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Synthesis of natural products containing the pyrrolic ring

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Received 6th July 2010
DOI: 10.1039/c0np00014k

Covering: up to the end of January 2010

This review provides an overview of the synthetic chemistry that has been utilised to prepare natural products containing a pyrrolic ring.

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Ian S. Young

Ian S. Young was born in Liverpool, Nova Scotia, Canada, and received his B.Sc. from Dalhousie University in 2002. His doctoral studies at the University of Western Ontario under the guidance of Professor Michael Kerr involved the reactions of cyclopropanes with nitrones, and then application of this methodology to the total synthesis of nakadomarin A. A two-year Natural Science and Engineering Research Council of Canada postdoctoral fellowship was tenured at the Scripps Research Institute working in the laboratory of Professor Phil Baran. At Scripps, he was part of the team that completed the total syntheses of the axinellamines, the massadines and palau'amine. In 2009, Ian started his career in the department of process research and development at Bristol-Myers Squibb.

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1 Introduction

The five-membered nitrogen-containing aromatic heterocycle, pyrrole, was first isolated through the distillation of bone oil, and its skeleton has been since noted in natural products from much of the world's flora and fauna.[1] The structure and reactivity of pyrrole, not to mention its propensity to polymerise given half an opportunity, renders pyrrole chemistry a relative speciality and certainly not something for the faint of heart.

Although pyrroles have been extensively reviewed previously,[2–8] most discussions are presented in terms of structure rather than synthetic chemistry. In contrast, this review focuses on the synthetic strategies used to construct the pyrrole moiety in pyrrole-containing natural products. Consequently, the document is organised courtesy of the chemistry involved, rather than by the structure of the natural product, with our aim being to provide an overview of and an inspiration as to the wonders and pitfalls of constructing the pyrrole heterocycle within complex systems. As such, several natural products appear multiple times in this document by virtue of the fact that they have been constructed using various synthetic strategies. Wherever possible we have highlighted the nuances of heterocyclic pyrrole chemistry, and we refer the reader to the original cited reports for full details. With the exception of some very simple substituted pyrroles that were isolated from flue-cured tobacco[9] we have, to the best of our knowledge, touched upon all aspects of known syntheses of pyrrole-containing natural products: we hope that we are forgiven for omissions. This review excludes polypyrroles (*e.g.*, prodigiosenes, porphyrins) and omits syntheses that generate the skeleton rather than the unadulterated natural product. Formal syntheses are included only where the strategy to generate or incorporate the pyrrole unit differed significantly from that of the total synthesis.

Alison Thompson

Alison Thompson's research interests include functionalised pyrroles, dipyrrinato complexes and prodigsenes. Born in Nottingham, England, Alison obtained her B.Sc. (Hons. Class I) from the University of Leicester and her Ph.D. from the University of Sheffield for research involving catalytic asymmetric aziridination and epoxidation with Professor Varinder Aggarwal. After a year as a Royal Society/NATO postdoctoral-fellow in Strasbourg, Alison joined the University of British Columbia, Canada, to work with Professor David Dolphin. She moved to Halifax, Nova Scotia, Canada in 2001 to take up a faculty position at Dalhousie University and was promoted to full professor in 2009. She has received an AstraZeneca Award (Canada) in Chemistry, and a Society and Journal of Porphyrins and Phthalocyanines Young Investigator Award.

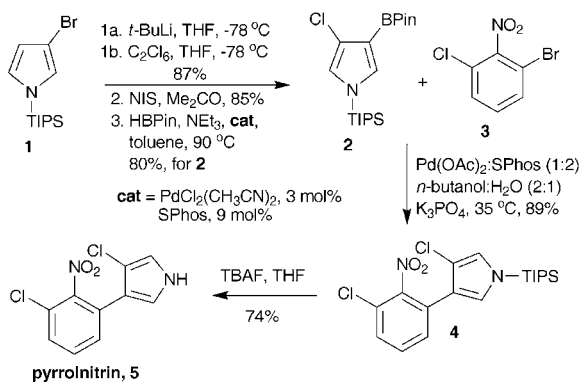
2 Syntheses utilising a premade pyrrolic unit

This section of the review details strategies that introduce a preformed pyrrole into the synthetic sequence. Syntheses of natural products that incorporate a simple (unfused) pyrrole unit are presented first, followed by the more complex fused pyrroles. Within each sub-section, syntheses of achiral natural products are detailed initially, followed by racemic, and then asymmetric, syntheses of natural products exhibiting chirality, where examples permit.

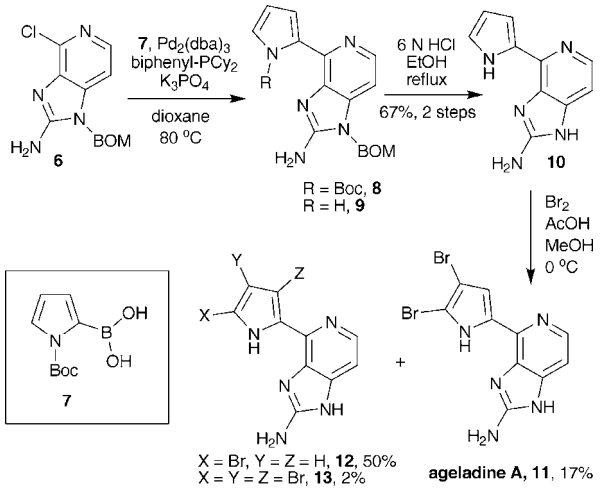
2.1 Premade pyrrole, simple pyrrolic moiety in natural product, achiral

2.1.1 Pyrrolnitrin. As for so many fields, the development of metal-mediated cross-coupling reactions has greatly increased the number of bond disconnections available to the synthetic chemist interested in pyrrole-containing natural products. The recent synthesis of pyrrolnitrin (**5**) by Pratt (Scheme 1)[10] demonstrates a stark difference in strategy when compared to the two previous syntheses reported in 1966 and 1972 (see Scheme 51 and Scheme 52, respectively). Pratt's installation of the 4-chloro substituent into the pyrrole **1** required an indirect route to ensure a high degree of regioselectivity. After boronic ester incorporation, compound **2** was smoothly coupled with **3** to yield TIPS-protected pyrrolnitrin (**4**) that was easily deprotected to give the natural product.

2.1.2 Ageladine A. The first synthesis of ageladine A (**11**) by Weinreb[11,12] also utilised metal-mediated cross-coupling. Thus, the boronic acid **7** was coupled with **6** to produce a mixture of compounds (**8** and **9**) that converged to **10** upon treatment with acid (Scheme 2). Conversion of this key intermediate to the natural product was problematic, as the degree of bromination was difficult to control. The mono-bromo compound **12** was the major product from this reaction, with ageladine A (**11**) being isolated in 17% yield. Forcing bromination conditions could not be used to increase the amount of isolated dibromopyrrole-containing ageladine A as then the tribromo compound **13** became prevalent, and separation was impractical. The challenges with the bromination step, and the fact that the starting chloropyridine **6** required nine steps for its construction, detracted from the efficiency of this route. Indeed, one year later



Scheme 1 Pratt's synthesis of pyrrolnitrin utilising a palladium-mediated cross-coupling.

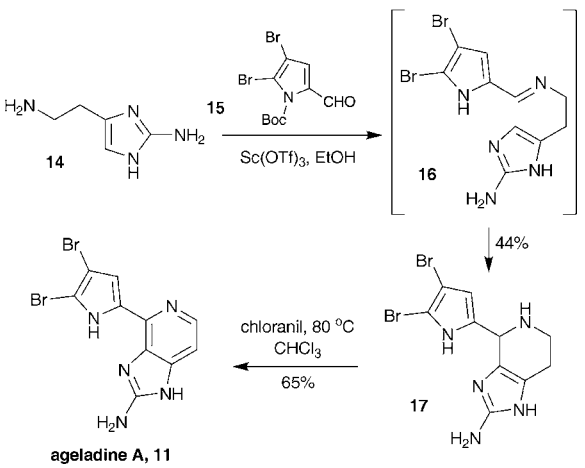


Scheme 2 Weinreb's first synthesis of ageladine A.

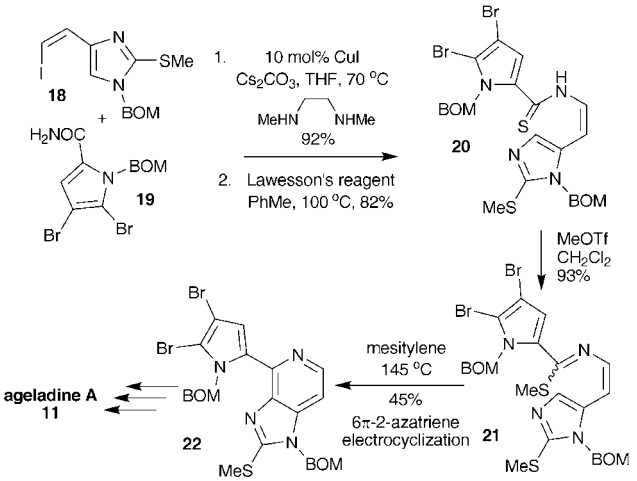
Weinreb published an alternative strategy to address these issues (Scheme 4).[13,14]

The same year as the initial report by Weinreb, Karuso published a synthesis of ageladine A that featured a biomimetic cyclisation as the key step (Scheme 3).[15] Condensation of 2-aminohistamine (**14**) and the dibrominated formylpyrrole **15** generated the imine **16** *in situ*, which, under the influence of scandium triflate, underwent a Pictet–Spengler-type cyclisation to form the core structure **17** of ageladine A. Chloranil treatment at elevated temperature induced oxidation to the natural product **11**. Following the disclosure of this result by Karuso,[15] similar cyclisation strategies were used by Ando[16] and Horne[17] to prepare ageladine A and analogs for biological testing.

To alleviate the issues encountered previously with late-stage bromination of the pyrrole (Scheme 2), Weinreb[13,14] cross-coupled the dibromopyrrole **19** with the vinyl iodide **18** (Scheme 4). Notably, the dibromo substitution of the pyrrole ring was tolerant of these conditions. Exposure of the resulting product to Lawesson's reagent yielded **20**. Treatment with methyl triflate gave **21** which, when heated to 145 °C, underwent a 6π-2-aza-triene electrocyclisation to produce the core (**22**) of ageladine A. Further manipulations yielded the natural product *via* a route that eliminated the requirement for late-stage bromination.



Scheme 3 Biomimetic synthesis of ageladine A by Karuso.

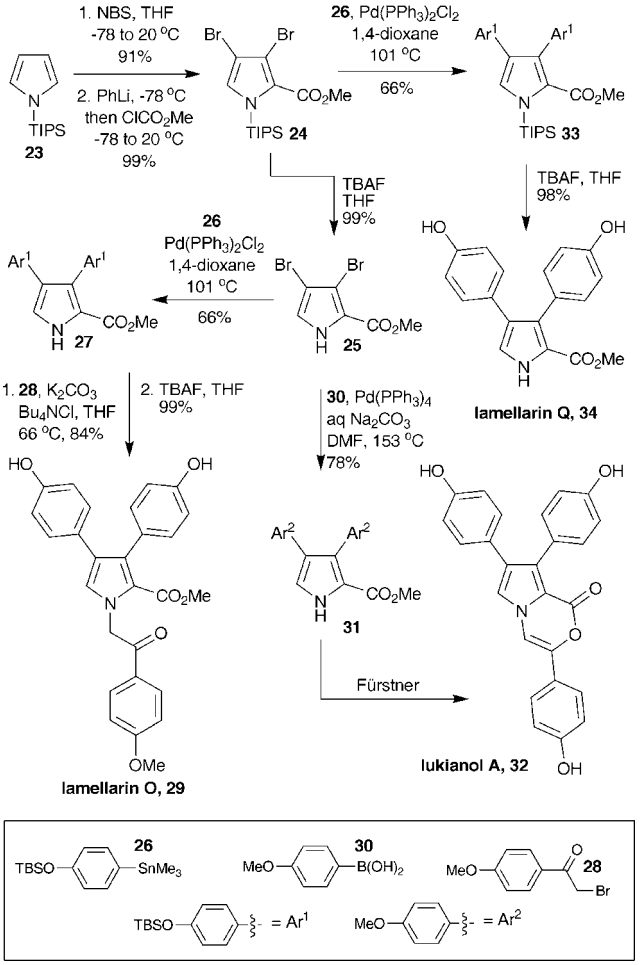


Scheme 4 Weinreb's second-generation synthesis of ageladine A.

2.1.3 Lamellarins and lukianol A. The lamellarins are part of a family of marine natural products that also includes the lukianols, the storniamides, the ningalins and the polycitones (*vide infra*). The compounds all contain the common functionality of a 3,4-diarylpyrrole with carbonyl functionality at the 2- (or both the 2- and 5-) position. When examining the syntheses of these molecules, of which there are many, it is apparent that two general strategies can be utilised: (i) begin with a simple pyrrole core, and incorporate the functionality in a linear manner; or (ii) generate the pyrrole foundation *en route* (see section 3 of this review), incorporating as much functionality in a single step as possible through the judicious choice of pyrrole precursors. As will be observed throughout this review, both strategies have been successfully utilised to overcome the synthetic challenges presented by the lamellarins. This section details routes involving the incorporation of a pre-constructed pyrrole. Due to the structural similarities of many of these natural products, it is common for one strategy to be applicable to the synthesis of more than one compound.

The first examples of the step-wise elaboration of a simple pyrrolic core to a natural product of this family were the syntheses of the lamellarins O (**29**) and Q (**34**) and the formal synthesis of lukianol A (**32**) by Banwell (Scheme 5).[18] Starting with the commercially available TIPS-protected pyrrole (**23**), regioselective 3,4-dibromination and installation of a methyl ester at the 2-position rendered the key intermediate **24**. Compound **24** was further elaborated *via* a series of cross-coupling events (Stille and Suzuki), as well as protecting group removal at the appropriate stage. For lamellarin O (**29**), alkylation of the pyrrolic nitrogen atom of **27** with the α-bromoketone **28** was required. Compound **25** served as a precursor to prepare an intermediate in Fürstner's synthesis of lukianol A (Scheme 80),[19] thus constituting a formal synthesis of this fused pyrrole natural product. After the report by Banwell,[18] Iwao[20] published the synthesis of the lamellarins O, P and R using a slight variation in strategy (not depicted).

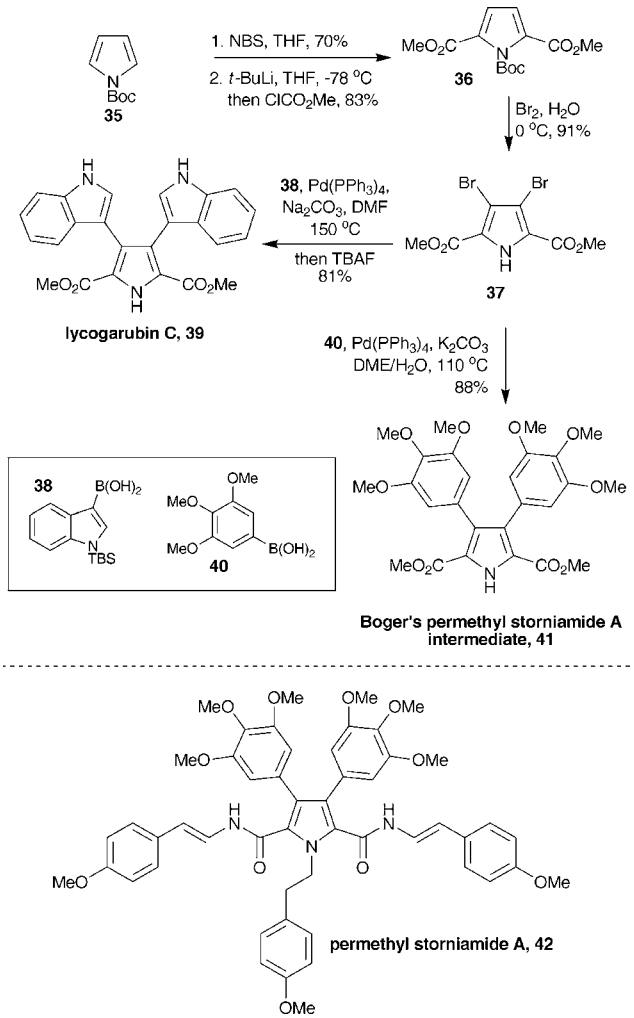
2.1.4 Lycogarubin C and permethyl storniamide A. A linear strategy towards lycogarubin C (**39**) and permethyl storniamide A (**42**) that utilised *N*-Boc pyrrole (**35**) as the starting material



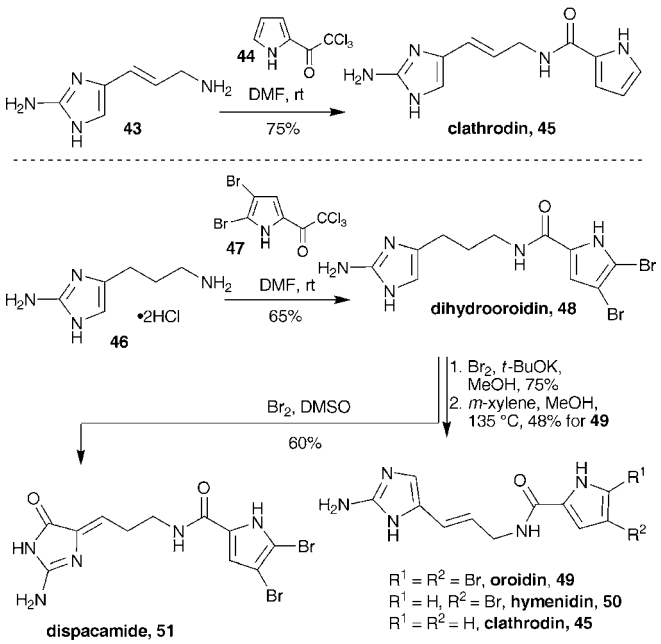
Scheme 5 Banwell's pyrrole functionalisation strategy to prepare lamellarin Q and O as well as an intermediate in Fürstner's synthesis of lukianol A.

was reported by Fürstner in 2002 (Scheme 6).[21] Elaboration of **35** through ester installation and subsequent dibromination produced a compound (**37**) with suitable handles for further divergent functionalisation. By cross-coupling **37** with the indole boronic acid **38** and subsequent silyl-group removal, lycogarubin C (**39**) was obtained. Alternatively, the boronic acid **40** was used to produce **41**, an intermediate in Boger's permethyl storniamide A synthesis (Scheme 53),[22] thus constituting a formal synthesis. It could be envisioned that **37** could also be used for the divergent synthesis of other members of this family.

