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

Nidhi Singh⁴, Snigdha Singh⁵, Sahil Kohli⁶, Aarushi Singh⁵, Hannah Asiki⁶, Garima Rathee⁵, Ramesh Chandra⁴,⁵* and Edward A. Anderson⁶*

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 pyroles both in the context of their innate reactivity, and their preparation in complex settings.

1. Introduction
2. Total syntheses of natural products utilizing premade pyrrole motifs
   2.1. Premade pyrrole motifs in syntheses of natural products containing a simple pyrrolic moiety
      2.1.1. Breitfussins A and B
      2.1.2. Tambjamine K
      2.1.3. Zyzyyanones A-D
      2.1.4. Marinopyrroles A and B
   2.2. Premade pyrrole motifs in asymmetric syntheses of natural products containing a simple pyrrolic moiety
      2.2.1. Heronapyrroles A, C and D
      2.2.2. Roseophilin
      2.2.3. Nitropyrrrolin A
      2.2.4. Mukanadin F
      2.2.5. Axinellamines A and B, and massadine
   2.3. Premade pyrrole motifs in syntheses of natural products containing a fused pyrrolic moiety
      2.3.1. Sanguinolentaquinone and mycenaflavin B
      2.3.2. Thiaplakortone A
      2.3.3. Aplidipiosamine A
      2.3.4. Lukianols A and B
      2.3.5. Dictyodendrin A and B
      2.3.6. Chlorizidine A dimethyl ether
      2.3.7. 2-Debromohymenin
   2.4. Premade pyrrole motif in asymmetric syntheses of natural products containing a fused pyrrolic moiety
      2.4.1. Cylindradines A and B
      2.4.2. Rhazinal and kopsiyunnanines C1-3
      2.4.3. Acortatarins A and B
      2.4.4. Mycenarubin A
      2.4.5. Curvulamine
      2.4.6. Exiguamines A and B
      2.4.7. Pollenopyrroside A and capparisine B
3. Total Syntheses of natural products entailing en route construction of the pyrrole motif
3.1. **En route generation of a pyrrole in syntheses of natural products containing a simple pyrrole motif**

3.1.1. Magnolamide and lobecine

3.1.2. Pyrrolostatin

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

3.2.1. Hemerocallismamine

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

3.3.2. Makaluvamine A and D, damirone B, batzelline C, makaluvone and isobatzelline C

3.3.3. Spiroindimicins B and C

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

3.4.1. Rhzacinine

3.4.2. Palau’amine

3.4.3. Polleenopyroside A

3.4.4. Xylapyroside A and B

3.4.5. Cycloprodigiosin

3.4.6. Marineosin A

3.4.7. Cycloooroidin

3.4.8. Streptorubin B

4. **Conclusions**

5. **Conflicts of Interest**

6. **Acknowledgements**

7. **Notes and References**

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, and first identified in 1834 by F.F. Runge as a constituent of coal tar. 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. Pyroles 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, antimarial and antipsychotic properties, among others. Prime examples include the multi-billion dollar drugs atorvastatin, zomipirac, and tolmetin. 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, isolated from marine invertebrates, which have been found to possess anti-HIV and antitumor activities, and halitulin, 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. The marinoypyroles 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 antimarial bioactivities. 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. The last review on the synthesis of pyrrole containing natural products was reported in 2010. 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, 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/facemic 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 Brietfussins A and B

The halogenated natural products brietfussin A and B were isolated from Arctic hydrozoan Thuiaria breitfussi. In 2015, Bayer et al. 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 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; metatation of this position and iodination resulted in the intermediate diiodooxazole 8. 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 brietfussin A 1. Alternatively, bromination at the C2 position of the pyrrole in compound 10 afforded product 11, which provided brietfussin B 2 in two further steps.

Sperry et al. developed an iridium-catalyzed iododeborylation process to install the C4 methoxy substituent in a formal synthesis of brietfussin B 2 (Scheme 2). Hydrolysis of the resulting protected tetrabromoprimidine 12, followed by amide coupling with 2-(chloroacetyl)pyrrole 13, provided amide intermediates 14, which intract with a previous synthesis of brietfussin B 2 by Khan and Chen. In Chen’s work, this was converted to 15 in two steps using DDQ and IBX, which underwent Robinson-Gabriel cyclisation ion treatment with POCl3 to obtain 16. This compound could be converted to the natural product via bromination. Sperry et al. synthesized the intermediate 14 in fewer steps compared to the synthesis of Chen and coworkers.

