scheme 37) contains a 2-formylpyrrole and 4-hydroxyglutamine side chain. Brimble and coworkers<sup>98</sup> applied the Maillard condensation used in earlier work as described above



Scheme 36 Synthesis of pyrrolostatin **283** (Knight *et al.*, 2016).<sup>97</sup>



Scheme 37 Synthesis of (-)-hemerocallisamine **290** (Brimble *et al.*, 2017).<sup>98</sup>

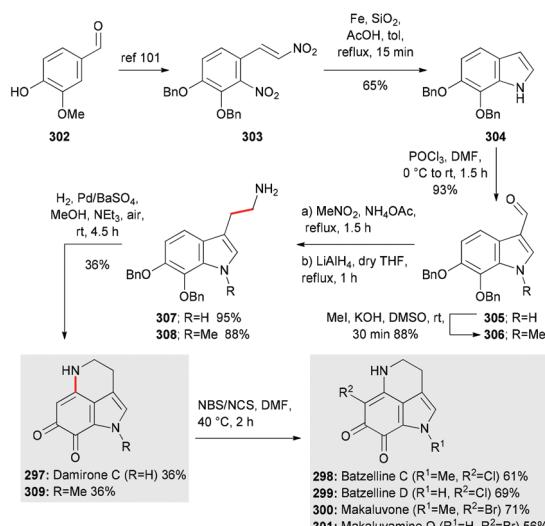


Scheme 35 Synthesis of magnolamide **275** and lobechine **276** (Brimble *et al.*, 2014).<sup>96</sup>

for the synthesis of this natural product. The synthesis commenced with construction of amine **294**<sup>99</sup> from (4*R*)-hydroxyproline **291** which was converted to pyroglutamate **293** by various functional group protections followed by oxidation with RuO<sub>2</sub> (20 mol%)/NaIO<sub>4</sub>. **293** was in turn converted to amine **294** by aminolysis with *p*-methoxybenzylamine (PMBNH<sub>2</sub>), followed by Boc-deprotection of the  $\alpha$ -amino group using TFA. Maillard condensation between **294** and **278** yielded 2-formylpyrrole **295**, which was treated with PTSA followed by DDQ to give (−)-hemerocallisamine **290**.

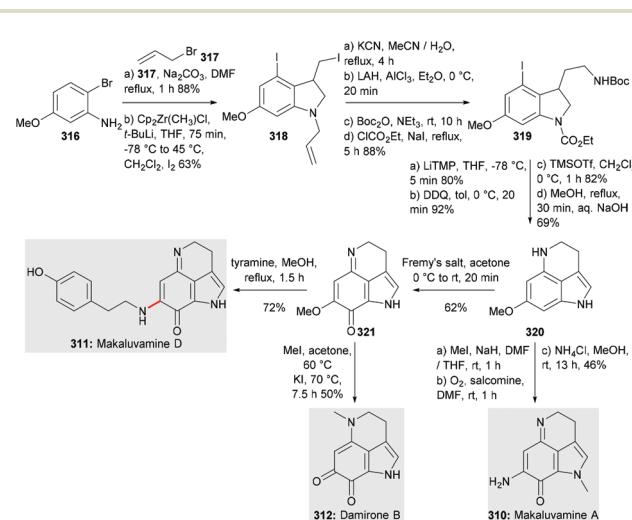
### 3.3. En route generation of a pyrrole in syntheses of natural products containing a fused pyrrole motif