2.1.5 Oroidin, clathrodin, keramadine and dispacamide. The oroidin alkaloids are a group of secondary metabolites that were isolated from marine sponges of the genera *Agelas*, *Hymeniacidon* and *Phakellia*. Oroidin (**49**),[23–25] hymenidin (**50**),[26] clathrodin (**45**),[27] dispacamide (**51**)[28] and keramadine (**55**)[29] are natural products of this group (see Scheme 7 and Scheme 8). These natural products share a 2-aminoimidazole or glucosamidine core, and a three-carbon bridge to an amide bearing a pyrrole that is sometimes brominated. Horne reported the total synthesis of oroidin, clathrodin and dispacamide from common starting materials (Scheme 7).[30] Thus, the aminoimidazole **43** was reacted



Scheme 6 Fürstner's divergent synthesis of lycogarubin C and permethyl storniamide A intermediate previously prepared by Boger.



Scheme 7 Horne's synthesis of oroidin alkaloids.

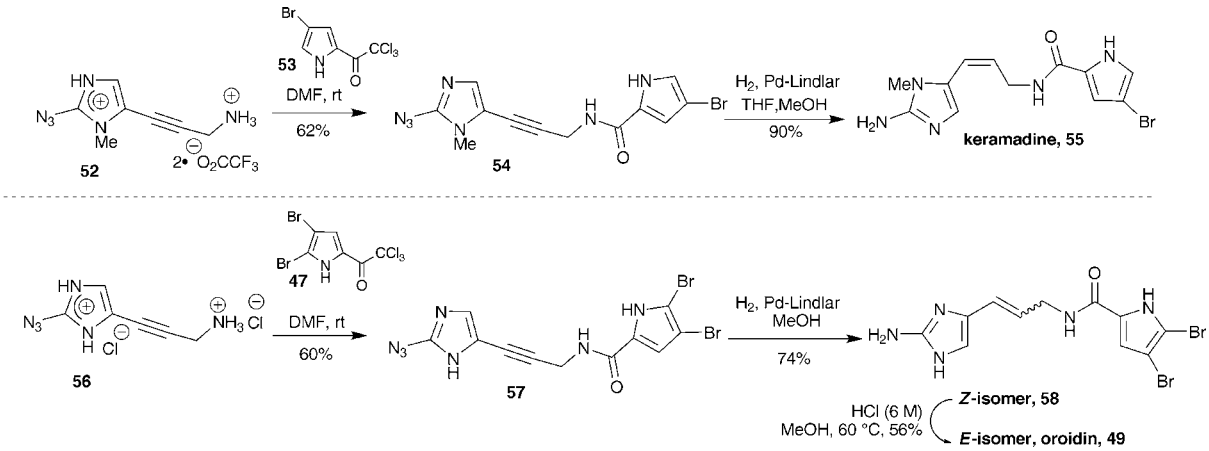
with 2-(trichloroacetyl)pyrrole (**44**) to give clathrodin. The saturated aminoimidazole **46** was reacted with 4,5-dibromo-2-(trichloroacetyl)pyrrole (**47**) to give dihydrooroidin (**48**). Oxidation of **48** using bromine in basic methanol gave a dimethoxy intermediate that, when heated in *m*-xylene–MeOH, gave oroidin (**49**). The preparation of dispacamide (**51**) required the oxidation of **48** using bromine in DMSO. These syntheses of the oroidin alkaloids are notable in that due to the methodology used to prepare the aminoimidazoles, **43** and **46**, and the late-stage introduction of the pyrrole, nitrogen protection was not required.[30]

Lindel published syntheses of oroidin[31] and keramadine[32] using propargylic aminoimidazoles (Scheme 8). For this work, **52** was treated with 4-bromo-2-(trichloroacetyl) pyrrole (**53**) to append the pyrrole unit of keramadine. Hydrogenation using Lindlar's catalyst reduced both the azide and the alkyne to give the natural product (**55**). This approach was also adaptable to the preparation of oroidin: reaction of **56** with 4,5-dibromo-2-(trichloroacetyl)pyrrole (**47**) gave the alkyne **57**, and hydrogenation provided the *Z*-olefin that was isomerised to oroidin (**49**) upon treatment with acid.[31]

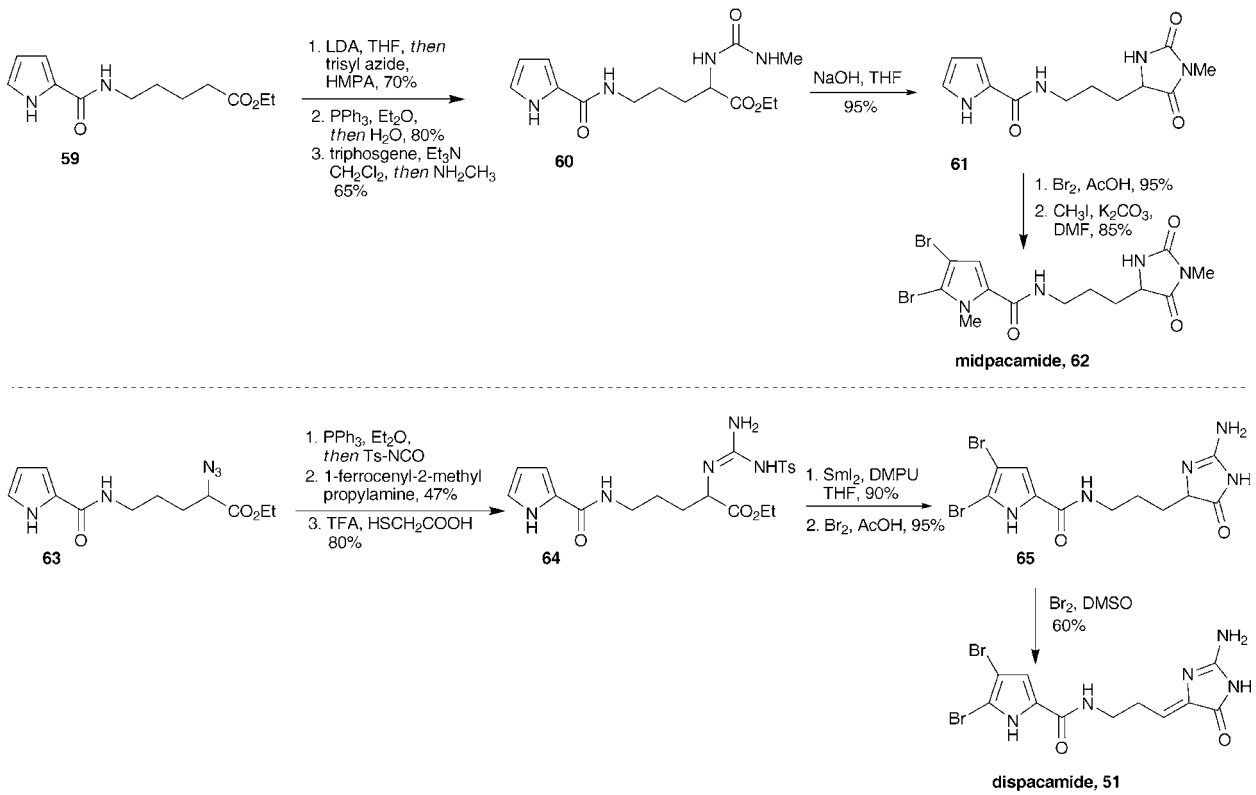
Fresneda reported total syntheses of midpacamide (**62**) and dispacamide (**51**, Scheme 9).[33] Midpacamide differs from other oroidin alkaloids in that it features a hydantoin, rather than an imidazole, and lacks a double bond in the three-carbon tether. In this work **59** was prepared by reaction of 2-(trichloroacetyl)pyrrole (**44**) with ethyl 5-aminovalerate hydrochloride. In the synthesis of midpacamide, **59** was converted to **60** *via* azidation, Staudinger reduction and subsequent treatment with triphosgene and methylamine. Base-promoted cyclisation gave **61**, and bromination followed by *N*-methylation completed the synthesis. The synthesis of dispacamide required that the azide **63** be converted to the guanidine **64** *via* an aza-Wittig-type reaction with tosyl isocyanate, and subsequent reaction with 1-ferrocenyl-2-methylpropylamine followed by treatment with TFA. Cleavage of the tosyl group using SmI_2 gave the imidazolinone, and subsequent bromination of the pyrrole and oxidation using conditions identical to Horne's[30] furnished dispacamide (**51**).

Al-Mourabit reported a synthesis of dispacamide that used pyrrole-2-carboxylic acid (**66**) and the methyl ester of L-proline (**67**) to form **68** (Scheme 10).[34] Treating **68** with Boc-guanidine in air led to **69** and **70**. This reaction is remarkable in that the carbon atom adjacent to the carbonyl of the 2-aminoimidazolinone was oxidised under very facile conditions. This may indicate a possible biosynthetic pathway for the oroidin alkaloids, and would indicate dispacamide as a precursor to oroidin. The mixture of regioisomers was converted to dispacamide (**51**) upon bromination, Boc deprotection and elimination.

Other syntheses of the oroidin natural products differ chiefly in the method for preparing the 2-aminoimidazole and its critical double bond. Once the 2-aminoimidazole is prepared, coupling it with the appropriate 2-(trichloroacetyl)pyrrole gives oroidin or its derivatives (Scheme 11). Ahond and Poupat prepared hymenidin, oroidin, and keramadine using a Wittig reaction to introduce the 2-aminoimidazole.[35] Webber also employed a Wittig reaction in his synthesis of 2-aminoimidazoles and oroidin.[36] Carboni prepared the 2-aminoimidazole of oroidin using a stereoselective hydroboration and Suzuki coupling.[37]



Scheme 8 Lindel's synthesis of keramadine and oroidin.

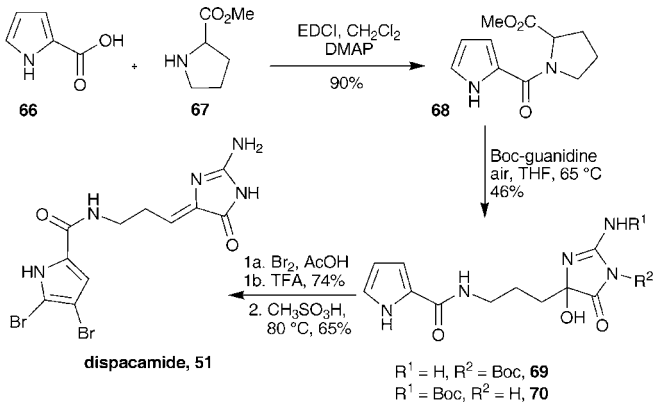


Scheme 9 Fresneda's total syntheses of midpacamide and dispacamide.

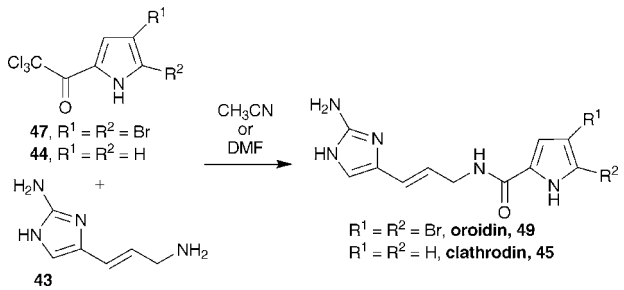
Ando[38] used a Julia olefination to complete the preparation of 2-aminoimidazole in his approach to oroidin and hymenidin.

2.2 Premade pyrrole, simple pyrrolic moiety in natural product, racemic syntheses

2.2.1 Sceptrin, ageliferin, nagelamide E, oxysceptrin and nakamuric acid (methyl ester). Upon examination of the structures of sceptrin (**78**) and ageliferin (**79**) it is tempting to propose that they arise biosynthetically from the [2 + 2] and [4 + 2] dimerisation, respectively, of hymenidin (**50**). However, there are no reports of the successful implementation of this approach in the synthesis of sceptrin and ageliferin. Furthermore, these materials do not occur as a racemic mixture in nature, suggesting that an alternative biosynthetic mechanism might be operational. The cyclobutane core (**75**) of sceptrin was prepared by rearrangement of **74**, with further elaboration leading to **76**. The two pyrrole moieties (**53**) were then attached *via* amide bond formation, after azide reduction. Aminoimidazole introduction completed Baran's total synthesis of sceptrin (Scheme 12).[39] Birman reported the synthesis of sceptrin using a similar strategy.[40] In exploring the possibility that sceptrin serves as a biosynthetic precursor to other more complex pyrrole-imidazole alkaloids, Baran disclosed that heating an aqueous solution



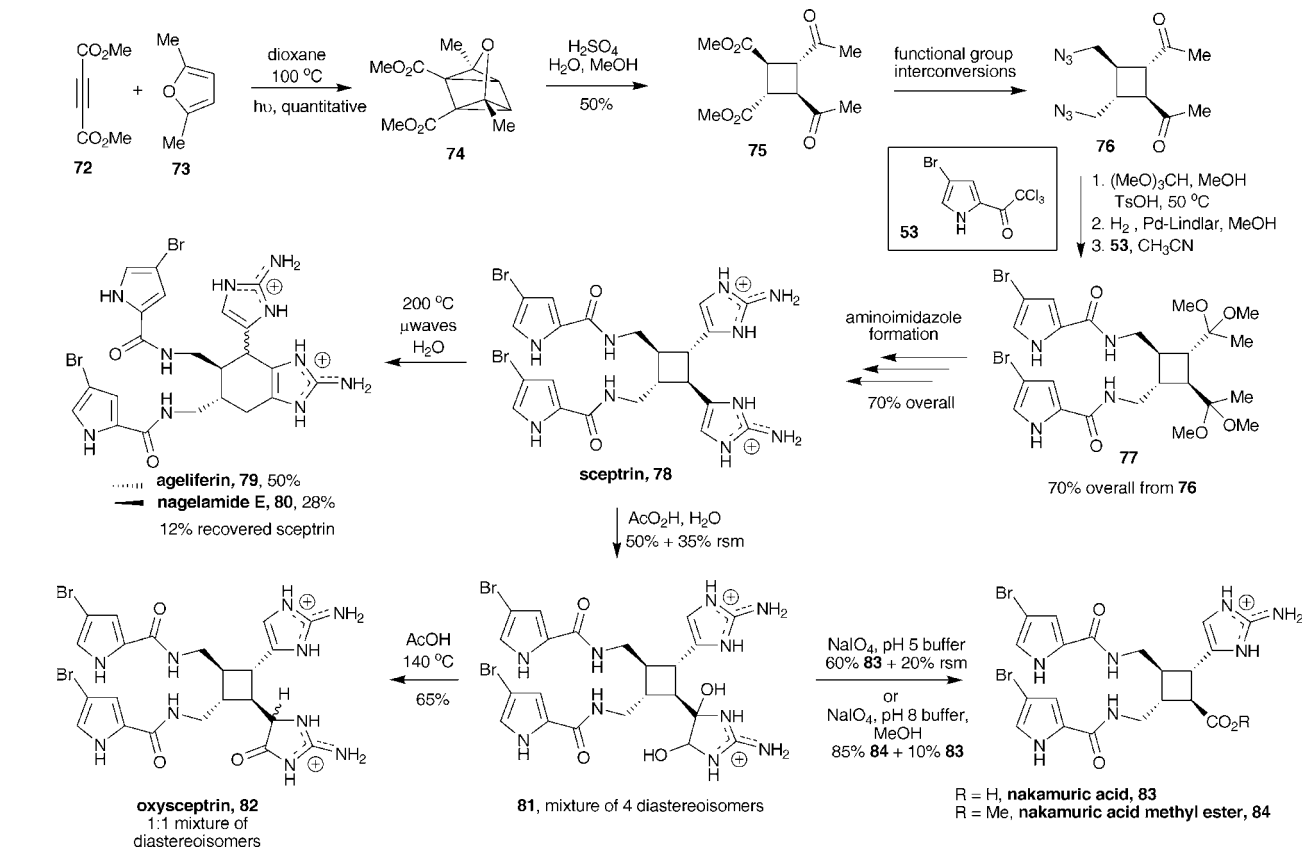
Scheme 10 Al-Mourabit's total synthesis of dispacamide.