2.1.2 Tambjamine K

Tambjamines A-J are members of a 2,2-bipyrrole family of alkaloids which differ in their aliphatic termini. The tambjamines show a broad range of bioactivities including anticancer, antimicrobial, and immunosuppressive properties. Tambjamine K 17 (Scheme 3), isolated from the Azorean nudibranch Tambja Ceutae and the subject of this section, showed antiproliferative activity and cytotoxicity against various cancer and noncancer cell lines. Lindsley et al. disclosed the first total synthesis of tambjamine K, starting from bromoenamine 18. This underwent Suzuki coupling with Boc-1H-pyrrrol-2-yl boronic acid 9 to deliver the Boc-protected product 19. Acid-catalyzed condensation between 19 and isopentylamine provided tambjamine K 17 in good yield.

2.1.3 Zyzzyanonones A-D

Zyzyanonones A-D (20-23, Scheme 4) are tetracyclic bis-pyrroloquinone alkaloids isolated from Zyzya fuliginosa, which contain a 2,2-bipyrrole motif. The first total syntheses of which were reported by Velu et al. in 2013 (Scheme 4). The zyzyanon framework was prepared from pyroloquinone 24, which first underwent Mn(OAc)3-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 zyzyanonone A 20 as its TFA salt. Alternatively, removal of the N-benzyl, N-tosyl, N-Boc and O-benzyl protecting groups from 28 afforded zyzyanonone B 21. Selective Boc deprotection of 27 and 28, followed by N-formylation and debenzylation afforded zyzyanonones 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.\textsuperscript{30,31} 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.\textsuperscript{32-34} Gulder et al.\textsuperscript{35} reported a synthesis of marinopyrrole A \textsuperscript{33} in 2016 (Scheme 5), which began with preparation of bipyrrole \textsuperscript{36} via condensation of aminopyrrole\textsuperscript{34} with δ-ketoacetal \textsuperscript{35}. The ester groups were converted to bis-Weinreb amide \textsuperscript{37}, which was reacted with ortho-lithiated anisole \textsuperscript{38} to give diketone \textsuperscript{39} in 86% yield. Perchlorination of the pyrrole rings was accomplished using NCS with a catalytic amount of iodobenzamide \textsuperscript{40} (10 mol%), which provided O,O-dimethylmarinopyrrole \textsuperscript{41} in 84% yield. Cleavage of the O-methyl groups under Lewis acidic conditions afforded \textsuperscript{33}. Clive et al.\textsuperscript{36} described the first synthesis of marinopyrrole B (\textsuperscript{42}, Scheme 6). Their route commenced with the commercially available trichloromethylketone \textsuperscript{13}, which via a sequence of chlorination and bromination steps afforded bromodichloropyrrole \textsuperscript{43}. Reaction of \textsuperscript{43} with allylic acetate \textsuperscript{44} gave pyrrole \textsuperscript{45} in 95% yield, ozonolysis of which, followed by alkylation with allyl bromide, provided O-allyl enol ether \textsuperscript{46}. An elegant Claisen rearrangement / ozonolysis sequence gave dicarboxyl \textsuperscript{47}, which underwent Paal-Knorr pyrrole cyclization giving \textsuperscript{48} and oxidation state adjustment to give the dialdehyde \textsuperscript{49}. Double addition of O-methoxyphenylmagnesium bromide to this compound afforded diol \textsuperscript{50}, which was then converted to marinopyrrole B \textsuperscript{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.\textsuperscript{37}
Morimoto et al.\textsuperscript{38} described a total synthesis of (+)-heronapyrrole A\textsuperscript{51} in 2015 (Scheme 7). Their strategy commenced with the preparation of epoxy bromide\textsuperscript{54} from known (15S)-diallo\textsuperscript{52} through a five step sequence, including a chemo-selective bromoetherification to form the tetrahydrofuran ring as a protecting group for the central trisubstituted alkene. The bromopyrrole\textsuperscript{55} was alkylated with\textsuperscript{54} following lithiation in THF/HMPA, and upon desilylation afforded pyrrole\textsuperscript{56}. After Boc protection of the pyrrole nitrogen,\textsuperscript{39} tempora\textsuperscript{58}ry silylation of the resulting hydroxyl group enabled pyrrole nitration; finally removal of the protecting groups yielded (+)-heronapyrrole A\textsuperscript{51}.