**3.3.1 Makaluvamine O, batzelline, damirone C and makaluvone.** The pyrroloquinone alkaloids makaluvamine O, isobatzellines, and damirones, which are isolated from various marine organisms, are of considerable biological interest. Spitteler *et al.*<sup>100</sup> reported total syntheses of damirone C **297**, batzelline C **298**, batzelline D **299**, makaluvone **300**, and makaluvamine O **301** (Scheme 38). The protected indole **304** was synthesised from vanillin **302** in seven steps,<sup>101</sup> the last of which involved a reductive cyclisation of the dinitro compound **303** using Fe powder/silica gel in AcOH/H<sub>2</sub>O to form the pyrrole ring. Vilsmeier formylation of indole **304** afforded aldehyde **305** which, with or without methylation (**306**), underwent Henry reaction followed by reduction of the nitroalkene to afford tryptamines **307** and **308**. Hydrogenolysis of the benzyl groups using Pd/BaSO<sub>4</sub> followed by aerobic oxidation to the *ortho*-quinone triggered an intramolecular aza-Michael addition. Reoxidation with oxygen afforded damirone C **297** and its *N*-methyl derivative **309**. Selective halogenation was carried out by adding one equivalent of NCS or NBS to compounds **309** and **297** to obtain the four natural products **298–301**.

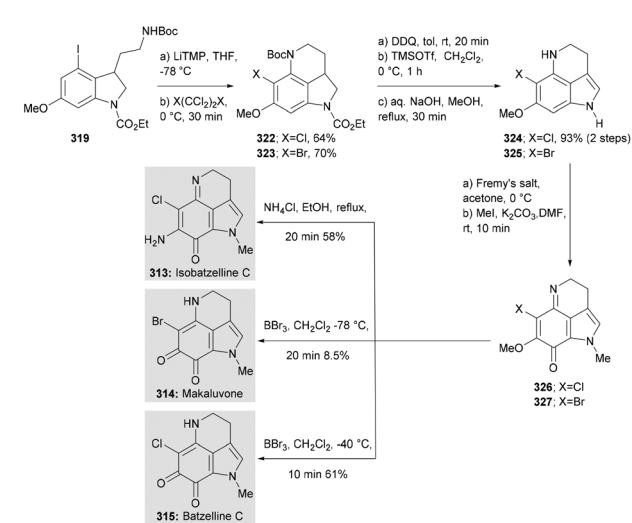


**Scheme 38** Syntheses of damirone C **297**, batzelline C **298**, batzelline D **299**, makaluvone **300** and makaluvamine O **301** (Spitteler *et al.*, 2017).<sup>100</sup>

**3.3.2 Makaluvamine A and D, damirone B, batzelline C, makaluvone and isobatzelline C.** Tokuyama *et al.*<sup>102</sup> also described the total syntheses of a series of these pyrroloquinoline natural products, namely makaluvamines A **310**, makaluvamine D **311**, damirone B **312**, isobatzelline C **313**, makaluvone **314** and batzelline C **315** (Schemes 39 and 40). The syntheses of **310–312** commenced with bromoaniline **316**, which after double allylation underwented zirconium-mediated cyclization/iodination to indoline **318**, with concurrent metalation/iodination of the arene. Chain extension of the iodomethyl group to dihydrotryptamine **319** was followed by construction of the tricyclic pyrrolo[4,3,2-*d*]quinoline skeleton *via* cyclization of the carbamate nitrogen atom onto a benzyne intermediate. This underwent aromatization and deprotection of the Boc and ethoxycarbonyl groups to give tricyclic product



**Scheme 39** Syntheses of makaluvamine A **310**, makaluvamine D **311** and damirone B **312** (Tokuyama *et al.*, 2012).<sup>102</sup>



**Scheme 40** Syntheses of isobatzelline C **313**, makaluvone **314** and batzelline C **315** (Tokuyama *et al.*, 2012).<sup>102</sup>

**320.** To access makaluvamine A **310**, indole **320** was subjected to selective methylation on the indole nitrogen, followed by treatment with salcomine, to afford an intermediate pyrrolo-iminoquinone. Treatment of this product with methanolic NH<sub>4</sub>Cl gave makaluvamine A **310**. Makaluvamine D **311** was synthesized through oxidation of **320** using Fremy's salt, then substitution of the methyl ether in product **321** by tyramine to give makaluvamine D. Alternatively, treatment of **321** with MeI and KI achieved selective methylation on the imine nitrogen atom; subsequent cleavage of the methyl ether afforded damirone B **312**.