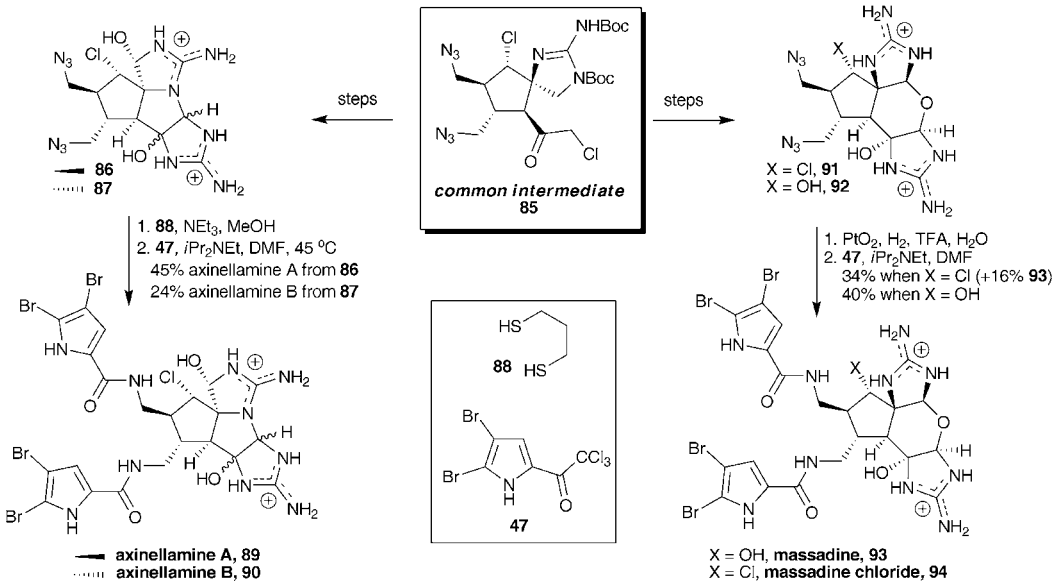
Scheme 11 Coupling 2-aminoimidazoles with 2-(trichloroacetyl)-pyrroles to give oroidin derivatives.

of the acetate salt of sceptrin to 200 °C with microwave irradiation led to a highly efficient rearrangement to ageliferin (**79**) and its epimer nagelamide E (**80**).[41] Treatment of sceptrin with peracetic acid induced aminoimidazole oxidation, and the intermediate **81** was then converted to oxysceptrin (**82**), *via* treatment with acetic acid, and nakamuric acid and its methyl ester (**83** and **84**, respectively), through periodate-mediated degradation.[42,43] Baran also reported an asymmetric synthesis of sceptrin and ageliferin utilising pig liver esterase to desymmetrise the bicyclic intermediate that arises from the reaction of **72** and **73** prior to irradiation.[44]

2.2.2 Axinellamine and massadine. The tetracyclic cores found within the axinellamines (**89** and **90**) and massadines (**93** and **94**) signify the next level in complexity in this family of alkaloids when compared to the simpler mono- and bicyclic sceptrin (**78**) and ageliferin (**79**). Through use of a common intermediate (**85**), Baran constructed both tetracyclic cores prior to pyrrole incorporation (Scheme 13). For the axinellamines,[45] the azides **86** and **87** were reduced with excess 1,3-propanedithiol (**88**) and triethylamine, whereas preparation of the massadine core required hydrogenation with PtO_2 due to sensitivity to base.[46] The natural products were then prepared *via* reaction of the newly formed primary amines with 4,5-dibromo-2-trichloroacetylpyrrole (**47**), a reaction that showed a high degree of chemoselectivity as aminoimidazole protection was not required to prevent unwanted acylation.



Scheme 12 Baran's synthesis of sceptrin, ageliferin, nagelamide E, oxysceptrin, and nakamuric acid (methyl ester) from a common intermediate.



Scheme 13 Baran's total synthesis of the axinellamines and massadines from a common intermediate.

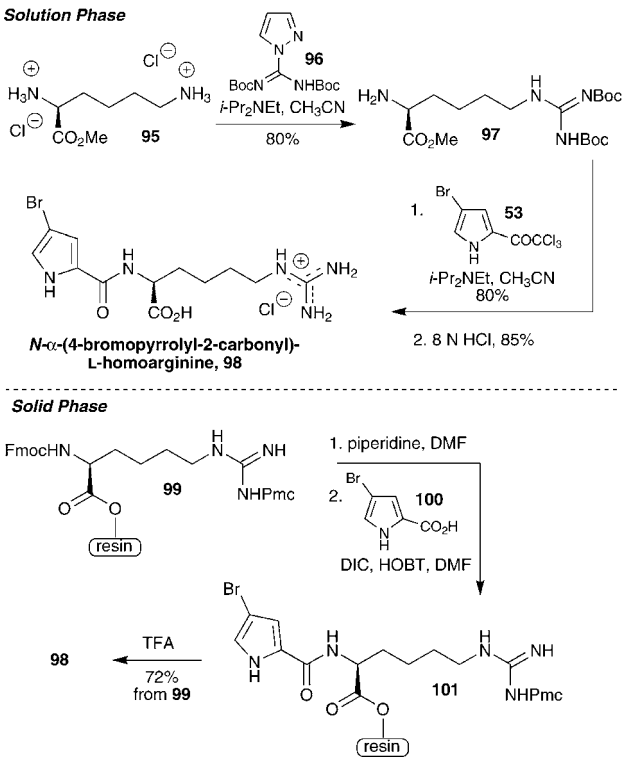
2.3 Premade pyrrole, simple pyrrolic moiety in natural product, asymmetric syntheses

2.3.1 Sceptrin and ageliferin. As described previously (Scheme 12), Baran reported an asymmetric synthesis of sceptrin and ageliferin utilising pig liver esterase to desymmetrise the desymmetrise the bicyclic intermediate that arises from the reaction of **72** and **73** without prior to irradiation.[44]

2.3.2 *N*-α-(4-Bromopyrrolyl-2-carbonyl)-L-homoarginine. The biosynthesis of the pyrrole-imidazole alkaloids has drawn much attention, and Köck and Lindel have proposed that the natural product *N*-α-(4-bromopyrrolyl-2-carbonyl)-L-homoarginine (**98**) may be a key intermediate *en route* to these natural products (Scheme 14). Pyrrole **98** was prepared in both solution (from lysine methyl ester, **95**, Scheme 14, top) and in the solid phase (from the protected arginine derivative **99**, Scheme 14, bottom), in both cases by late-stage incorporation of the 4-bromopyrrole-2-carboxylate unit.[47]

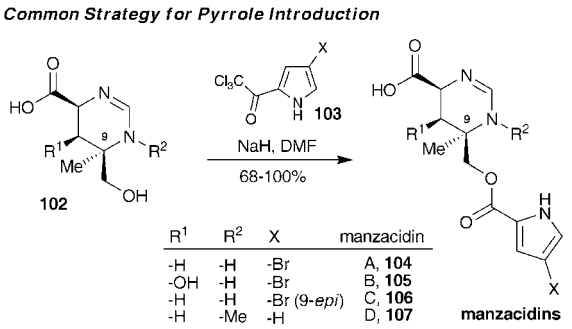
2.3.3 Manzacidins. The unusual and highly functionalised 3,4,5,6-tetrahydropyrimidine ring of the manzacidins (**104–107**, Scheme 15) represents a significant synthetic challenge. Although a number of unique methodologies have been developed to overcome the difficulties associated with the generation of the tetrahydropyrimidine core, the method by which the suitably substituted pyrrole is introduced is quite facile. All reported syntheses[48–54] follow the first example by Ohfune[55] in which the pyrrole is introduced in the final step *via* reaction of an alkoxide formed from the general structure **102** with the appropriately functionalised trichloroacetyl pyrrole **103** (Scheme 15).

2.3.4 Calcimycin (A-23187). Calcimycin (also known as A-23187, **111**, Scheme 16) received much attention in the late 1970s and early 1980s due to its potential as a tool with which to study metal ion transport in a variety of biological processes.



Scheme 14 Lindel and Köck's preparation of *N*-α-(4-bromopyrrolyl-2-carbonyl)-L-homoarginine.

Synthetic efforts towards this natural product have generally incorporated the pyrrole late-stage, as outlined in Scheme 16. Evans utilised an aldol reaction between the zinc-enolate of the ketopyrrole **108** and the aldehyde **109** to produce a mixture of the *threo* and *erythro* products (**110**).[56] This mixture was used directly in the next step, with purification occurring at a later stage. Kishi utilised the magnesium enolate of **108** and exploited an aldol reaction with the linear substrate **112**.[57] Greico

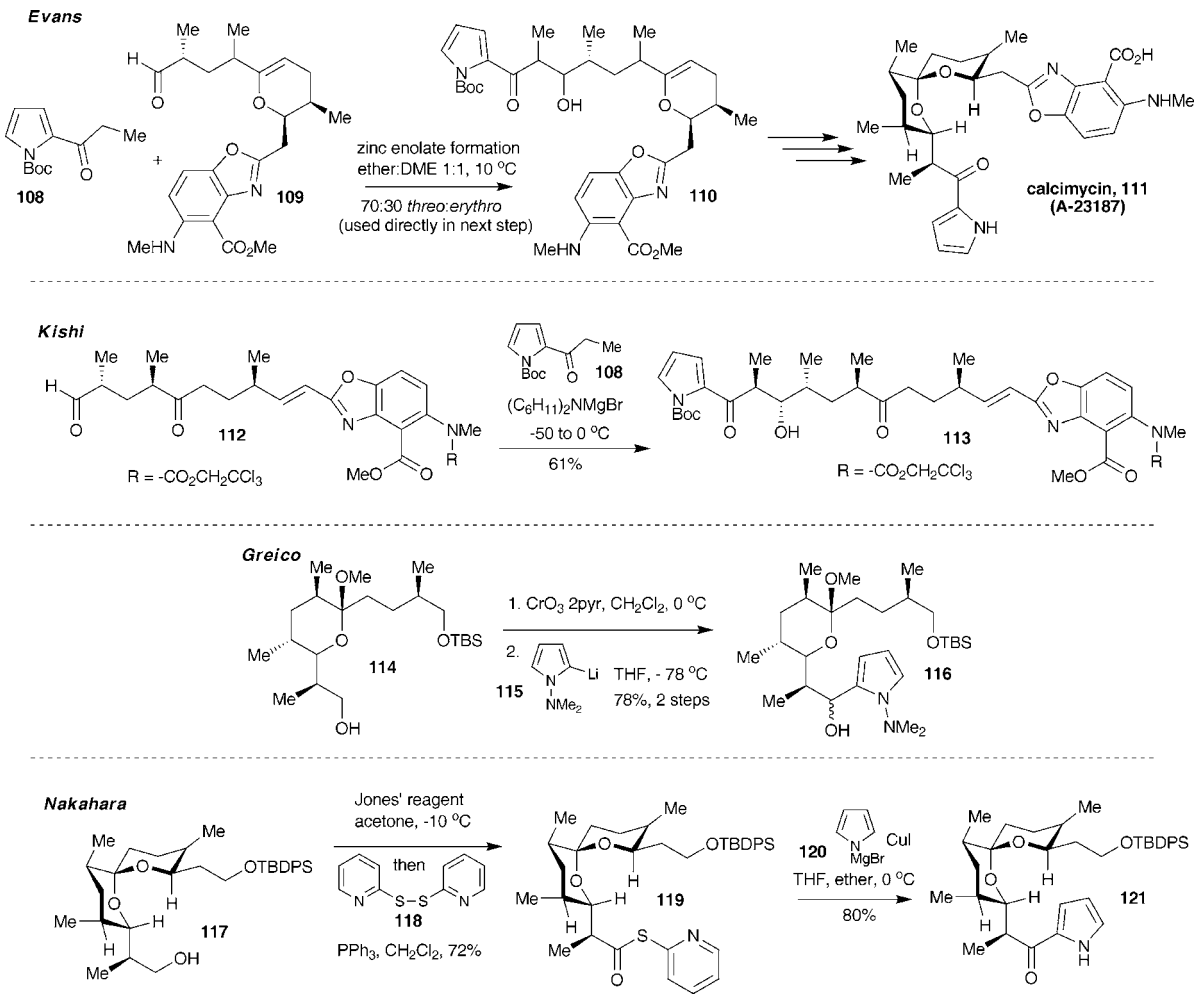


Scheme 15 Strategy based on Ofune's work for late-stage pyrrole introduction onto the manzacidin core.

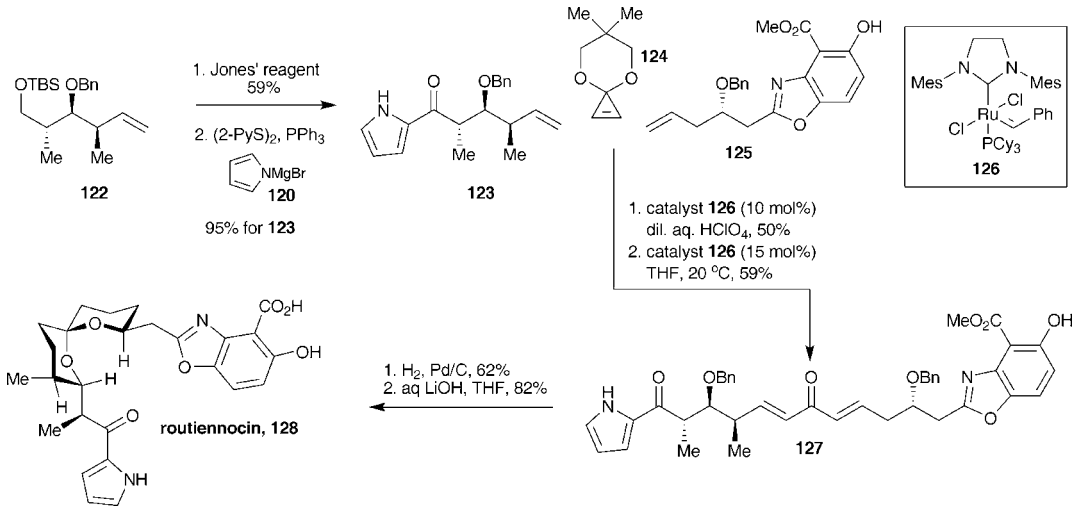
incorporated the pyrrole heterocycle *via* addition of the lithiopyrrole **115** to the aldehyde derived from the oxidation of **114**.[58] This strategy required alteration of the oxidation state of the resulting alcohol. Nakahara added pyrrole magnesium bromide (**120**) to the 2-thiopyridyl ester **119** (derived from the alcohol **117**), in the presence of copper iodide.[59] Boeckman also utilised a 2-thiopyridyl ester coupling strategy in his synthesis of calcimycin (not depicted).[60]

2.3.5 Routiennocin (CP-61,405). Despite the similarities in structure and biological function to calcimycin (**111**), there has been much less attention directed towards routiennocin (also known as CP-61,405, **128**, Scheme 17), with only two total syntheses being reported. Kozmin's synthesis of routiennocin,[61] although it used a similar strategy to Nakahura's synthesis of calcimycin[59] for pyrrole introduction (see Scheme 16), is unique as it involved introduction of the pyrrole at a much earlier stage (Scheme 17). Preparation of the 2-thiopyridylester from **122** and subsequent coupling with magnesium pyrrole bromide (**120**) gave **123**, which participated in two subsequent cross-metathesis steps with **124** and **125** to produce **127**. Removal of the benzyl ethers induced the required spiroketal formation, and ester hydrolysis returned the natural product. Although many of the reactions illustrated in Scheme 17 do not involve the pyrrole heterocycle, the latter steps demonstrate how the development of modern methodologies (cross-metathesis) can lead to highly efficient syntheses (longest linear sequence of 8 steps), with the mildness of the metathesis conditions facilitating carriage of the pyrrole moiety.