Subsequent to this work, Brimble et al.\textsuperscript{39} reported total syntheses of (+)-heronapyrrole C\textsuperscript{60} and (−)-heronapyrrole D\textsuperscript{59} (Scheme 8). Their strategy focused on sp\textsuperscript{2}-sp\textsuperscript{3} Stille coupling to attach the pyrrole motif to the tetrahydrofuran-containing side chain, and involved an early stage nitration. Iodomethyl nitropyrrrole\textsuperscript{63} was first efficiently obtained via a formylation / reduction / iodination sequence from 2-nitropyrrrole\textsuperscript{61}. The stannane partner for the planned coupling was prepared from triene\textsuperscript{64}, which underwent a chemo-selective asymmetric dihydroxylation of the terminal trisubstituted alkene\textsuperscript{65}, followed by Shi epoxidation of the C7–C8 olefin of\textsuperscript{65} and acid-catalyzed cyclization to tetrahydrofuran\textsuperscript{66}. This was converted to stannane\textsuperscript{67} using a Hunsdieker decarboxylation to transform the carboxyl group into an alkyl iodide, and subsequent lithiation / stannylation. The key cross-coupling of alkenyl stannane\textsuperscript{67} with iodomethylpyrrrole\textsuperscript{63} afforded compound\textsuperscript{68}, deprotection of which gave (−)-heronapyrrole D\textsuperscript{59}. A further asymmetric epoxidation / CSA-catalyzed epoxide ring-opening / cyclization afforded diastereomERICALLY pure (+)-heronapyrrole C\textsuperscript{60}.

2.2.2 Roseophilin

Ansà-brided prodiginines are lipochromephores which are produced by marine and terrestrial bacteria.\textsuperscript{60,62} Roseophilin (69, Scheme 9) is a relatively new addition to this family; its structure contains two C–C o bonds connecting its hydrocarbon core to its bis-heterocyclic tail. Harran et al.\textsuperscript{43} reported an asymmetric synthesis of (+)-roseophilin\textsuperscript{69} in 2013 (Scheme 9). This began with linked pyrrole-furan\textsuperscript{70}, which was obtained by lithiation of the corresponding 3-methoxyfuran at the 2-position, followed by treatment with ZnBr\textsubscript{2} and Pd-catalyzed carboxylation. Activation of the carboxylic acid with benzotriazole\textsuperscript{71} provided an intermediate benzotriazole amide, which underwent TiCl\textsubscript{3}-mediated acylation with 2-(8-nonenyl)pyrrrole\textsuperscript{72} to give the bis-heteroarylketone\textsuperscript{73} in good yield. This pyrrrole was protected by treatment with diethyl chlorophosphite to provide the phosphoramidate\textsuperscript{74}, presumably via aerobic oxidation of the intermediate N-phosphinyl derivative. Cross metathesis of\textsuperscript{74} with ketone\textsuperscript{75} using Grubbs II catalyst (5 mol%), followed by\textsuperscript{76} in situ reduction of the resultant enone through Pd-catalyzed hydrosilylation, yielded diketone\textsuperscript{76}. The macrocycle\textsuperscript{77} was then obtained in good yield (66%) by aldol condensation on treatment of\textsuperscript{76} with KHMD\textsubscript{5}/18-crown-6. At this point, prochiral pyrrolophanes\textsuperscript{77} was subjected to hydrogenation using Rh(cod):OTf (5 mol%) / Josiphas ligand\textsuperscript{78} (5 mol%) as catalyst, to produce\textsuperscript{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-azafulvene 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 2010.44 Produced by the MAR4 strain CNQ-509,44 nitropyrrolins A, B and D showed cytotoxicity towards human colon carcinoma cells. Morimoto et al.45 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.46 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 TsNH₂, 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-Benzylxoyymethyl) group delivering (+)-nitropyrrolin A 80.

### 2.2.4 Mukanadin F

Numerous linear C9-substituted bromopyrrrole alkaloids have been isolated from sponges of the *Agelasida* and *Axinellida* genera. Barker et al.47 reported an enantioselective synthesis of (S)-mukanadin F 87 (Scheme 11), which began with alcohol (R)-88.47 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 bromopyrrrole alkaloids.48 In 1999, Quinn et al.49 reported the first members of this family, namely axinellamines A and B (92 and 93). A few years later, Fusetani et al.50 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.\textsuperscript{51} 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 polyolycyclic core, and oxidative installation of the C20 hemiaminal, 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, hypervalent iodide, potassium persulfate, potassium ferrate), with the most satisfactory results obtained by employing silver(II) picolinate \textsuperscript{96} in aqueous trifluoroacetic acid, which delivered \textsuperscript{97a} and \textsuperscript{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 diaminines in sufficient purity to undergo double acylation with (trichloroacetyl)pyrrole \textsuperscript{91}, to give (\textsuperscript{\textdagger})-axinellamine \textsuperscript{A} \textsuperscript{92} and (\textsuperscript{\textdagger})-axinellamine \textsuperscript{B} \textsuperscript{93}.