Compound **319** could also undergo cyclization/halogenation (Scheme 40) using LiTMP at -78 °C, followed by chlorination/bromination using Cl(CCl<sub>2</sub>)<sub>2</sub>Cl or Br(CCl<sub>2</sub>)<sub>2</sub>Br. The halogenated compounds **322** and **323** were then transformed to the unprotected dihydropyrroloquinoline **324** and **325** in three steps. As before, oxidation with Fremy's salt, followed by pyrrole N-methylation afforded **326** and **327**. Reaction of iminoquinone **326** with NH<sub>4</sub>Cl/EtOH gave isobatzelline C **313**, while cleavage of the methyl ether with BBr<sub>3</sub> followed by spontaneous isomerization, led to makaluvone **314** and batzelline C **315**.

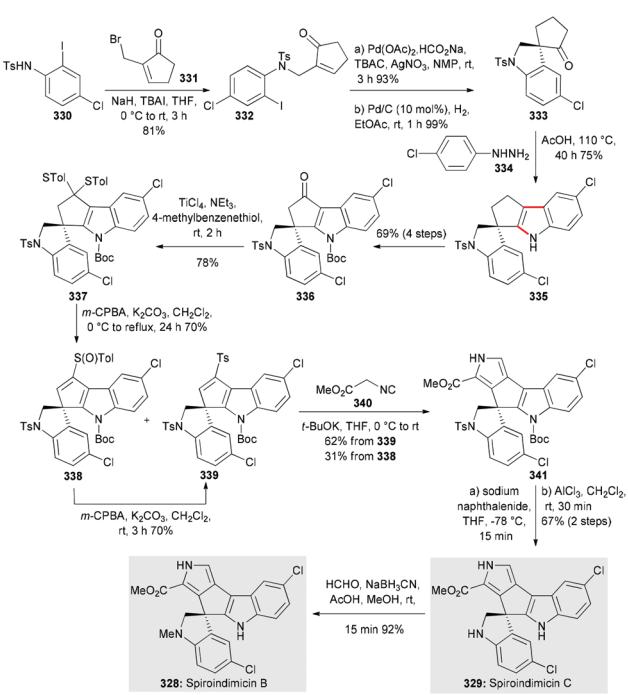
**3.3.3 Spiroindimicins B and C.** The natural products spiroindimicins A–D were isolated from marine actinomycete *Streptomyces* sp. SC5IO03032.<sup>103</sup> Spiroindimicins B–D exhibit moderate cytotoxicity against various cancer cell lines, while spiroindimicin A does not show any activity. Sperry *et al.*<sup>104</sup> reported the first total syntheses of (±)-spiroindimicins B **328** and C **329** in 2016 (Scheme 41). Beginning with iodoaniline **330**, alkylation with bromide **331** gave **332**, which underwent

spirocyclization *via* a Heck reaction, followed by alkene hydrogenation to give intermediate **333**. A Fischer indole synthesis between **333** and 4-chlorophenylhydrazine **334** afforded **335** in good yield. After conversion to ketone **336**, treatment with excess TiCl<sub>4</sub>, Et<sub>3</sub>N, and 4-methylbenzenethiol afforded dithioacetal **337**. This underwent double oxidation/sulfoxide elimination to deliver a mixture of vinylsulfoxide **338** and vinylsulfone **339** (1 : 1.3). Reaction of vinylsulfone **339** with methyl isocyanoacetate **340** afforded **341**, the protecting groups in which were removed to afford spiroindimicin C **329**. Finally, reductive amination of **329** afforded *N*-methylated spiroindimicin B **328**.

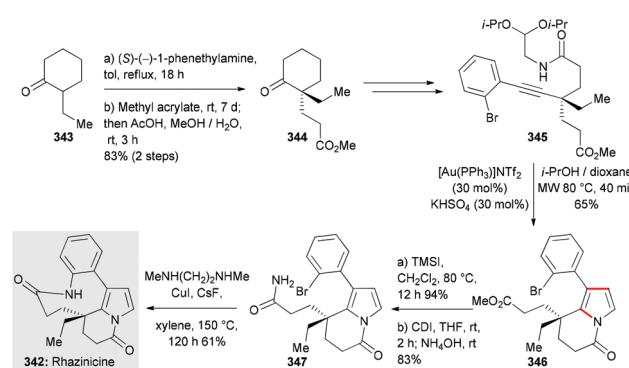
### 3.4. En route generation of a pyrrole in asymmetric syntheses of natural products containing a fused pyrrole motif