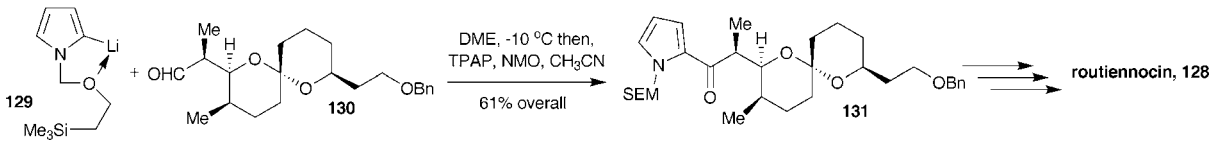
Ley introduced the pyrrole of routiennocin *via* the reaction of the SEM-protected lithiopyrrole **129** with the aldehyde **130**.[62] The resulting alcohol was then oxidised using TPAP to



Scheme 16 Methods for pyrrole introduction used by various groups in their total syntheses of calcimycin.



Scheme 17 Synthesis of routiennocin by Kozmin that requires eight steps in the longest linear sequence.

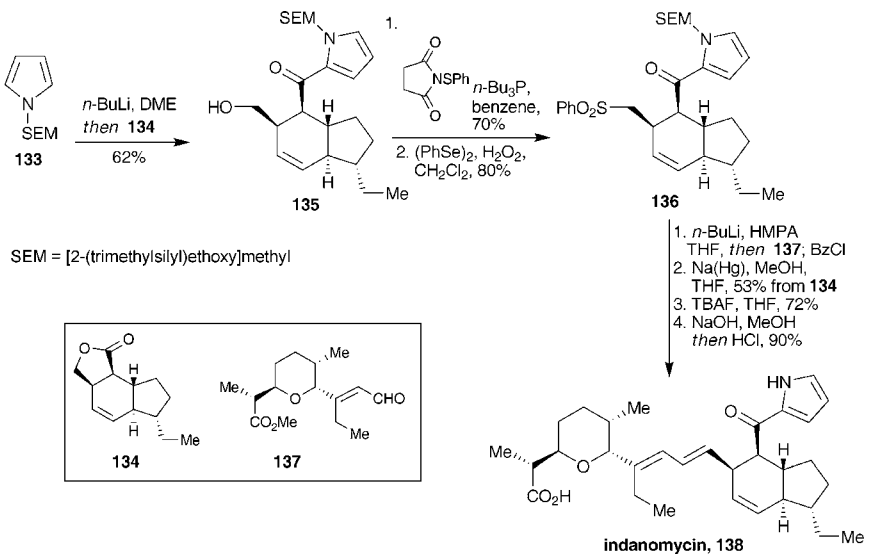


Scheme 18 Incorporation of the pyrrole unit in Ley's total synthesis of routiennocin.

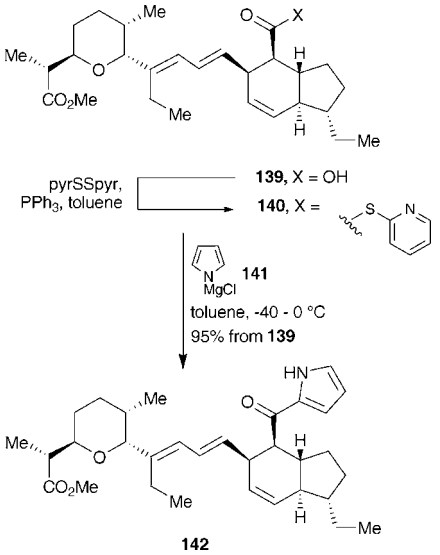
prepare **131**, which was elaborated to the natural product (Scheme 18).

2.3.6 Indanomycin. Indanomycin (X-14547 A, **138**, Scheme 19) is an antibiotic that was isolated at Hoffman La-Roche from a culture of *Streptomyces antibioticus*.[63] The ionophore antibiotic activity of indanomycin,[64] along with its unusual structure, have made it a popular target for synthesis. The molecule consists of a "left-hand" tetrahydropyran unit and a "right-hand" hydrindane bearing a ketopyrrole. The two portions of indanomycin are joined *via* a 1,3-diene. Ley,[65] Nicolaou[66] and Burke[67] have reported asymmetric total syntheses of indanomycin, and this section of the review briefly highlights the incorporation of the ketopyrrole unit.

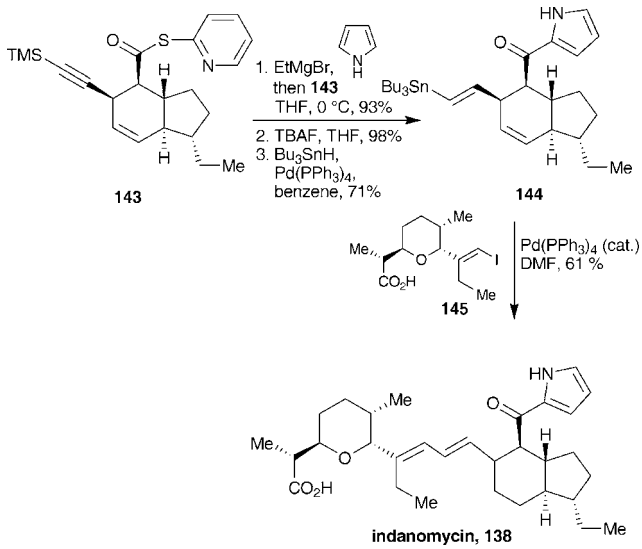
Ley's synthesis (Scheme 19) involved **134**, prepared using a lengthy route including an intramolecular Diels–Alder reaction.[65] The incorporation of the pyrrole component of the natural product was accomplished by treating SEM-protected pyrrole (**133**) with *n*-BuLi, followed by the addition of **134** to produce the advanced intermediate **135**. Conversion of this compound to the sulfone **136** was accomplished in two steps and set the stage for the critical Julia olefination with the



Scheme 19 Ley's total synthesis of indanomycin.



Scheme 20 Nicolaou's late-stage introduction of the pyrrole unit in the total synthesis of indanomycin.



Scheme 21 Final stages of Burke's total synthesis of indanomycin.

tetrahydropyran **137**. This reaction gave the required diene system that was then subjected to SEM deprotection and ester hydrolysis to provide indanomycin (**138**).

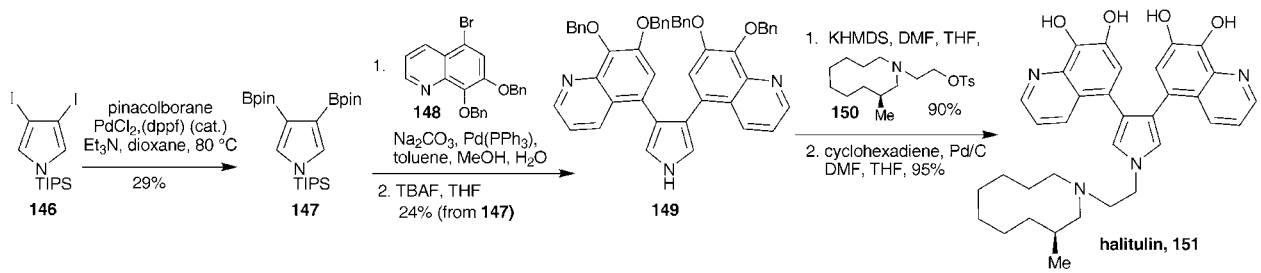
Nicolaou used a strategy very similar to Ley's in the preparation and fusion of the two halves of indanomycin.[66] One notable difference was the incorporation of the pyrrole unit towards the end of the total synthesis (Scheme 20). Initial experiments conducted in Nicolaou's group indicated that when the reagent derived from pyrrole and methylmagnesium chloride was added to γ-butyrolactone, N–C bond formation was favoured at room temperature, while at 100 °C, C–C bond formation dominated and gave the desired 2-ketopyrrole.[66] Nicolaou elected to use a different method to install the pyrrole on a late-stage intermediate. After experimentation using model substrates, it was found that conversion of acids to their 2-thiopyridyl ester derivatives and subsequent treatment with pyrrole magnesium chloride (**141**) gave the required 2-ketopyrrole under very mild conditions.[66,68] Thus, the acid **139** was converted to its 2-thiopyridyl ester derivative (**140**) to then create indanomycin methyl ester (**142**, Scheme 20).

Burke's total synthesis of indanomycin[67] employed Nicolaou's methodology[68] for the formation of the 2-ketopyrrole **144** (Scheme 21). With the right-hand hydrindane portion almost fully assembled, cleavage of the TMS group and then palladium-mediated hydrostannylation of the alkyne gave the vinylstannane **144**. This reaction set the stage for a Stille coupling to join the two halves of the natural product. It is noteworthy that in this synthesis of indanomycin the carboxylic acid functionality did not require masking for the palladium-mediated final coupling step.

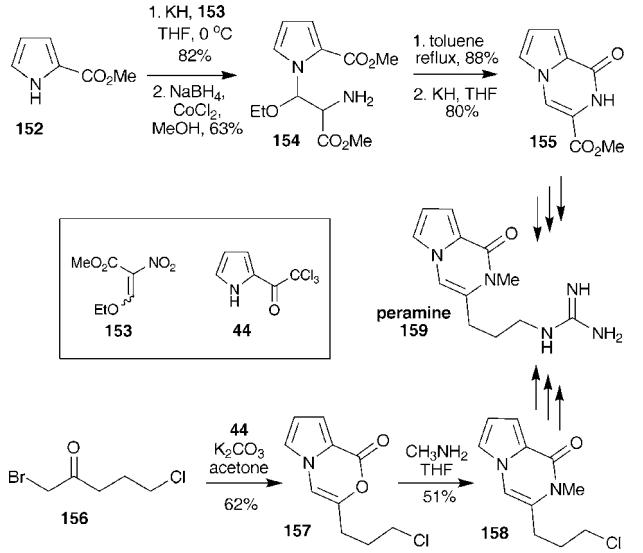
2.3.7 Halitulin. Halitulin (**151**, Scheme 22) was isolated from the South African marine sponge *Haliclona tulearensis*.[69] The cytotoxicity of halitulin, and its unusual structure of a pyrrole attached to two dihydroxyquinoline groups, prompted Banwell to complete a total synthesis.[70,71] TIPS-protected 3,4-diiodopyrrole[72] (**146**) was converted to **147** upon treatment with two equivalents of pinacolborane in the presence of a palladium catalyst. Crude **147** was used in a Suzuki coupling with the bromoquinoline **148**, and subsequent cleavage of the TIPS moiety gave the pyrrole **149**. *N*-Alkylation of this compound with **150** was followed by transfer hydrogenation to provide the natural product.[71] This synthesis again illustrates the potential of the pyrrole unit to undergo functionalisation *via* palladium-mediated chemistry.

2.4 Premade pyrrole, fused pyrrolic moiety in natural product, achiral

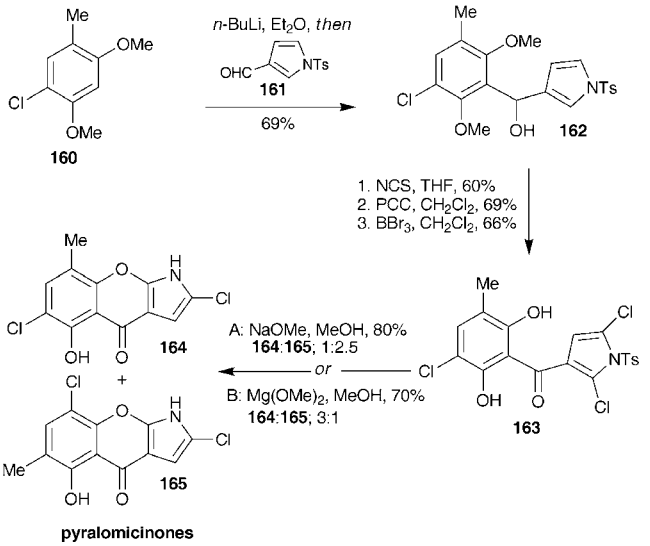
2.4.1 Peramine. Peramine (**159**, Scheme 23) was isolated from *Acremoium loliae*[73,74] and it exhibits insect antifeedant



Scheme 22 Banwell's total synthesis of halitulin.



Scheme 23 First synthesis of peramine by Brimble (top), which was shortly followed by Dumas' synthesis (bottom).

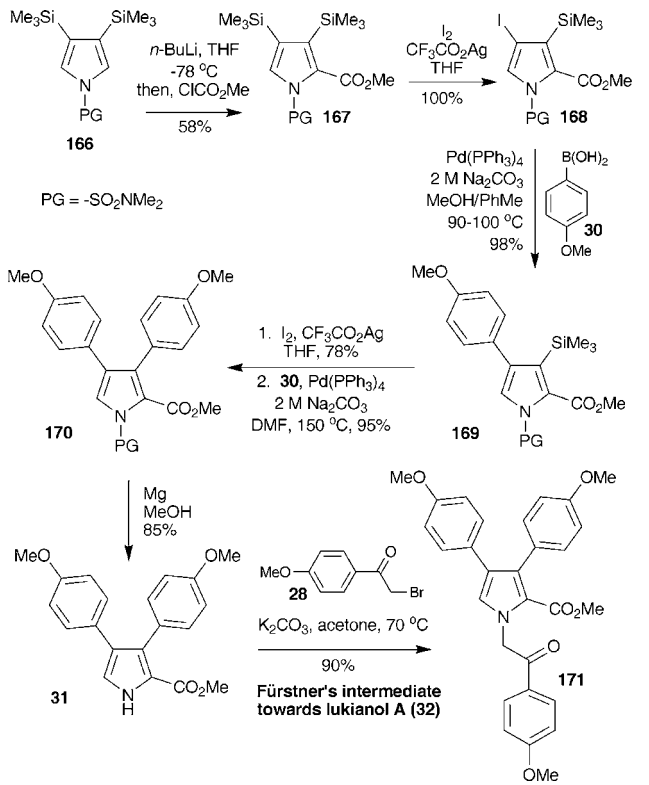


Scheme 24 Kelly's preparation of the pyralomicinones.

activity. The unusual 1-oxo-2,3-disubstituted-pyrrolo[1,2-*a*]pyrazine ring system of this natural product prompted Brimble to complete the first total synthesis.[75,76] Aza-Michael addition of the potassium salt of pyrrole **152** to the nitroalkene **153** with ensuing reduction of the nitro group with sodium borohydride and cobalt chloride produced the amine **154**. Heating in toluene induced cyclisation *via* amide formation, and subjection to base prompted elimination of the ethoxy group to form the heterocyclic core (**155**) of the natural product. Elaboration *via* side chain elongation and guanidine installation completed the synthesis of peramine. Shortly after, Dumas[77] introduced the pyrrole unit *via* *N*-alkylation of 2-(trichloroacetyl)pyrrole (**44**) with 1-bromo-5-chloro-2-pentanone (**156**). The trichloroacetyl group was sufficiently electrophilic to undergo lactonisation, thus leading directly to the bicycle **157**. Treatment with methylamine, yielded **158**, a viable substrate for guanidine installation and completion of the total synthesis.