The main challenge in the approach to massadine \textsuperscript{99} (Scheme 13) is control over the C20 oxidation state of the massadine skeleton. Use of the silver(II) picolinate salt \textsuperscript{96} again provided the solution, enabling oxidation of \textsuperscript{100} to \textsuperscript{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 \textsuperscript{102} in good yield. Oxidation of \textsuperscript{102} to a transient epoxide with DMDO, followed by acid-promoted cyclization, gave the desired epimer \textsuperscript{103a} in low yield. Azide hydrogenolysis, followed by acylation of the resulting amines with pyrrole \textsuperscript{91}, provided the natural product \textsuperscript{98} and \textsuperscript{99} in a 2:1 ratio.

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

2.3.1 Sanguiolentaquinone and mycenaflavin B

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

The synthesis of \textsuperscript{105} used the same indole starting material \textsuperscript{106}, which in this case underwent C3-alkylation with Eschenmoser’s salt, and then Somei-Kametani substitution of the dimethylamino group with imine \textsuperscript{111} to give \textsuperscript{112}. Treatment with aqueous HCl liberated the amine group, and the side chain was introduced by reductive amination with aldehyde \textsuperscript{113} to afford amine \textsuperscript{114}. Hydrogenolysis of the benzyl groups, and then aerobic oxidation gave the corresponding quinone \textsuperscript{115}. Saponification of the ethyl ester group in \textsuperscript{115}, followed by
treat strategy to aplidiopsamine A for Plasmodium falciparum to achieve significant growth inhibition of drug activity. The alkaloid aplidiopsamine A was deprotected affording the HCl salt of thiaplakortone A. The aminoethanesulfinic acid was then coupled with dichloroacetone to give dihydrothiazine dioxide. Conjugate addition/oxidation sequence on reaction with 2-Fremy’s salt. The resulting quinone then underwent a double dehydrogenation followed by oxidation of the unstable intermediate phenol with NBS. This reaction was triggered by the presence of caesium carbonate to give 211. Reaction of bromide 211 with di-Boc-protected adenine 212 in the presence of caesium carbonate gave 213, which on acidic deprotection afforded aplidiopsamine A 219 in high yield.

2.3.4 Lukianols A and B

Scheuer et al. isolated lukianol A 214 (Scheme 18) and B 215 (Scheme 19) from a tunicate collected from a lagoon of the Palmya atoll. Lukianol B 215 exhibited high h-ALR2 inhibitory activity. Iwao et al. developed approaches to lukianol A 214 and lukianol B 215; the key steps in the total syntheses are pyrrole lithiation, and Pd-catalyzed cross-coupling to install the phenol side chains. Thus, lithiation of 216 at -78 °C (Scheme 17) was subjected to Suzuki coupling with p-isopropoxybenzylboronic acid, followed by removal of the sulfonyl protecting group to afford 218. Alkylation of 218 with p-methoxyphenacyl bromide afforded 219, and hydrogenolysis of the benzyl protecting group to afford 220. Finally, heating in Ac2O followed by deprotection of the aryl isopropyl and methyl ethers with BBr3 afforded lukianol A 214.

The synthesis of lukianol B 215 requires differentiation of the phenol side chains and commenced with a Pd-catalyzed coupling of 216 with p-isopropoxyphenylboronic acid. The mono coupling product 213 was treated with LDA/benzyl o-coupling, afforded lukianol A 214, and commenced with a Pd-catalyzed coupling of 216 with p-isopropoxyphenylboronic acid. The mono coupling product 213 was treated with LDA/benzyl o-coupling, afforded lukianol A 214. Finally, reaction of 216 with Zn-Cu couple, followed by demethylation with BBr3, afforded lukianol B 215.

2.3.2 Thiapkortone A

Thiaplakortone A 216 (Scheme 16) was isolated from the marine sponge Plakortis lita. Quinn et al. 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-aminoethanesulfonic acid to give dihydrothiazine dioxide 118. The dihydrothiazine ring was then oxidized, with Boc deprotection affording the HCl salt of thiapkortone A 116.

2.3.3 Aplidiopsamine A

The alkaloid aplidiopsamine A 119 (Scheme 17), obtained from the Australian ascidian, Aplidapis confluata, exhibited significant growth inhibition of drug-resistant strains of Plasmodium falciparum. Takasu et al. 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 in the presence of caesium carbonate gave 123, which on acidic deprotection afforded aplidiopsamine A 119 in high yield.

decarboxylation under acidic conditions and THP deprotection, afforded mycenaflavin B 205.