**3.4.1 Rhazinicine.** Due to its biological relevance, rhazinicine **342**<sup>105</sup> (Scheme 42) is of considerable interest, having activity as an anticancer agent. Rhazinicine **342** contains a nine-membered lactam ring fused to a quaternary carbon center and a 5,6,7,8-tetrahydroindolizine organic skeleton. Tokuyama *et al.*<sup>106</sup> described an elegant total synthesis of (−)-rhazinicine **342** in 2013. This commenced with reaction of 2-ethylcyclohexanone **343** with (S)-1-phenethylamine to give a chiral enamine intermediate, which was treated with methyl acrylate to give ketoester **344**. **344** was subjected to an Eschenmoser–Tanabe-type fragmentation to give an aldehyde/terminal acetylene intermediate. Oxidation/amide bond formation of the former, and Sonogashira coupling of the latter, afforded diisopropyl acetal **345**. This was subjected to a gold-catalyzed 5-*exo-dig* cyclization by intermittent microwave irradiation in the presence of catalytic KHSO<sub>4</sub> to yield methyl ester **346**. Treatment of this ester with TMSI, followed by activation of the resultant acid with CDI and reaction with ammonium hydroxide yielded **347**. Finally, an impressive intramolecular Ullmann macrocyclization afforded (−)-rhazinicine **342**.

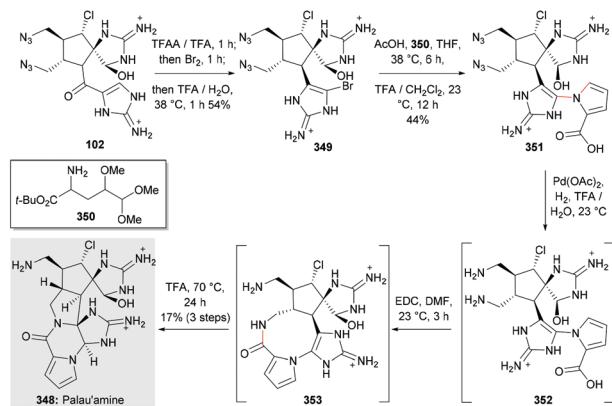
**3.4.2 Palau'amine.** In 1993, Scheuer *et al.*<sup>107</sup> isolated palau'amine from the sponge *Stylorella agminate*. Baran *et al.*<sup>51</sup> reported the first enantioselective total synthesis of palau'amine **348** in 2011 (Scheme 43). Compound **102** (see Scheme 13) was brominated by treatment with bromine and



**Scheme 41** Syntheses of (±)-spiroindimicins B **328** and C **329** (Sperry *et al.*, 2017).<sup>104</sup>



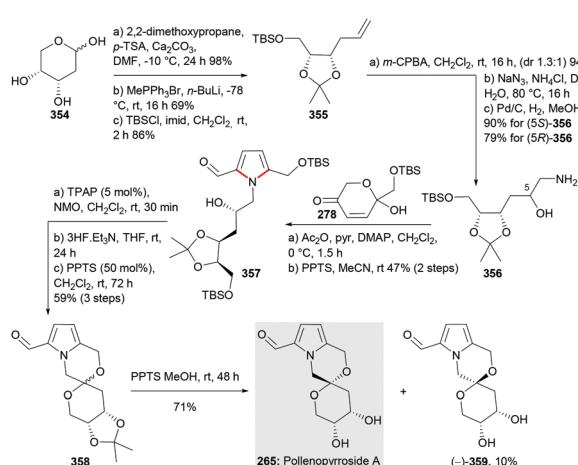
**Scheme 42** Synthesis of (−)-rhazinicine **342** (Tokuyama *et al.*, 2013).<sup>106</sup>



**Scheme 43** Enantioselective synthesis of (–)-palau'amine 348 (Baran et al., 2011).<sup>51</sup>

trifluoroacetic anhydride, affording 349 in moderate yield. The pyrrole precursor 350 was then attached to 349 under acidic conditions, affording 351 in 44% yield. The azide moieties in 351 were hydrogenated over palladium acetate, giving diamine 352, which underwent cyclization mediated by EDC·HCl. Exposure of the intermediate 9-membered lactam 353 to hot TFA afforded (–)-palau'amine 348.