2.4.2 Pyralomicinones. Pyralomicinones (**164** and **165**, Scheme 24) are the aglycons of the pyralomicin antibiotics, unique heterocyclic natural products isolated from the microorganism *Microtetraspora spiralis*.[78,79] Kelly's preparation[80] of these isomeric natural products began with the lithiation of the arene **160** and addition of the protected pyrrole-3-carbaldehyde (**161**) to give **162**. A three-step sequence resulted in chlorination of the pyrrole, oxidation of the secondary alcohol and cleavage of the methyl ethers to give **163**. Treatment of this compound with various metal alkoxides in methanol prompted nucleophilic aromatic substitution to give the pyralomicinones **164** and **165**. The choice of metal alkoxide was significant, as using $Mg(OMe)_2$ in place of sodium methoxide led to a reversal in the modest regioselectivity.[80]

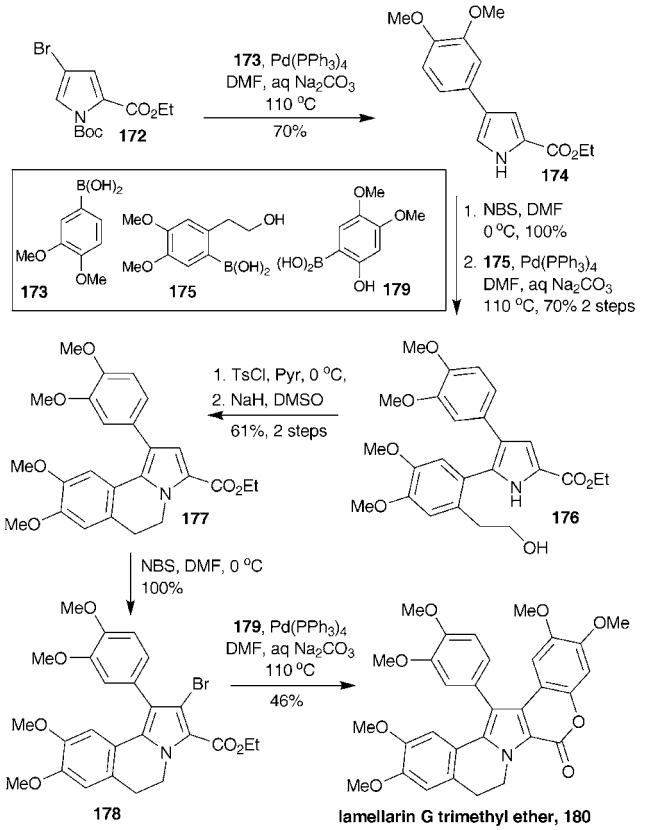
2.4.3 Lukianol A. A formal synthesis of lukianol A (**32**, Scheme 6) was completed by Wong,[81] starting with the *N*-protected 3,4-di(trimethylsilyl)pyrrole **166** (Scheme 25). A series of trimethylsilyl–iodine exchanges and subsequent Suzuki



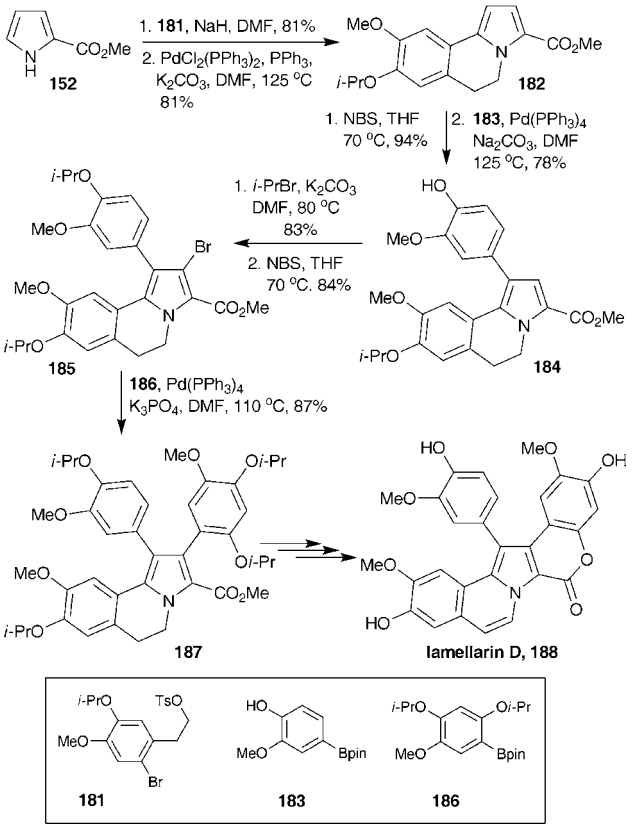
Scheme 25 Formal synthesis of lukianol A by Wong that converges with Fürstner's intermediate.

couplings with **30** gave **170**, which was then deprotected and *N*-alkylated to form **171**, an intermediate in Fürstner's route to lukianol A (Scheme 80).[19]

2.4.4 Lamellarins. Handy's synthesis of lamellarin G trimethyl ether (**180**, Scheme 26)[82] begins with the pyrrole **172** and features three iterative Suzuki cross-couplings with three different boronic acids (**173**, **175** and **179**), as well as an



Scheme 26 Handy's synthesis of lamellarin G trimethyl ether.

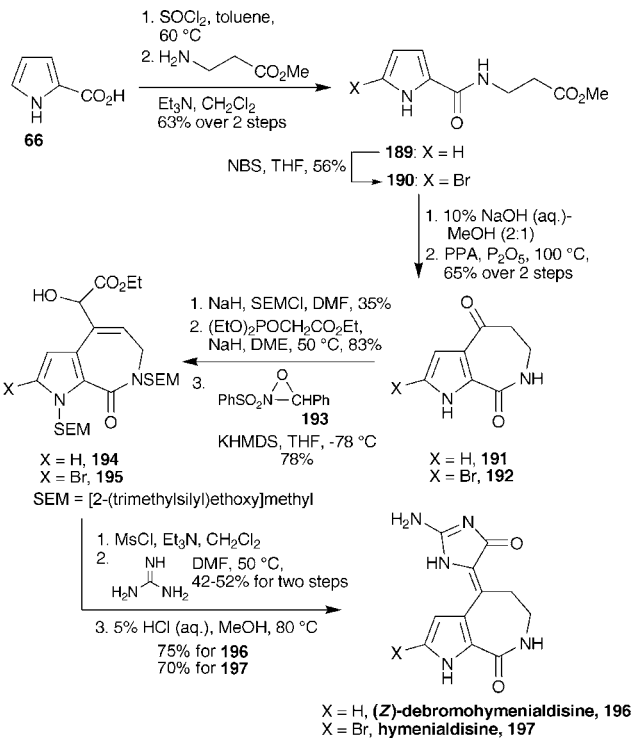


Scheme 27 Modular synthesis of lamellarin D by Alvarez.

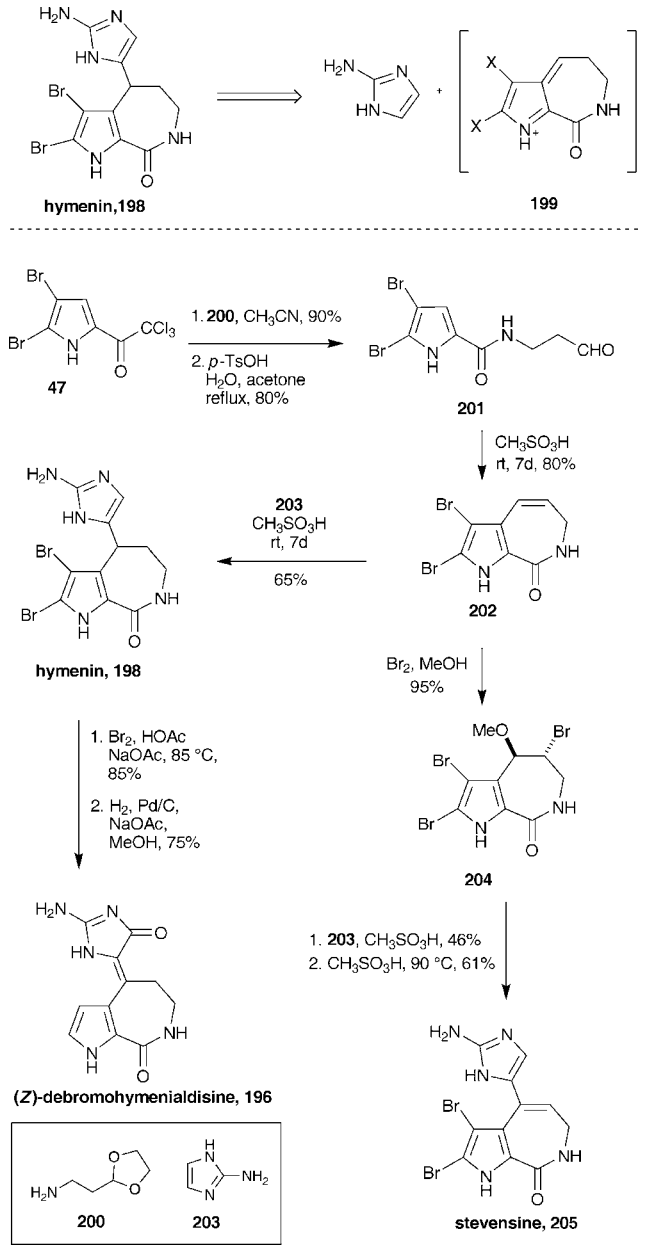
intramolecular alkylation and lactonisation to form both fused rings of the natural product.

The synthesis of lamellarin D (**188**) by Alvarez[83] uses similar disconnections to Handy's route[82] to lamellarin G trimethyl ether (**180**, Scheme 26), applied in a modified order (Scheme 27). The main difference between the two strategies is that the Alvarez synthesis introduces the aromatic rings with the oxygen substituents differentiated (either –OMe *vs.* –OH, or –OMe *vs.* –O*i*-Pr), a strategy which allows for the chemoselective unmasking of the phenols of the natural product.

2.4.5 Hymenin, stevensine, hymenialdisine and debromohymenialdisine. The tricyclic natural products (*Z*)-debromohymenialdisine (**196**), hymenialdisine (**197**),[84] hymenin (**198**)[85] and stevensine (**205**)[86] were isolated from various marine sponges (Scheme 28 and Scheme 29).[87] These structures are strongly reminiscent of oroidin-type alkaloids envisaged to have undergone cyclisation at the 3-position of the pyrrole. The first total syntheses of hymenialdisine and (*Z*)-debromohymenialdisine were accomplished by Annoura.[88] Pyrrole-2-carboxylic acid (**66**) was coupled with the methyl ester of β-alanine to give the pyrrole **189** (Scheme 28). Regioselective bromination at the 5-position of the pyrrole gave **190**. Cyclisation of either **189** or **190** was achieved *via* ester hydrolysis and then treatment with polyphosphoric acid (PPA) and phosphorous pentoxide. *N*-Protection of the resulting compounds **191** and **192** was followed by Horner–Wadsworth–Emmons homologation and regioselective oxidation with 2-benzenesulfonyl-3-phenyloxaziridine (**193**) to give the alcohols **194** and **195**, respectively. Conversion of these



Scheme 28 Annoura's total synthesis of hymenialdisine and debromohymenialdisine.



Scheme 29 Horne's synthesis of hymenin, stevensine and (*Z*)-debromohymenialdisine.

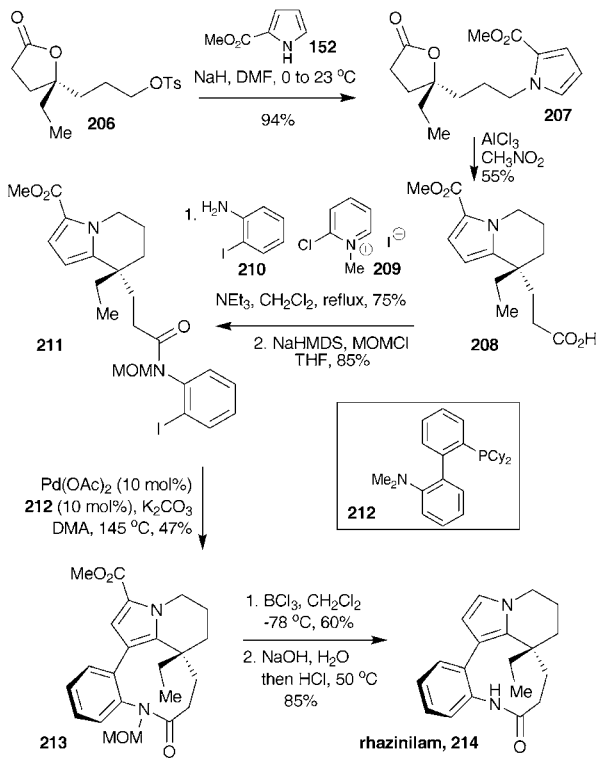
substrates to their mesylates and treatment with guanidine followed by SEM deprotection gave the natural products.

Horne reported the syntheses of (*Z*)-debromohymenialdisine (**196**),[89] hymenialdisine (**197**), hymenin (**198**) and stevensine (**205**), and followed the initial report with a gram-scale preparation of hymenin and (*Z*)-debromohymenialdisine[90] (Scheme 29). The aldehyde **201** was readily prepared from 4,5-dibromo-2-(trichloroacetyl)pyrrole (**47**) and the amino acetal **200**. Under strongly acidic conditions, the bicyclic pyrrole **202** was formed in good yield. In the presence of methanesulfonic acid the azafulvenium cation of **202** was formed and the addition of 2-aminoimidazole (**203**) provided hymenin (**198**).[89] Stevensine (**205**) was also accessed through the bicycle **202** *via* formation of **204**. Treatment with strong acid in the presence of 2-aminoimidazole (**203**) gave the substitution product, which was converted to stevensine (**205**) *via* elimination.[89] Later, hymenin was oxidised using bromine in the presence of sodium acetate and acetic acid, thus giving (*Z*)-debromohymenialdisine (**196**) after hydrogenation.[90]

2.5 Premade pyrrole, fused pyrrolic moiety in natural product, racemic syntheses

2.5.1 Hymenin. As summarised above (Scheme 29), Horne reported the synthesis of hymenin (**198**)[89] in racemic form, both on small and gram-scale.[90]

2.5.2 Rhazinilam, rhazinal and rhazinicine. The unique structural features of rhazinilam (**214**, Scheme 30), *i.e.*, biaryl axis, 9-membered macrocycle and quaternary center fused to a pyrrole, render it an attractive target for the advent of new methodologies. Although the synthetic challenge alone could be responsible for the substantial body of work directed towards this molecule, its anticancer properties through effects on tubulin polymerisation further fuel the attractiveness of this target. The synthesis of rhazinilam (**214**) by Trauner[91] began in a manner similar to that of Smith (Scheme 85)[92] in that the tosyl lactone **206** was coupled with the anion of the pyrrole **152**, and a subsequent Friedel–Crafts reaction was used to produce the quaternary center and the piperidine ring of **208** (Scheme 30). Amide bond formation between iodoaniline (**210**) and the carboxylic acid moiety of **208** using Mukaiyama's reagent (**209**) produced the direct-coupling substrate **211**, after MOM-protection. Treatment of **211** with $Pd(OAc)_2$ and the ligand **212** allowed for the nucleophilic pyrrole to intercept the Pd(II) center resulting

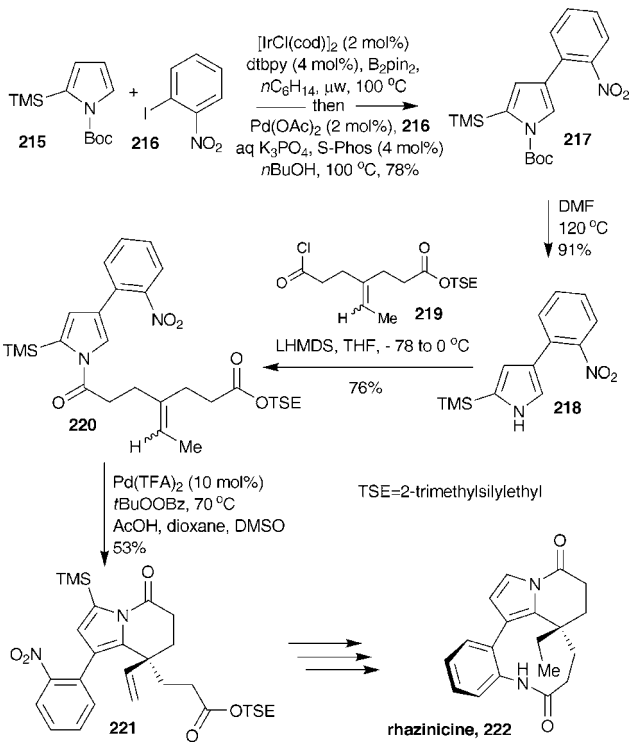


Scheme 30 Trauner's synthesis of rhazinilam utilising a direct-coupling as a key step.

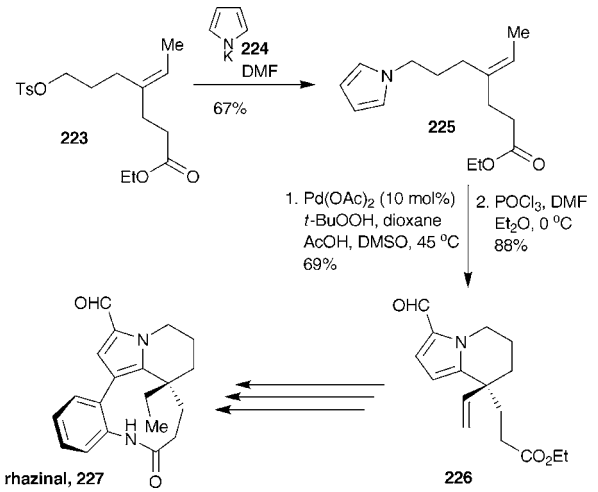
from oxidative addition into the C–I bond. Reductive elimination forged the key pyrrole–aryl bond, and **213** was then converted to rhazinilam *via* a series of deprotections.

As has been observed throughout this review, transition metal catalyzed processes have the ability to enhance the efficiency of total synthesis, as they allow for disconnections that were not previously imaginable. Further increasing the power of this concept, C–H functionalisation eliminates the necessity of pre-functionalising one (or both) of the coupling partners. An excellent example of the utilisation of this strategy was reported by Gaunt for the total synthesis of rhazinicine **222** (Scheme 31).[93] The biaryl **217** was formed by the one-pot, regioselective borylation of the pyrrole **215** (without prior halogenation) and subsequent Suzuki cross-coupling with 2-iodonitrobenzene (**216**). Acylation of the anion of **218** with the acid chloride **219** gave the key oxidative-Heck substrate **220**. Treatment of this compound with $Pd(TFA)_2$ and *t*-BuOOBz, as the oxidant, invoked a Heck reaction to yield **221**, again without prior functionalisation of the pyrrole. This key tetrahydroindolizidine core was further elaborated to complete the first total synthesis of rhazinicine.