Scheme 14: Synthesis of sanguinolentaquinone 104 (Spiteller et al., 2018)

Scheme 15: Synthesis of mycenaflavin B 205 (Spiteller et al., 2018)

Scheme 16: Synthesis of thiaplakortone A 116 (Quinn et al., 2013)

Scheme 17: Synthesis of aplidiopsamine A 119 (Takasu et al., 2014)
2.3.5 Dictyodendrins A and B

Dictyodendrin A 137 (Scheme 20) exhibits anticancer activity by telomerase inhibition.62–64 Davies et al.62 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 6π-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.65 developed a route to dictyodendrin B 146 (Scheme 21) using a gold-catalyzed cascade cyclization of a conjugated diyne aryl azide with pyrrole to generate three bonds and two aromatic rings in a single step. Thus, treatment of azido diyne 147 with Boc protected pyrrole 148 led to the 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 pyrrole 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.66 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 5H-pyrrolo[2,1-a]isoindol-5-one. Mhaske et al.67 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-hydroxypthalimide to afford 159, the N–O bond in which was cleaved using Mo(CO)6 to afford alcohol 160. The ester in 160 underwent hydrolysis with LiOH, and the resultant acid was treated with Pd(OAc)2/PPh3 to effect a decarboxylative cyclization of the aryl bromide onto the pyrrole ring, followed by benzylic oxidation with MnO2 to afford...
aldehyde 161. Reaction of this aldehyde with bromoketone 162 under Reformatsky conditions led to β-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 KMnO₄ to afford methyl-protected chlorozidine A 155.

### 2.3.7 2-Debromohymenin

2-Debromohymenin 165 (Scheme 23) was isolated from Stylissa carteri (syn. Axinella carteri). Lovely et al. 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 AuCl₃ in dioxane led effect 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 H₂; subsequent lithiation with LDA and reaction with TsN₃ 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 SmI₂ 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 Mo(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, and exhibit diverse biological activities including immunosuppressive, adrenoceptor agonistic and anticancer activities. Uno et al. 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. As with other members of the family, cylindradine A 175 also features a characteristic N,N'-aminal in the cyclic guanidine moiety; the enantioselective

![Scheme 21: Synthesis of dicyodendrin B 146 (Ohno et al., 2017)](image1)

Scheme 21: Synthesis of dicyodendrin B 146 (Ohno et al., 2017)

[14]
construction of this aminal is the key challenge in the construction of the cylindradine skeleton.

The first total synthesis of (+)-cylindradine A 175 (Scheme 24) was disclosed by Nagasawa et al. 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 and acid using EDC.HCl and DMAP, which gave amine. Friedel-Crafts cyclization was achieved in good yield on treatment of with CSA to give as the major product isomer. Stereoselective azidation of with DPPA and DBU, followed by reduction under Staudinger conditions gave amine. Guanidine was then synthesised by reaction with PIDA in the presence of MgO. 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. described the first total synthesis of (+)-cylindradine B 176, based on an improved version of their synthesis of cylindradine A. The strategy involves a diastereoselective Pictet-Spengler reaction for the synthesis of amine from pyrrole, employing phosphoric acid catalyst. Amine was treated with H₂ and 10% Pd/C to deprotect the Cbz group, followed by reaction of the resultant pyrrole with to give in 75% yield. After desilylation, the S-methylisothiourea was converted into the synthesis of amine from pyrrole, employing phosphoric acid catalyst. Amine was treated with H₂ and 10% Pd/C to deprotect the Cbz group, followed by reaction of the resultant pyrrole with to give in 75% yield. After desilylation, the S-methylisothiourea was converted into the

---

This journal is © The Royal Society of Chemistry 20xx

J. Name., 2013, 00, 1-3 | 11

---
target guanidine motif by reaction with NH₃/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 rhazinilam derived alkaloids, kopsiyunnanines C1-C3, were isolated from *Yunnan Kopsia Arborea* in 2009. Kopsiyunnanines C1 and C2 (194 and 195, Scheme 26) contain ethoxymethyl or methoxymethyl sidechains, while C3 (196, Scheme 27) features the corresponding free alcohol. Gu et al. presented the first asymmetric total synthesis of kopsiyunnanine 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 201 (Scheme 26) under the influence of ligand 203, and then Pdcatalyzed C3 arylation with 202, to give fused ring pyrrole 204. Both the nitro group and alkene of 204 were reduced with Pd/C and H₂; the resulting intermediate was treated with TFA, followed by addition of the Mukaiyama reagent 200 to achieve cyclization leading to the formation of (+)-rhazinal 197. The aldehyde group in 197 was reduced with NaBH₄/EtOH to afford (+)-kopsiyunnanine C3 196.