**3.4.3 Pollenopyrroside A.** Brimble *et al.*<sup>108</sup> reported another application of the Maillard condensation described above in a convergent synthesis of (+)-pollenopyrroside A 265 (Scheme 44) in 2016. In this case, it involved a reaction between primary amine 356 and dihydropyranone 278, the former being prepared in a number of steps from deoxy-D-ribose 354. In the event, it was found that condensation of 356 with 278 was sensitive to temperature and pH. Reaction selectivity was improved by initial transformation of dihydropyranone 278 into its acetate derivative, followed by reaction with PPTS, which afforded 2-formylpyrrole 357 in good yield. Ley–Griffith oxidation of the secondary alcohol, TBS removal, and treatment with catalytic PPTS promoted cyclization to spiroketals

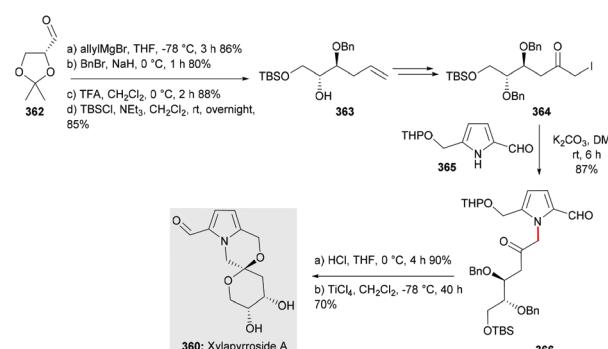


**Scheme 44** Synthesis of (+)-pollenopyrroside A 265 (Brimble et al., 2016).<sup>108</sup>

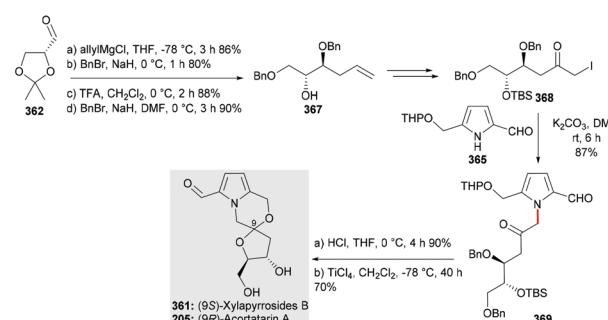
358 as a 1.5 : 1 mixture of diastereomers. Acetonide removal using PPTS in methanol afforded a 7 : 1 ratio of (+) pollenopyrroside A 265 and (–) 9-*epi*-pollenopyrroside A 359.

**3.4.4 Xylapyrroside A and B.** In 2015 Hu *et al.*<sup>109</sup> isolated the pyrrole alkaloids xylapyrroside A (360, Scheme 45) and B (361, Scheme 46), along with two previously known PSAs (pollenopyrroside A and acortatarin A) from *Xylaria nigripes*. They also reported total syntheses of (–)-xylapyrroside A 360, (–)-xylapyrroside B 361, and (+)-acortatarin A 205, all of which showed moderate antioxidant activity. These syntheses began with treatment of commercially available (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 362 with allylmagnesium bromide, followed by protecting group adjustment to give alkene 363. Epoxidation of the terminal olefin in 363, followed by epoxide ring opening with cerium chloride heptahydrate and sodium iodide, then oxidation of the hydroxyl group delivered ketone 364. This α-iodo ketone 364 was used to alkylate pyrrole 365, giving 366 in 87% yield. This compound underwent intramolecular spiroketalization under acidic conditions to afford a pair of C-9 epimers, which enabled the synthesis of (–)-xylapyrroside A 360 in 70% yield on treatment with TiCl<sub>4</sub>.