Trauner also utilised an oxidative Heck coupling strategy in the context of a total synthesis of rhazinal (**227**, Scheme 32).[94] Displacement of the tosylate of **223** by the anion of pyrrole (**224**) yielded the substrate **225** which, when treated with $Pd(OAc)_2$ and an oxidant (*t*-BuOOH), underwent cyclisation to give the tetrahydroindolizidine **226**. To complete the synthesis of rhazinal, a strategy (direct pyrrole–iodoarene coupling) similar to that used in Trauner's synthesis of rhazinilam was employed (see Scheme 30).

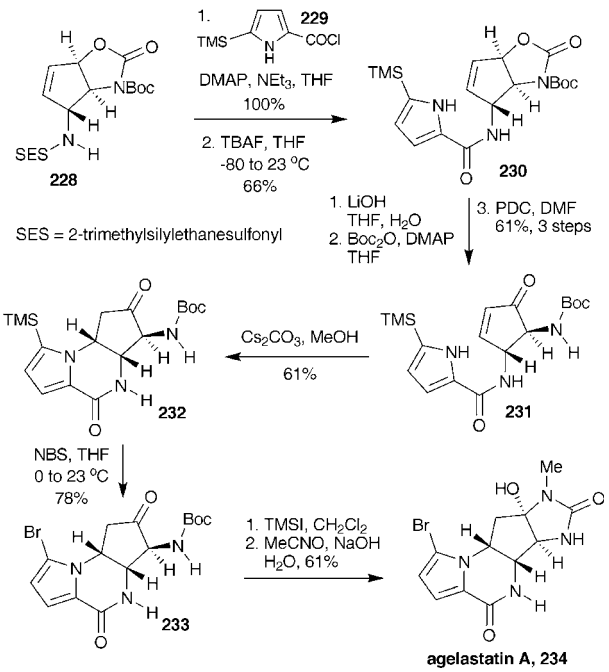


Scheme 31 The use of C–H functionalisation and an oxidative Heck reaction in the total synthesis of rhazinicine by Gaunt.



Scheme 32 Synthesis of rhazinal by Trauner using an oxidative Heck reaction to form the tetrahydroindolizidine ring system.

2.5.3 Agelastatin. The synthesis of the highly substituted cyclopentane core within the agelastatins has acted as the stage for the display of numerous synthetic methodologies. Although many varied and creative strategies have been utilised to access this core, the majority of the total syntheses utilise similar bond formations for the incorporation of the pyrrole and alkylation of its nitrogen atom to form the requisite six-membered ring. Weinreb (Scheme 33)[95] set the precedence, and introduced the pyrrole **229** onto the already highly functionalised cyclopentene ring (**228**). Unmasking of the alcohol functionality and subsequent oxidation with PDC yielded the enone **231** which, when treated with caesium carbonate, underwent an aza-Michael addition to yield the tricyclic core **232** *en route* to agelastatin A (**234**).



Scheme 33 The first synthesis of agelastatin A by Weinreb.

2.5.4 Phakellin, phakellstatin, isophakellin and dibromoagelaspongin. The phakellins and related compounds (Fig. 1) constitute another class of natural products that has seen substantial utilisation as a showcase for new synthetic methodologies. Most of the total syntheses can be divided into two general strategies: (i) biomimetic cyclisations; and (ii) functionalisation of the tricyclic pyrrole-containing core by appendage of the urea or guanidine motifs.

The first synthesis of dibromophakellin (**237**, Scheme 34) by Büchi, although racemic, set a high standard for efficiency in the preparation of members of this class of compound.[96] Based on the biomimetic cyclisation of dihydrooroidin (**48**) (prepared by coupling the amine **46** and the trichloroacetylpyrrole **47**), compound **48** was treated with bromine in acetic acid to produce an insoluble material that was not fully characterised (no yield reported). However, upon treatment of this solid with potassium *tert*-butoxide, dibromophakellin was recovered in quantitative yield.

Ten years later, Horne applied Büchi's cyclisation conditions to the total synthesis of the closely related dibromophakellstatin (**235**) (Scheme 35, top), and found that slight differences in the

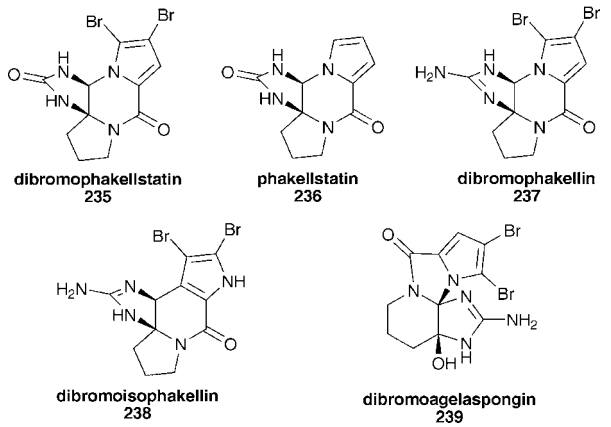
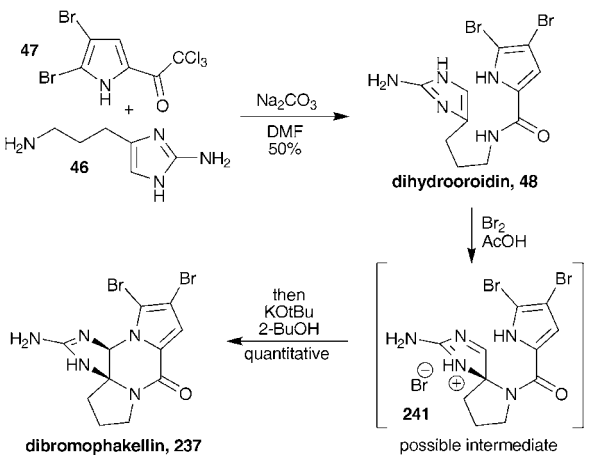
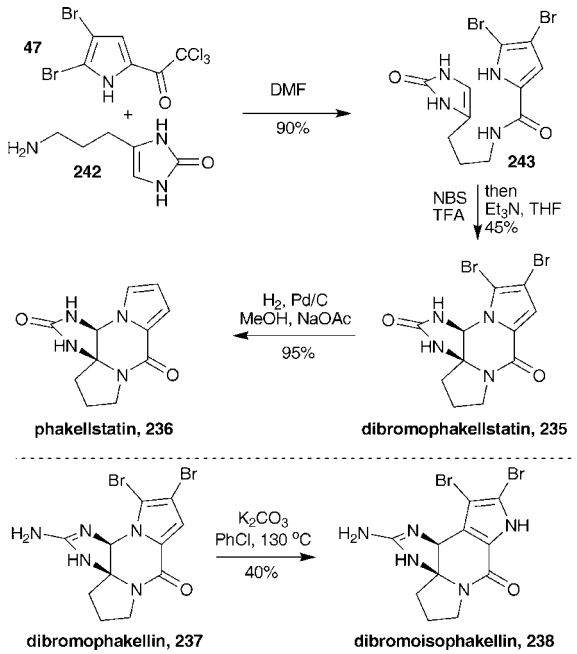


Fig. 1 Dibromophakellin and structurally related pyrrole-imidazole alkaloids.



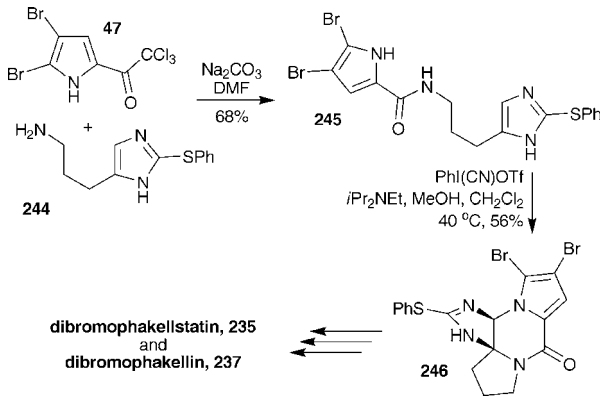
Scheme 34 Biomimetic synthesis of dibromophakellin completed by Büchi.



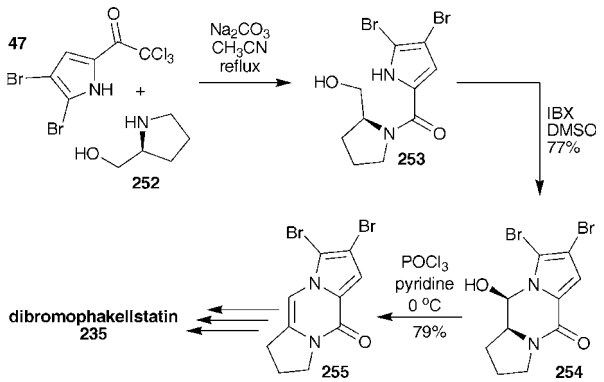
Scheme 35 Synthesis of dibromophakellstatin, phakellstatin and dibromoisophakellin by Horne.

structure of the substrate (**243** *vs.* **48**, Scheme 34) required minor modification of the reaction conditions.[97] Indeed, the strength of the brominating source was attenuated (NBS *vs.* Br) and a stronger acid was used (TFA *vs.* AcOH). Furthermore, instead of isolating the unstable intermediate, the crude reaction mixture was immediately treated with triethylamine in THF. This procedure gave dibromophakellstatin (**235**), in 45% yield, which was debrominated *via* hydrogenation to prepare phakellstatin (**236**). In the same publication, it was reported that dibromophakellin (**237**) could be converted to dibromoisophakellin (**238**) by heating **237** in the presence of base, constituting the first synthesis of this natural product (Scheme 35, bottom). Although the mechanism of this transformation was not discussed in the original report, it may be proposed that deprotonation of the guanidine leads to formation of the corresponding imine and rupture of the carbon–pyrrole nitrogen bond. Recombination at the 3-position of the pyrrole, with retention of configuration, would lead to dibromophakellin (**238**). It was reported that residual starting material remained, indicating that a thermodynamic ratio may have been reached.

Feldman has had significant success synthesising the phakellins and phakellstatins, contributing an alternative biomimetic cyclisation strategy to those outlined by Büchi and Horne above. Feldman used Pummerer chemistry to activate the imidazole of **245**, although the use of the sulfoxide equivalent of **245** gave only intractable material (Scheme 36).[98,99] Treatment of **245** with the somewhat exotic oxidant PhI(CN)OTf (Stang's reagent) gave a good yield of the tetracycle **246**. Unlike the procedures reported by Büchi and Horne (Scheme 34 and Scheme 35, respectively), the Pummerer-induced cyclisation did not require treatment with base to coax the pyrrole into attacking the electrophilic imidazole. Compound **246** was converted to dibromophakellstatin (**235**) and dibromophakellin (**237**) using straightforward chemistry.



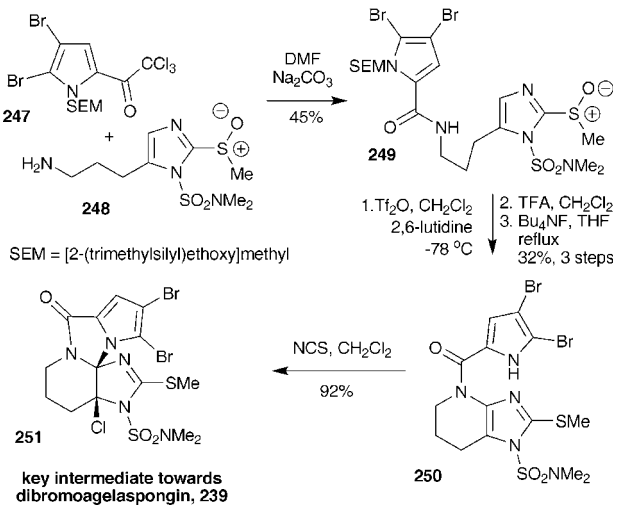
Scheme 36 Feldman's synthesis of dibromophakellstatin and dibromophakellin.



Scheme 38 Preparation of key intermediate by Lindel used for the urea installation of dibromophakellstatin; Austin prepared the debrominated equivalent using similar chemistry.

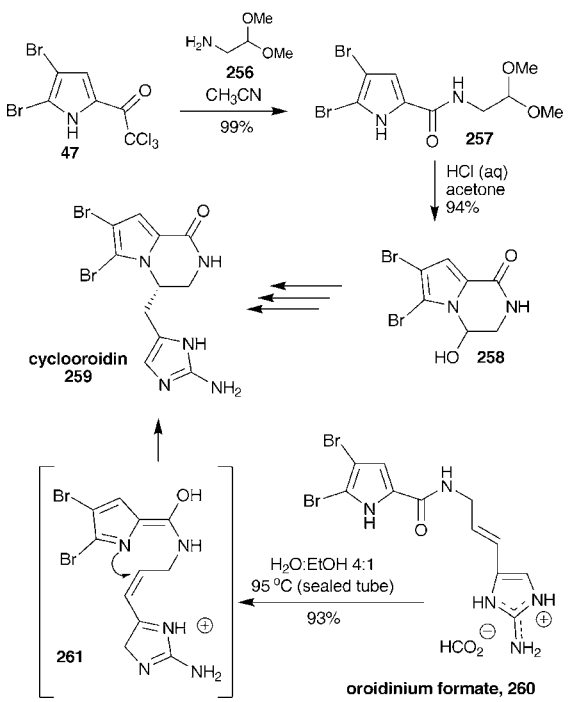
Feldman also reported the first, and to date only, synthesis of dibromoagelaspongin (**239**, Fig. 1) using a two-stage cyclisation strategy, the first stage of which again involved a Pummerer-type rearrangement.[100] Unlike Feldman's syntheses of dibromophakellin and dibromophakellstatin (Scheme 36) where the first step in the cyclisation cascade involved interception of the activated imidazole to form the spiro 5-membered ring, in this case treatment of the sulfoxide **249** (Scheme 37) with triflic anhydride led to formation of the fused six-membered ring of **250** (after functional group manipulations). This outcome was attributed to the substituent on the imidazole nitrogen atom ($-SO_2NMe_2$ of **249** *vs.* –H of **245**) and the pyrrole nitrogen atom protecting group (–SEM of **249** *vs.* –H of **245**). Subsequent treatment of **250** with NCS induced the second cyclisation to form the tetracyclic core **251** of dibromoagelaspongin, which was converted into the natural product **239** in five steps.

As mentioned above, a common alternative to the biomimetic cyclisation strategies towards the phakellin family is based on the functionalisation of the unsaturated tricyclic core (or non-brominated variants) through the installation of the urea or guanidine functionalities. The key precursor **255** was prepared by Lindel[101] *via* the coupling of 4,5-dibromo-2-trichloroacetylpyrrole (**47**) and prolinol (**252**) to form **253** (Scheme 38). Oxidation of the alcohol gave the hemi-aminal (**254**) with a high degree of diastereoselectivity, and treatment with $POCl_3$ provided the unsaturation of **255** that is necessary for functionalisation. Austin[102] used a similar strategy to prepare the debrominated equivalent of **255** (starting with **44**), which was also advanced to dibromophakellstatin (**235**).



Scheme 37 Synthesis of dibromoagelaspongin by Feldman utilising a Pummerer-type cyclisation.

2.5.5 Cyclooroidin. Cyclooroidin (**259**, Scheme 39) represents one of the simplest members of the fused pyrrole-imidazole alkaloids. The first total synthesis by Papeo[103] began with the coupling of aminoacetaldehyde dimethylacetal (**256**) and 4,5-dibromo-2-trichloroacetylpyrrole (**47**) (Scheme 39, top). Unmasking of the aldehyde induced formation of the



Scheme 39 First synthesis of cyclooroidin by Papeo (top) and biomimetic synthesis by Lindel (bottom).

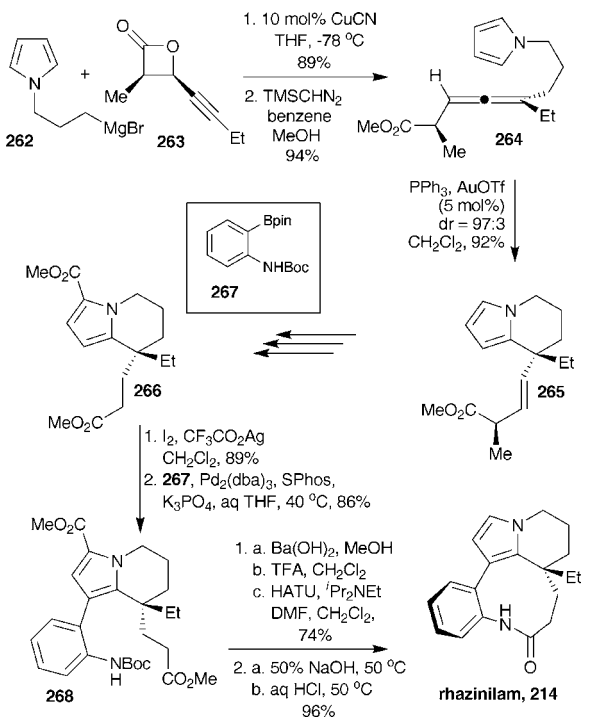
hemi-aminal **258**, a compound that required six additional steps to install the aminoimidazole and render the natural product.