The same group pursued a number of strategies to synthesize (+)-kopsiyunnanines C1 and 2 from t-buty] ester 198 (Scheme 27); eventually it was found that the t-buty] group could be hydrolyzed by TFA, followed by reduction of the aldehyde with NaBH₄ and acidification with HCl to give ethers 199a and 199b. These were treated with the Mukaiyama reagent 200 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*. Tan *et al.* 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 0-ribal. This intermediate underwent C1 formylation and reduction to give TIPS-protected C1-hydroxymethyl-D-ribbon which was then converted to D-ribal iodide 208 upon treatment with iodine and PPh₃. 208 was alkylated with pyrrole dicarboxaldehyde 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-mercural spiroketals, which were reduced by NaBH₄ to give spiroketalts 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 pyrrologlycal 210 underwent epoxidation using DMDO; treatment with Bu₃NH₄ afforded the desired β-spiroketal 215 in good yield and diastereoselectivity at the C3 position. Desilylation provided (−)-acortatarin B 206 and its C1-epimer.

In 2017, Pale *et al.* developed a different synthetic route to (+)-
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. Ullmann coupling between 220 and 221 was achieved using a Cul-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. in 2014.

2.4.4 Mycenarubin A

The first total synthesis of (+)-mycenarubin A 226 (Scheme 31), isolated from Mycena rosea, was reported by Spiteller et al. in 2018 (Scheme 31). Their strategy commenced with the synthesis of bromomethyl indole 228 from known compound 227 in three steps. 228 was combined with N-(diphenylimethyleneglycine ethyl ester 229 in the presence of Corey’s cinchona catalyst 230 (1.4 mol%) and CsOH·H₂O to afford product 231 in high yield and enantiomeric 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 MnO₂ allowed access to (+)-mycenarubin A 226 in two further steps.

2.4.5 Curvulamine I

Tan et al. isolated the bispyrrole alkaloid curvulamine 236 (Scheme 32) from Curvularia sp. IFB Z10 in 2014. Marimone et al. reported the first enantioselective synthesis of (+)-curvulamine and related alkaloids, which was completed in just ten steps. The synthesis commenced with the preparation of racemic cyanohydrin 237 and pyrrole 238. The former was assembled by Sn2 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 (±)-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 KHMDMS, then reacted with CICSOPh 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 3-formyl-CBS-oxazaborolidine 251 and BH3·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.* 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 protected 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 debenzylated 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 BBr3, to afford 264. Reaction of this catechol with silver(II) oxide effected double cyclization to give exiguamine 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 exiguamine 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,* 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.* also reported total syntheses of (−)-pollenopyrroside A 265 and (+)-capparisine B 266 (Scheme 34). The synthesis began with the known preparation of pyrrole 268 from d-fructose 267. 268 was transformed into bis-hydroxymethyl pyrrole 269 under microwave irradiation with formaldehyde. 269 was oxidized using MnO2, 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 pyrrole 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 chinenesis* respectively. Brimble *et al.* 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.* 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 deprotonation of dithiane-carbamate 284 using n-BuLi / DMPU, followed by alkylation with bromide 285. Ketone 286 was then revealed using N-chlorosuccinimide / silvernitrate. Nucleophilic addition of O-TBS-propargyl alcohol 287 to 286 produced propargyl 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 applied the Maillard condensation used in earlier work as described above for the synthesis of this natural product. The synthesis commenced with construction of amine 294 from (4R)-hydroxyproline 291 which was converted to pyroglutamate 293 by various functional group protections followed by oxidation with RuO₂ (20 mol%) / NaO₂. 293 was in turn converted to amine 294 by aminolysis with p-
methoxybenzylamine (PMBNH2), followed by Boc-deprotection of the α-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. Spiteller et al.100 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, the last of which involved a reductive cyclisation of the dinitro compound 303 using Fe powder / silica gel in AcOH / H2O 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/BaSO4 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.

3.3.2 Makaluvamine A and D, damirone B, batzelline C, makaluvone and isobatzelline C

Tokuyama et al.102 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 (Scheme 39 and 40). The syntheses of 310–312 commenced with bromoaniline 316, which after double allylation underwent zirconium-mediated cyclization / iodination to indoline 318, with concurrent metalation / iodination of the arene. Chain extension of the iodomethyl group to dihydrotryptamine was followed by construction of the tricyclic pyrrolo[4,3,2-de]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 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 pyrroloiminoquinone. Treatment of this product with methanolic NH4Cl gave makaluvamine A 310. Makaluvamine D 311 was synthesized through oxidation of

Scheme 38: Syntheses of damirone C 297, batzelline C 298, batzelline D 299, makaluvone 300 and makaluvamine O 301 (Spiteller et al., 2017)100