(–)-Xylapyrroside B 361 and (+)-acortatarin A 205 were accessed using a very similar route (Scheme 46), which differs only in the arrangement of benzyl and TBS protecting groups. Specifically, ketone 368<sup>109</sup> was prepared using equivalent chemistry and was converted to 369 *via* pyrrole alkylation.



**Scheme 45** Stereoselective synthesis of (–)-xylapyrroside A 360 (Hu et al., 2015).<sup>109</sup>

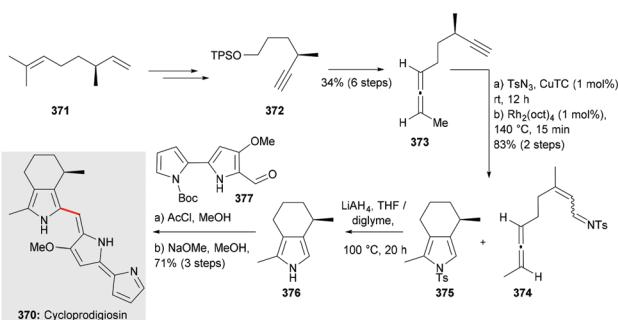


**Scheme 46** Stereoselective syntheses of (–)-xylapyrroside B 361 and (+)-acortatarin A 205 (Hu et al., 2015).<sup>109</sup>

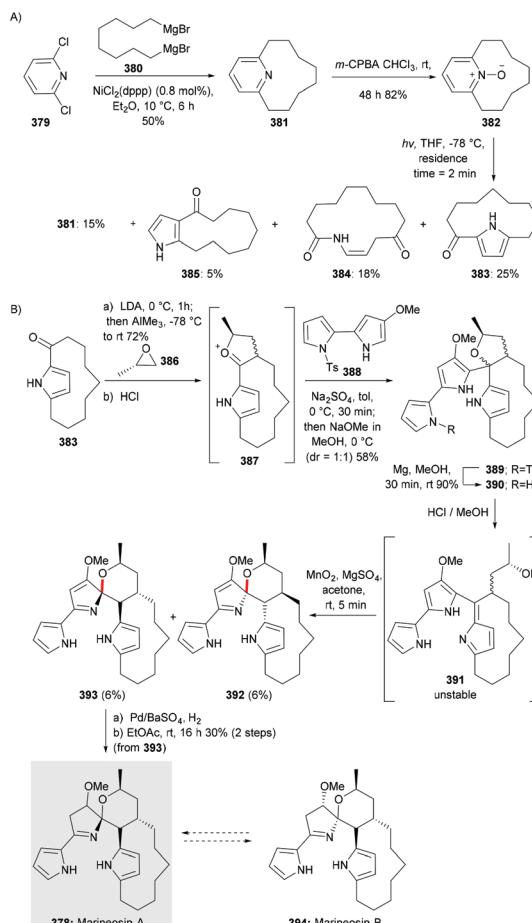
However, in this case the 5,6-PSA natural products resulted *via* desilylation, then debenzylation.

**3.4.5 Cycloprodigiosin.** The natural product cycloprodigiosin **370** (Scheme 47) is produced by various bacteria including *Pseudoalteromonas denitrificans*, *Pseudoalteromonas (Alteromonas) rubra* and *Vibrio gazogenes*,<sup>110</sup> with its structure first identified in 1983.<sup>111,112</sup> This natural product has emerged as a potent anticancer and immunosuppressant agent.<sup>113</sup> Over the past decades, only Fukuyama<sup>114</sup> had reported a synthesis of cycloprodigiosin **370** (in 1984) until the first enantioselective synthesis of (*R*)-cycloprodigiosin **370** was described by Sarpong *et al.*<sup>115</sup> Their synthetic strategy commenced with enantioenriched allenyl alkyne **373**, which was prepared in six steps from known alkyne **372**.<sup>116</sup> **373** was converted into a 1:1 mixture of imines **374** and the desired pyrrole **375**, *via* treatment with copper(II) thiophene carboxylate and tosyl azide followed by Rh<sub>2</sub>(oct)<sub>4</sub> in chloroform. The tosyl group in **375** was removed using lithium aluminium hydride to afford **376**. Under Lindsley conditions, condensation of **376** with **377** afforded cycloprodigiosin **370** in good yield.