One year later, Lindel reported a total synthesis of cyclooroidin based on a biomimetic cyclisation of oroidin formate (Scheme 39, bottom).[104] In the process of studying the Diels–Alder reaction of oroidin with various dienophiles, it was found that if the dienophile was omitted, the oroidinium formate (**260**) underwent near-quantitative cyclisation to produce cyclooroidin (**259**), presumably proceeding through the azafulvenium tautomer **261**.

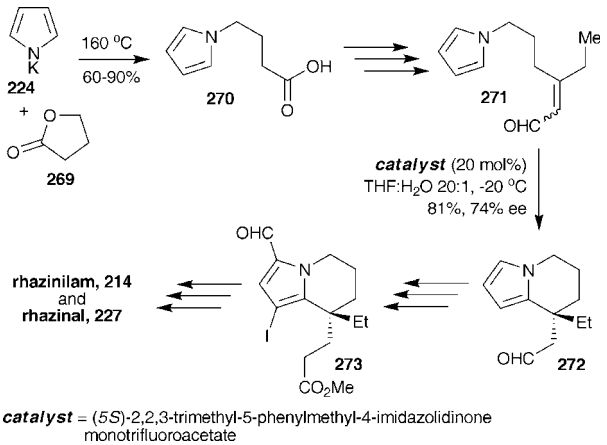
2.6 Premade pyrrole, fused pyrrolic moiety in natural product, asymmetric syntheses

2.6.1 Rhazinilam. Chiral allenes can serve as valuable synthetic building blocks, as the allene axial chirality can be transferred to the products that result from the addition of nucleophiles. *En route* to rhazinilam (**214**, Scheme 40), Nelson prepared the chiral allene **264** from the S_N2' addition of the cuprate derived from the pyrrole Grignard **262** to the chiral alkynyl lactone **263** (99% ee, 98% de).[105] Treatment of **264** with AuOTf/PPh_3 induced interception of the activated allene by the 2-position of the pyrrole to provide the fused tetrahydroindolizidine ring system of **265** with 94% de, demonstrating efficient transfer of allene chirality to the product. As was observed in the Sames rhazinilam synthesis (Scheme 95),[106,107] attenuating the reactivity of the pyrrole through ester installation allowed for regioselective iodination and Suzuki coupling of **266** with **267** to form the intermediate **268**, which was converted to the natural product through a series of simple functional group manipulations.

Banwell's syntheses of rhazinilam (**214**) and rhazinal (**227**) introduced the pyrrole in the first step *via* the opening of



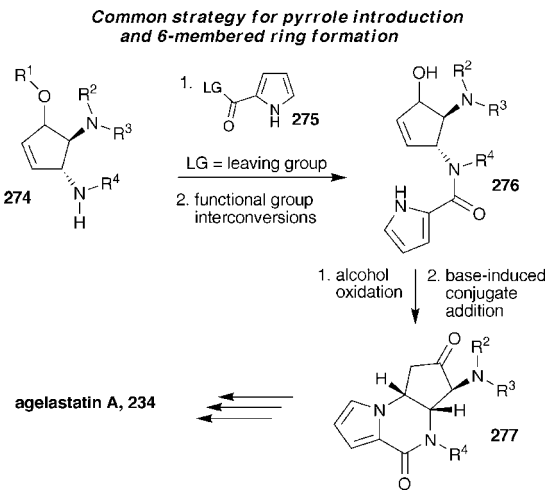
Scheme 40 Nelson's synthesis of rhazinilam utilising a pyrrole/chiral allene cyclisation.



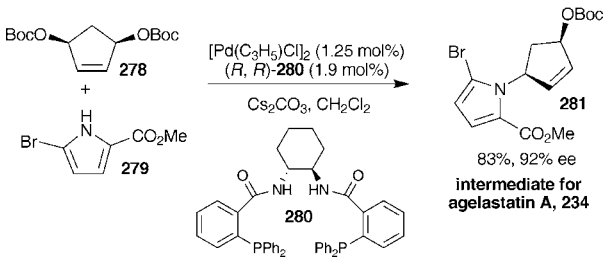
Scheme 41 Utilisation of an organocatalytic, asymmetric Michael addition in the total synthesis of rhazinilam and rhazinal by Banwell.

γ-butyrolactone (**269**) with the potassium salt of pyrrole (**224**) to yield **270** (Scheme 41).[108] Further elaboration produced **271**, the key substrate for the utilisation of an asymmetric Michael addition *en route* to rhazinilam. Treatment of **271** with MacMillian's first-generation organocatalyst induced cyclisation and gave the tetrahydroindolizidine **272** in 74% ee, and further examination of the catalyst structure and counterion did not offer an improvement in enantioselectivity. Compound **272** was then converted to **273**, a common intermediate for the synthesis of rhazinilam and rhazinal.

2.6.2 Agelastatin. Many of the reported syntheses of agelastatin A invoke a strategy similar to that of Weinreb for the incorporation of the pyrrole (Scheme 33).[95] Following pyrrole installation, generally an aza-Michael addition has been used to form the six-membered ring of the agelastatin skeleton. Although numerous creative methodologies have been developed for the preparation of the highly functionalised cyclopentane ring, given the nature of this review total syntheses[109–116] of the agelastatins that do not involve chemistry of the pyrrole that differs greatly from that in Scheme 42 will not be discussed further.



Scheme 42 Common strategy for pyrrole introduction and aza-Michael addition in the synthesis of the agelastatins.

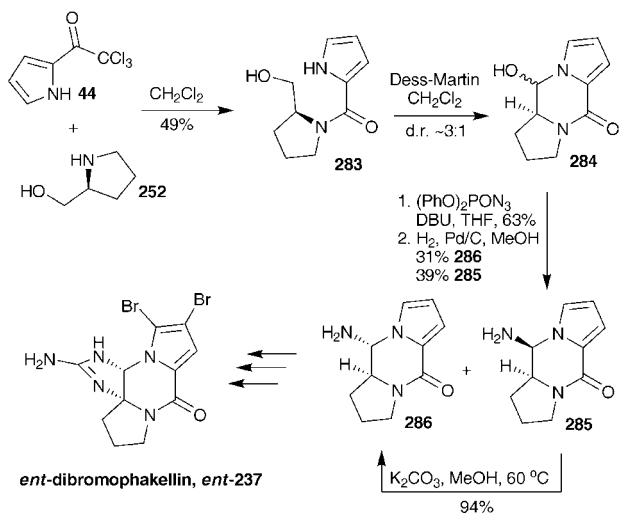


Scheme 43 Early-stage pyrrole incorporation by Trost towards the synthesis of agelastatin A.

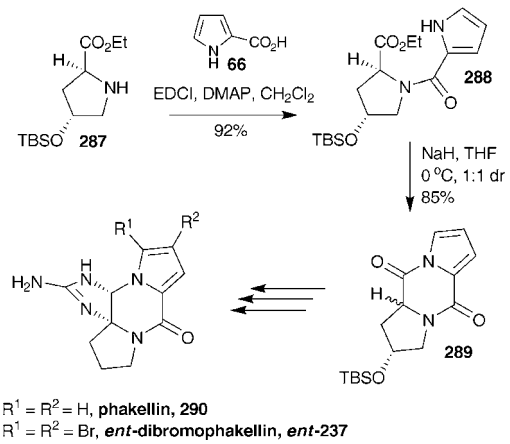
In contrast to the widely used strategy for agelastatin pyrrole incorporation outlined above (Scheme 42), Trost installed the pyrrole in the first step *via* asymmetric allylic alkylation (AAA) utilising the pyrrole nitrogen atom as the nucleophile (Scheme 43),[117,118] akin to his strategy for the preparation of cyclooroidin and related compounds (Scheme 46).[119] Thus, reaction of the pyrrole **279** with the Boc-activated cyclopentene 1,4-diol (**278**) yielded **281** with 92% ee. This intermediate required only nine further manipulations to yield agelastatin A (**234**).

2.6.3 Dibromophakellin. Romo[120] reported an asymmetric synthesis of *ent*-dibromophakellin (*ent*-**237**, Scheme 44) using a derivative of an early intermediate (**284**) from the Lindel[101] racemic synthesis (**254**, Scheme 38). This is the same intermediate that Austin[102] used for the synthesis of phakellstatin (not depicted in Scheme 38). To prepare the racemic target, Austin removed the chiral center through dehydration of **284** but Romo used the asymmetry derived from the prolinol (**252**) to direct the diastereoselective azidation of the mixture of the hemi-aminals **284**. After azide reduction, the diastereomers **285** and **286** were separated, and **285** was converted into the desired **286** *via* treatment with base. Compound **286** was advanced to *ent*-dibromophakellin (Scheme 44).

Nagasawa completed an asymmetric synthesis of both phakellin (**290**, Scheme 45) and dibromophakellin (**237**) through the utilisation of a chiral proline derivative as a starting material.[121]



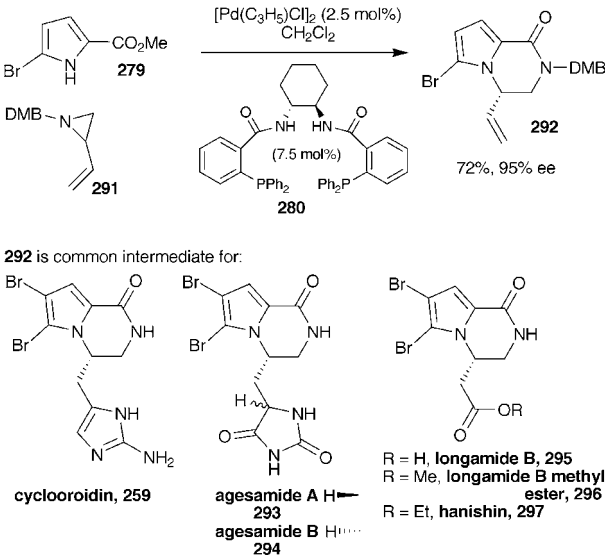
Scheme 44 Use of the chirality of the Lindel/Austin intermediate by Romo for the asymmetric total synthesis of dibromophakellin.



Scheme 45 Preparation of the Overman rearrangement substrate for the asymmetric synthesis of (dibromo)phakellin by Nagasawa.

Coupling pyrrole-2-carboxylic acid (**66**) and TBS-protected *trans*-4-hydroxy-L-proline (**287**) yielded the intermediate **288** which, upon treatment with sodium hydride, cyclised to the tricyclic core (**289**) of the phakellins with a pendant protected alcohol (Scheme 45). Nagasawa used this alcohol in a subsequent step to direct the stereochemistry of aminal formation courtesy of nitrogen introduction *via* an Overman rearrangement.

2.6.4 Longamide B, hanishin, cyclooroidin and agesamides A and B. Through the use of an Pd-catalyzed AAA reaction, Trost prepared a common intermediate that allowed access to longamide B (**295**) and its methyl ester (**296**), hanishin (**297**), cyclooroidin (**259**) and agesamide A (**293**) and B (**294**) (Scheme 46).[119] The bromopyrrole **279** was a competent nucleophile in the regioselective opening of the aziridine **291** under the influence of palladium and the chiral ligand **280**, to yield the pyrrolopiperazinone **292** after intramolecular cyclisation. Thus, the intermediate **292** served as the key precursor to the six



Scheme 46 Trost's utilisation of an asymmetric allylic alkylation reaction to synthesise six structurally related natural products.

natural products listed above. Trost used a similar AAA reaction for the enantioselective synthesis of agelastatin A (Scheme 43).[117,118]

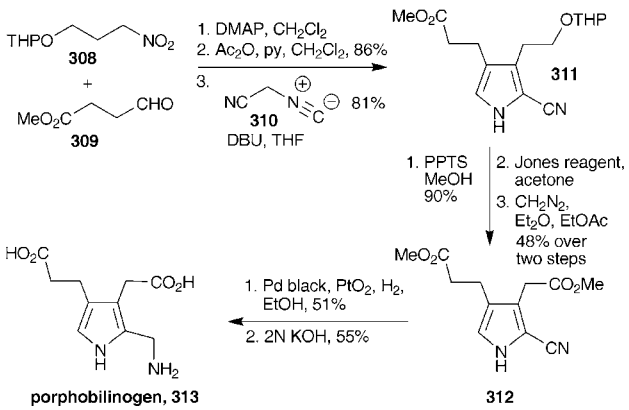
2.6.5 Dragmacidin F. Based on the successful synthesis of dragmacidin D (not depicted),[122] Stoltz targeted the structurally complex dragmacidin F (**307**, Scheme 47), which contains a bicyclic core fused to a trisubstituted pyrrole. The synthesis commenced with the acid **298** (derived from quinic acid) and, after formation of the corresponding Weinreb amide, addition of the lithiopyrrole **129** produced **299**.[123,124] Oxidative carbocyclisation, induced by palladium acetate, between the deactivated 3-position of the pyrrole and the alkene led to the bridged bicyclic system **300**. Subsequent reduction of the alkene and methylation of the alcohol gave **301**. Regioselective borylation at the 4-position (*via* the bromide) produced the cross-coupling substrate **304**. Treatment of **304** with **305** in the presence of $Pd(PPh_3)_4$ induced a halogen-selective Suzuki coupling that favoured reaction of the pyrazine bromo substituent. The skeleton (**306**) of dragmacidin F was thus prepared, with installation of the aminoimidazole and subsequent deprotection being all that was required to complete the total synthesis of this natural product.

3 Syntheses involving *en route* generation of the pyrrolic unit

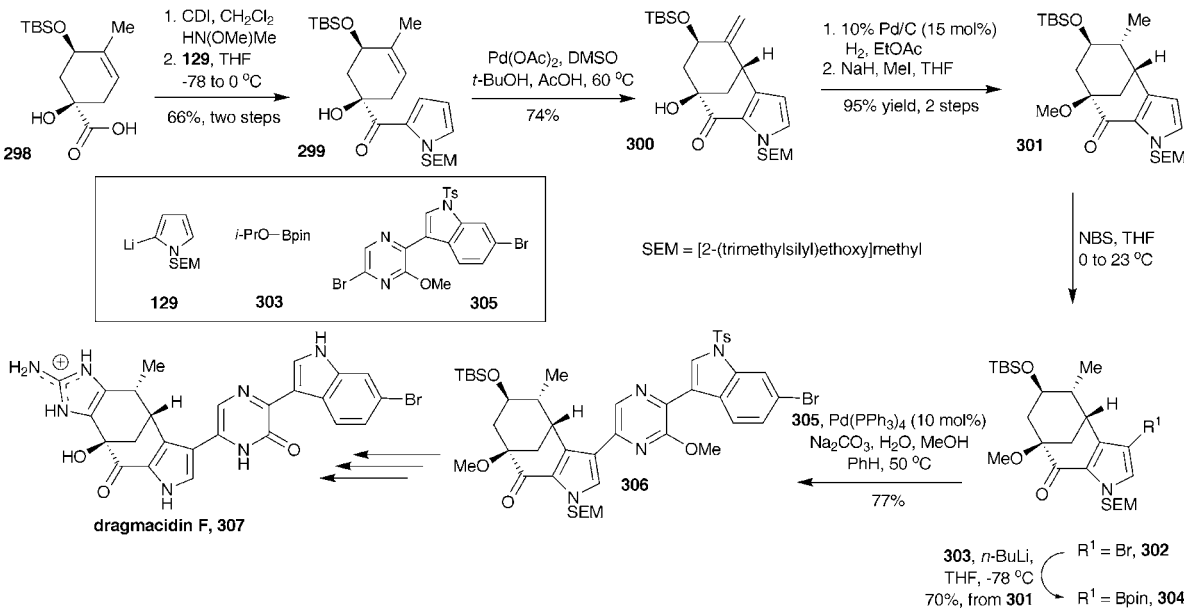
This section of the review details strategies that involve the generation of the pyrrolic moiety as a key step within the synthetic sequence. Although the distinction between "*en route*" and "premade" is inevitably hazy, we have used the term "*en route*" when significant functional and substituent complexity has been incorporated prior to formation of the heterocycle. Syntheses of natural products that incorporate a simple (unfused) pyrrole unit are presented first, followed by the more complex fused materials. Within each sub-section, syntheses of achiral natural products are detailed initially, followed by natural products exhibiting chirality as racemic syntheses and then as asymmetric variants, where examples permit.