Scheme 39: Syntheses of makaluvamine A 310, makaluvamine D 311 and damirone B 312 (Tokuyama et al., 2012)102
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(CCl₄)₂Cl or Br(CCl₄)₂Br. 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 NH₄Cl/EtOH gave isobatzelline C 313, while cleavage of the methyl ether with BBr₃ 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. SCSIO03032.103 Spiroindimicins B-D exhibit moderate cytotoxicity against various cancer cell lines, while spiroindimicin A does not show any activity. Sperry et al.104 reported the first total syntheses of (±)spiroindimicins B 328 and C 329 in 2016 (Scheme 41). Beginning with iodoanilline 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 steps. As before, oxidation with Fremy’s salt, followed by 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

Scheme 41: Syntheses of (±) spiroindimicins B 328 and C 329 (Sperry et al., 2017)104

Reaction of vinylsulfone 334 with methyl isocyanoacetate 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 342105 (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.,106 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 acetel 345. This was subjected to a gold-catalyzed 5-exo-dig cyclization by intermittent microwave irradiation in the presence of catalytic KH₂SO₄ 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 macro cyclization afforded (−)-rhazinicine 342.

3.4.2 Palau’amine

This journal is © The Royal Society of Chemistry 20xx J. Name., 2013, 00, 1-3 | 17

Please do not adjust margins
In 1993, Scheuer et al.\textsuperscript{107} isolated palau’amine from the sponge Stylotella agminate. Baran et al.\textsuperscript{51} reported the first enantioselective total synthesis of palau’amine \textit{348} in 2011 (Scheme 43). Compound \textit{102} (see Scheme 13) was brominated by treatment with bromine and trifluoroacetic anhydride, affording \textit{349} in moderate yield. The pyrrole precursor \textit{350} was then attached to \textit{349} under acidic conditions, affording \textit{351} in 44% yield. The azide moieties in \textit{351} were hydrogenated over palladium acetate, giving diamine \textit{352}, which underwent cyclization mediated by EDC.HCl. Exposure of the intermediate 9-membered lactam \textit{353} to hot TFA afforded (–)-palau’amine \textit{348}.

### 3.4.4 Xylapyrrosides A and B

In 2015 Hu et al.\textsuperscript{109} isolated the pyrrole alkaloids xylapyrrosides A (\textit{360}, Scheme 45) and B (\textit{361}, Scheme 46), along with two previously known PSAs (pollenopyrrosides A and acortatarin A) from Xylaria nigripes. They also reported total syntheses of (–)-xylapyrrosides A \textit{360}, (–)-xylapyrrosides B \textit{361}, and (+)-xylapyrrosides A \textit{360}, (–)-xylapyrrosides B \textit{361}, and (+)-

### 3.4.3 Pollenopyrroside A

Brimble et al.\textsuperscript{108} reported another application of the Maillard condensation described above in a convergent synthesis of (+)-pollenopyrroside A \textit{265} (Scheme 44) in 2016. In this case, it involved a reaction between primary amine \textit{356} and dihydropyranone \textit{278}, the former being prepared in a number of steps from deoxy-D-ribose \textit{354}. In the event, it was found that condensation of \textit{356} with \textit{278} was sensitive to temperature and pH. Reaction selectivity was improved by initial transformation of dihydropyranone \textit{278} into its acetate derivative, followed by reaction with PPTS, which afforded 2-formylpyrrole \textit{357} in good yield. Ley-Griffith oxidation of the secondary alcohol, TBS removal, and treatment with catalytic PPTS promoted cyclization to spiroketals \textit{358} as a 1.5:1 mixture of diastereomers. Acetonide removal using PPTS in methanol afforded a 7:1 ratio of (+)-pollenopyrroside A \textit{265} and (–)-9-epipollenopyrroside A \textit{359}.

### 3.4.3 Pollenopyrroside A

Brimble et al.\textsuperscript{108} reported another application of the Maillard condensation described above in a convergent synthesis of (+)-pollenopyrroside A \textit{265} (Scheme 44) in 2016. In this case, it involved a reaction between primary amine \textit{356} and dihydropyranone \textit{278}, the former being prepared in a number of steps from deoxy-D-ribose \textit{354}. In the event, it was found that condensation of \textit{356} with \textit{278} was sensitive to temperature and pH. Reaction selectivity was improved by initial transformation of dihydropyranone \textit{278} into its acetate derivative, followed by reaction with PPTS, which afforded 2-formylpyrrole \textit{357} in good yield. Ley-Griffith oxidation of the secondary alcohol, TBS removal, and treatment with catalytic PPTS promoted cyclization to spiroketals \textit{358} as a 1.5:1 mixture of diastereomers. Acetonide removal using PPTS in methanol afforded a 7:1 ratio of (+)-pollenopyrroside A \textit{265} and (–)-9-epipollenopyrroside A \textit{359}.