**3.4.6 Marineosin A.** Marineosins A **378** and B **394** were isolated from a *Streptomyces*-related actinomycete in 2008.<sup>117</sup> Marineosins A and B consist of two pyrrole moieties, a macrocyclic ring, and a spiro tetrahydropyran-dihydropyrrole iminal. Xu *et al.*<sup>118</sup> reported the first total synthesis of marineosin A **378**; their synthetic approach was completed from the readily available (*S*)-6-methyl-5,6-dihydro-2-pyrone, but with low overall yield (1.2%). Harran *et al.*<sup>119</sup> recently reported an asymmetric synthesis of marineosin A **378** and also reassigned its stereochemistry (Scheme 48). The route employed a photochemical rearrangement of pyridine *N*-oxide **382** (prepared in two steps by the Ni-catalyzed cross-coupling of 2,6-dichloropyridine with a bis-Grignard) to construct cyclophane pyrrole **383**. After enolate alkylation with epoxide **386**, the resultant putative oxocarbenium ion intermediate underwent addition of bipyrrrole **388**<sup>120</sup> to build the C-9 linked ansa-bridge **389**. Cleavage of the sulfonamide group (Mg/MeOH) gave **390**, which under acidic conditions rearranged to **391**. This unstable intermediate was converted to spiroiminals **392** and **393** in very low yield on oxidation with MnO<sub>2</sub>. Hydrogenation using Pd/BaSO<sub>4</sub> afforded (+)-marineosin A **378**.



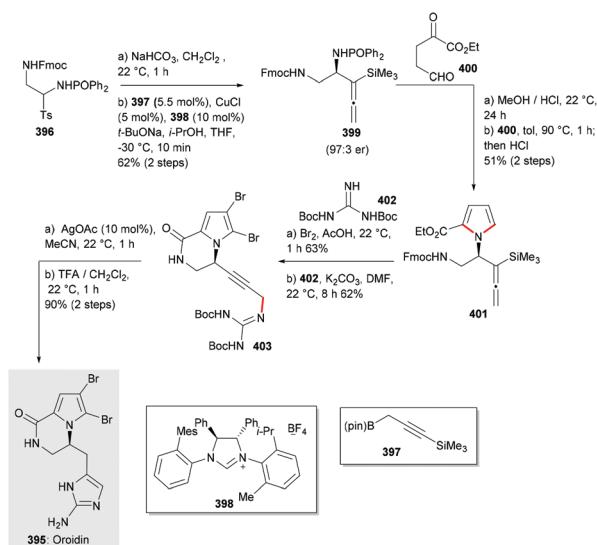
**Scheme 47** Enantioselective synthesis of (*R*)-cycloprodigiosin **370** (Sarpong *et al.*, 2013)<sup>115</sup>



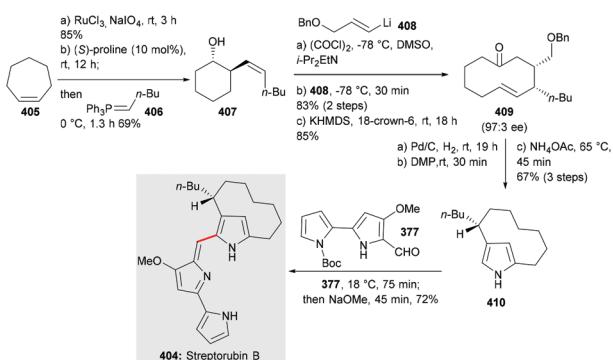
**Scheme 48** Asymmetric synthesis of (+)-marineosin A **378** (Harran *et al.*, 2019).<sup>119</sup>