### 3.4.4 Xylapyrrosides A and B

In 2015 Hu et al.\textsuperscript{109} isolated the pyrrole alkaloids xylapyrrosides A (\textit{360}, Scheme 45) and B (\textit{361}, Scheme 46), along with two previously known PSAs (pollenopyrrosides A and acortatarin A) from Xylaria nigripes. They also reported total syntheses of (–)-xylapyrrosides A \textit{360}, (–)-xylapyrrosides B \textit{361}, and (+)-xylapyrrosides A \textit{360}, (–)-xylapyrrosides B \textit{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 alkylylate 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 TiCl4.

(−)-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 368109 was prepared using equivalent chemistry and was converted to 369 via pyrrole alkylation. 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,110 with its structure first identified in 1983.111,112 This natural product has emerged as a potent anticancer and immunosuppressant agent.113 Over the past decades, only Fukuyama114 had reported a synthesis of Marineosins A 378 and B 394 were isolated from a Streptomyces-related actinomycete in 2008.117 Marineosins A and B consist of two pyrrole moieties, a macrocyclic ring, and a spiro tetrahydropyran-dihydropyrrrole iminal. Xu et al.,118 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-pyrrone, but with low overall yield (1.2%). Harran et al.,119 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 pyrrrole 383. After enolate alkylation with epoxide 386, the resultant putative oxocarbenium ion intermediate underwent addition of bipyrrole 388120 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 spirowthemines 392 and 393 in very low yield on oxidation with MnO2. Hydrogenation using Pd/BarSO4 afforded (+)-marineosin A 378.

3.4.7 Cyclooroidin

Hoveyda et al.,121 reported an enantioselective synthesis of (−)-cyclooroidin 395 (Scheme 49) in 2014. Treatment of 396 with NaHCO3 in dichloromethane generated the phosphinoylimine, direct subjection 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 cycloorodigiosin 370 (in 1984) until the first enantioselective synthesis of (R)-cycloorodigiosin 370 was described by Sarpong et al.115 Their synthetic strategy commenced with enantioenriched allenyl alkene 373, which was prepared in six steps from known alkene 372.116 373 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 Rh2(Oct)4 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 cycloorodigiosin 370 in good yield.

3.4.6 Marineosin A
treatment with aqueous HCl, and the resulting enantioenriched amine was converted to pyrrole by reaction with ketoaldehyde. Next, the silyl-substituted allene was transformed into dibromopyrrole by brominative desilylation of the allenylsilane to a propargyl bromide (and concurrent pyrrole bromination), followed by treatment with bis-Boc-guanidine. The dibromide was subjected to an intramolecular silver catalyzed hydroamination, and Boc removal afforded the target molecule in high yield. This synthetic strategy compared favourably with earlier reported enantioselective syntheses.

### 3.4.8 Streptorubin B

Streptorubin B (Scheme 50) features a highly strained pyrrolephane core that is formed by oxidative ring closure from undecylprodigiosin. Weyland et al. found that streptorubin A exists as two atropdiastereomers, related by the relative stereochemistry of the bis-pyrole side arm and butyl side chain. Thomson et al. described an enantioselective total synthesis of (R)-streptorubin B from commercially available cycloheptene. This was treated with RuCl₃ and NaIO₄ to give a diahydroxylation, which upon aldehyde cyclization promoted by 10 mol% (S)-proline, and reaction with ylide, produced homoaliphatic alcohol. Oxidation of, followed by addition of vinyl anion and exposure of the resulting alcohol to KHMD and 18-crown-6 produced 10-membered ring via a Cope rearrangement ring expansion. This intermediate then underwent alkene reduction along with simultaneous cleavage of the benzylation ethers; oxidation of the intermediate diol and paal-Knorr pyrrole synthesis affording pyrrole core in 67% yield. underwent an acid-mediated condensation reaction with aldehyde, 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, 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 C2-symmetric bisthiourea catalysis, arene–yanamide 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 Supporting Information) 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.

5 Conflicts of Interest

The authors declare no conflict of interest.

6 Acknowledgements

RC and AS are thankful to DST-SERB (EEQ/2016/000489) for providing financial assistance for conducting research. NS would like to acknowledge CSIR-SRF for providing the fellowship. AS is thankful to DST-SERB (EEQ/2016/000489) for providing Senior Research Fellowship. SS is thankful to ICMR (45/66/2018-PHA/BMS/OL) for providing a Senior Research Fellowship. HA thanks the Wellcome Trust for support (218514/Z/19/Z). EA thanks the EPSRC for support (EP/S013172/1).

7 Notes and References


M. van Rensburg, B.R. Copp and D. Barker, Synthesis and Absolute Stereochemical Reassignment of Mukanadin F: A


Please do not adjust margins

ARTICLE