**3.4.7 Cyclooroidin.** Hoveyda *et al.*<sup>121</sup> reported an enantioselective synthesis of (–)-cyclooroidin **395** (Scheme 49) in 2014. Treatment of **396** with NaHCO<sub>3</sub> in dichloromethane generated the phosphinoylimine, direct subjectation of which to enantioselective allenylation with propargyl boronic ester **397** (catalyzed by a copper complex with ligand **398**) gave homoallenylamide **399** in 62% yield. The phosphinoyl group present in **399** was selectively removed on treatment with aqueous HCl, and the resulting enantioenriched amine was converted to pyrrole **401** by reaction with ketoaldehyde **400**.<sup>122</sup> Next, the silyl-substituted allene **401** was transformed into dibromopyrrole **403** by brominative desilylation of the allenylsilane to a propargyl bromide (and concurrent pyrrole bromination), followed by treatment with bis-Boc-guanidine **402**. The dibromide **403** was subjected to an intramolecular silver catalyzed hydroamination, and Boc removal afforded the target molecule **395** in high yield. This synthetic strategy compared favourably with earlier reported enantioselective syntheses.<sup>123,124</sup>

**3.4.8 Streptorubin B.** Streptorubin B **404** (Scheme 50) features a highly strained pyrrolephane core that is formed by oxidative ring closure from undecylprodigiosin. Weyland *et al.*<sup>125</sup> found that streptorubin B exists as two atropdiastereomers,



**Scheme 49** Enantioselective synthesis of (*-*)-cyclooroidin **395** (Hoveyda *et al.*, 2014).<sup>121</sup>



**Scheme 50** Enantioselective synthesis of (*R*)-streptorubin B **404** (Thomson *et al.*, 2011).<sup>126</sup>

related by the relative stereochemistry of the bis-pyrrole side arm and butyl side chain. Thomson *et al.*<sup>126</sup> described an enantioselective total synthesis of (*R*)-streptorubin B **404** from commercially available cycloheptene **405**. This was treated with  $\text{RuCl}_3$  and  $\text{NaIO}_4$  to give a dialdehyde, which upon aldol cyclization promoted by 10 mol% (*S*)-proline, and reaction with ylide **406**, produced homoallylic alcohol **407**. Oxidation of **407**, followed by addition of vinyl anion **408** and exposure of the resulting alcohol to KHMDS and 18-crown-6 produced 10-membered ring **409** via a Cope rearrangement ring expansion. This intermediate then underwent alkene reduction along with simultaneous cleavage of the benzyl ethers; oxidation of the intermediate diol and Paal-Knorr pyrrole synthesis affording pyrrole core **410** in 67% yield. **410** underwent an acid-mediated condensation reaction with aldehyde **377**,<sup>127</sup> followed by deprotection of the Boc group to obtain a 10 : 1 mixture of two compounds. The major product did not match the spectroscopic data of the natural product, but after

10 days the mixture had entirely transformed to **404**, as revealed by the reexamination of the NMR sample.

## 4 Conclusions

The discovery of natural products with useful biological activities has an important role in the future of human health. Pyrrole containing natural products have established medicinal importance, and hence provide the chemist with an array of fascinating targets. In past years, significant advances have been made in the development of effective methods for the syntheses of pyrrole containing natural products, and various new natural products incorporating pyrrole motifs have been isolated and successfully prepared using such tactics. In this review, we have described synthetic methodologies for the construction of achiral and chiral pyrrole-containing natural products. Some of the more innovative strategies employed include *C*2-symmetric bisthiourea catalysis, arene-ynamide cyclization, intramolecular Friedel-Crafts type cyclizations, oxidative cyclizations, gold catalysed annulation reactions, benzyne-mediated cyclizations and so on, which enable synthesis of the target molecule in fewer steps. For further details on strategy, Table S1 (see the ESI†) summarises the various key transformations which have been used in this review for the total syntheses of pyrrole containing natural products. As ever, challenges nonetheless remain which we hope will inspire the synthetic community to seek ever more efficient approaches to these useful molecules.

## Conflicts of interest

The authors declare no conflict of interest.

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