3.1 *En route* pyrrole generation, simple pyrrolic moiety in natural product, achiral

3.1.1 Porphobilinogen. Porphobilinogen (**313**, Scheme 48) is a monopyrrolic natural product that is a building block in the biosynthesis of tetrapyrrolic natural products (*e.g.*, heme, porphyrins, vitamin B_{12}).[125,126] Physiologically, it is formed by the enzyme-mediated condensation of two molecules of 5-aminolevulinic acid. Adamczyk used cyanopyrroles in the synthesis of porphobilinogen.[127] The pyrrole core (**311**) of porphobilinogen was rapidly assembled using a Henry reaction, generation of a nitro alkene and subsequent Michael addition of the anion of isocyanoacetonitrile (Scheme 48), akin to the Barton–Zard protocol.[128] The total synthesis was furthered by removal of the THP group and conversion of the primary alcohol into the



Scheme 48 Adamczyk's total synthesis of porphobilinogen.

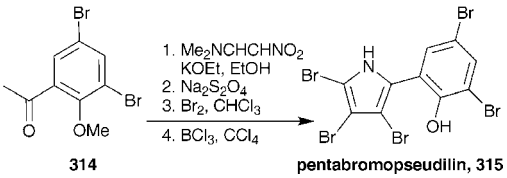


Scheme 47 Stoltz's synthesis of dragmacidin F.

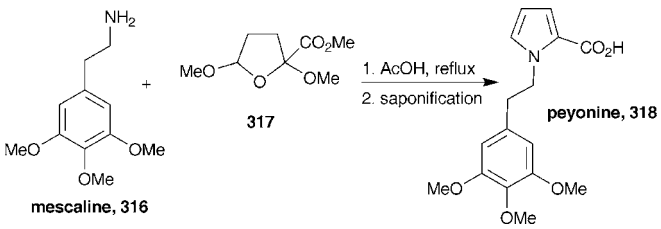
methyl ester **312**. Hydrogenation of the nitrile gave a lactam that was opened using KOH to give porphobilinogen (**313**).

3.1.2 Pentabromopseudilin. A nitroalkene was also used in the synthesis of pentabromopseudilin (**315**, Scheme 49), a marine natural product with antibacterial properties.[129] Condensation of 1-nitro-2-dimethylaminoethene and 3,5-dibromo-2-methoxyacetophenone (**314**) in the presence of base gave the corresponding *aci*-nitro salt that underwent reductive cyclisation to the pyrrole. Bromination and then demethylation gave the natural product. Yields were not stated in the original manuscript.

3.1.3 Peyonine. The structure of the *N*-substituted pyrrolecarboxylic acid peyonine (**318**, Scheme 50) was verified *via* Highet's synthesis.[130] Accordingly, mescaline (**316**) was reacted with methyl 2,5-dimethoxytetrahydro-2-furanoate (**317**), and subsequent saponification of the methyl ester gave the natural product in an unspecified yield.



Scheme 49 Synthesis of pentabromopseudilin by Hanessian and Kaltenbronn.



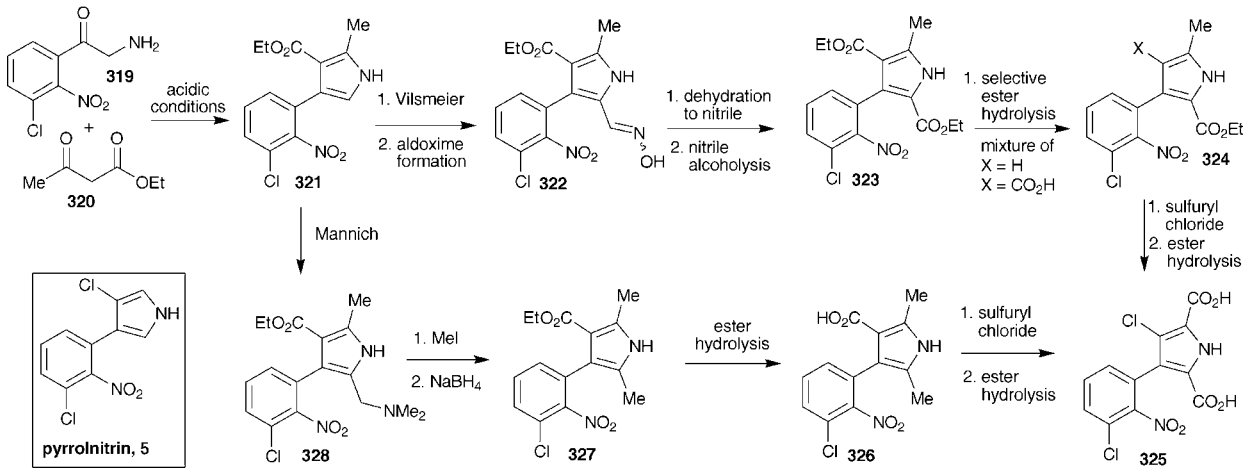
Scheme 50 Highet's synthesis of peyonine.

3.1.4 Pyrrolnitrin. In contrast to the pyrrolnitrin (**5**) synthesis reported by Pratt in 2009 (Scheme 1),[10] the 1966 account by Morimoto features more classical chemistry, and arrived at the natural product *via* two routes (Scheme 51).[131] Key to this early synthesis was the condensation of the aminoketone **319** and ethyl acetoacetate (**320**) to form the biaryl compound with the appropriately substituted benzene ring (**321**). The two strategies diverged at this point, and both routes offered regioselective installation of the 3-chloro substituent by the incorporation of removable blocking groups at the other positions of the pyrrole ring. These superfluous groups were then modified as necessary to provide the natural product. Yields were not provided.

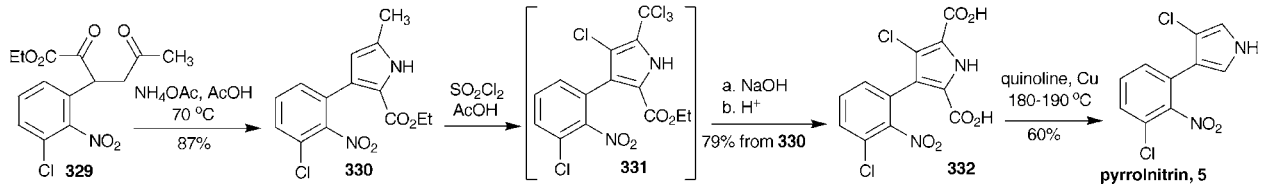
Six years after Morimoto's report of the synthesis of pyrrolnitrin (**5**) (Scheme 51),[131] Gosteli prepared the pyrrole **330** using the reaction of the 1,4-diketone **329** and ammonia (Scheme 52).[132] The substitution pattern thus produced left only the desired 4-position of the pyrrole available for chlorination, eliminating the additional steps required in the Morimoto synthesis to ensure regiospecificity. The conclusion of the synthesis was similar to above (conversion of the blocking groups to the acids, which were then decarboxylated).

3.1.5 Permethyl storniamide A. As will be observed in the following sections, Boger developed a strategy that allows facile access to the majority of members of the storniamide, ningalin, lukianol and lamellarin families. The transformation is based on the Diels–Alder reaction of the 1,2,4,5-tetrazine **333** and functionalised tolans bearing the correct substitution for the natural product in question. The synthesis of permethyl storniamide A[22] (**42**, Scheme 53) highlights this strategy, and the use of the same approach to synthesise natural products containing fused pyrroles is detailed in Scheme 77. Reaction of the tetrazine **333** and the symmetrical tolan **334** led to the diazene **335** (Scheme 53), which after reductive ring contraction provided the pyrrole intermediate **41**. Alkylation of **41** with the alkyl bromide **336** yielded **337**, which was elaborated to permethyl storniamide A (**42**).

Iwao's formal synthesis of permethyl storniamide A (**42**)[133] converged with the key intermediate **337** prepared by Boger (Scheme 53).[22] Bis-alkylation of the amine **338** with two



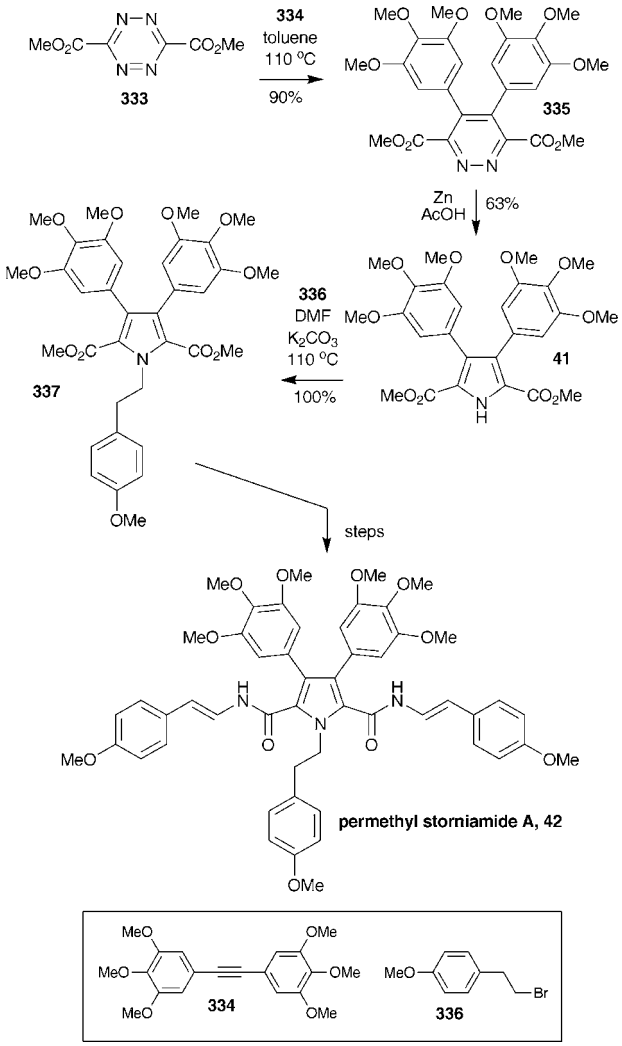
Scheme 51 Morimoto's classical 1966 synthesis of pyrrolnitrin.



Scheme 52 Gosteli's 1972 pyrrolnitrin synthesis.

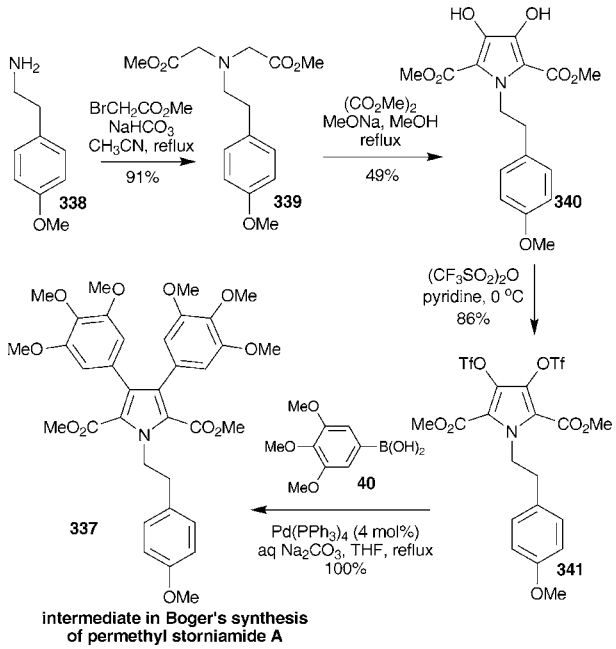
equivalents of methyl bromoacetate yielded the tertiary amine **339**, which was condensed with methyl oxalate to form the 3,4-dihydroxypyrrole-2,5-dicarboxylate **340** *via* a Hinsberg-type pyrrole synthesis (Scheme 54). Conversion of **340** to the bis-triflate **341** allowed the installation of both substituted phenyl rings, *via* Suzuki reaction with the boronic acid **40**, to provide Boger's intermediate **337**.

Gupton completed a formal synthesis of permethyl storniamide A[134] (**42**) that converged with Boger's tetrasubstituted pyrrole intermediate **41** (Scheme 53).[22] Reaction of ethyl glycine (**343**) with the vinylogous imine salt **342** in the presence of base



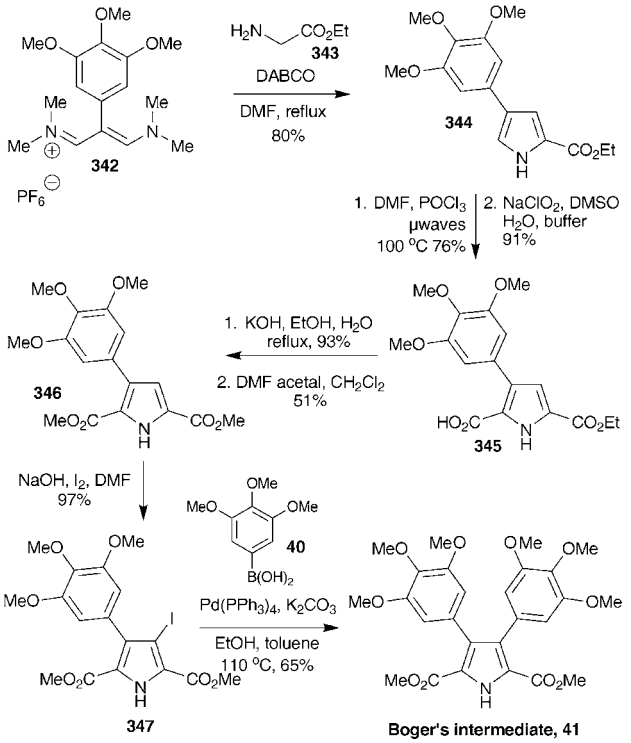
Scheme 53 The first synthesis of permethyl storniamide A by Boger.

led to the disubstituted pyrrole **344** (Scheme 55). Installation of the bis-methyl esters contained within Boger's intermediate required a rather circuitous route consisting of Vilsmeier–Hack formylation, oxidation to the acid with sodium chlorite, ethyl ester hydrolysis, and re-esterificaiton of the bis-acid to the bis-methyl ester **346**. With the trisubstituted pyrrole in hand, all that was necessary was iodination and Suzuki coupling with **40** to converge with Boger's intermediate **41**.

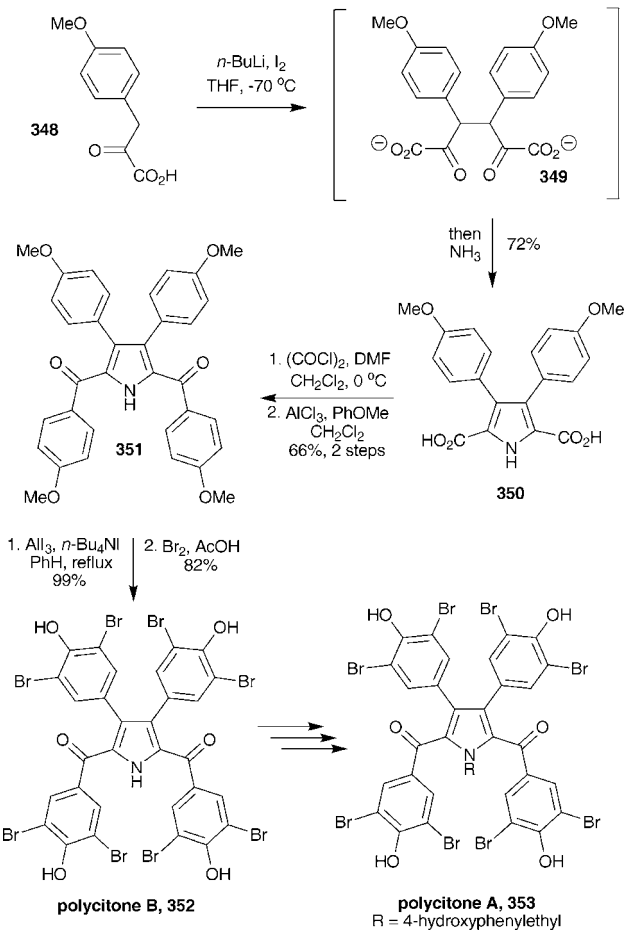


Scheme 54 Iwao's formal synthesis of permethyl storniamide A.

3.1.6 Polycitones A and B. Steglich's synthesis[135] of polycitones A (**353**) and B (**352**) is based on a possible biosynthetic hypothesis for this family of compounds. Oxidative coupling of the dianion of the substituted phenylpyruvic acid **348** gave the intermediate 1,4-dicarbonyl species (**349**), which was quenched with ammonia to form the tetrasubstituted pyrrole **350** in a single operation (Scheme 56). After conversion to the bis-acid chloride, Friedel–Crafts acylation with anisole, catalyzed by $AlCl_3$, produced **351**, a key intermediate in subsequent formal syntheses of these natural products by other groups. Phenol liberation, *via* treatment with AlI_3, and subsequent bromination of the four electron-rich aromatic rings produced polycitone B (**352**). Polycitone B was converted to polycitone A (**353**) *via* a three-step sequence, which involved protection of the phenols *via* acetylation, alkylation of the pyrrole nitrogen atom, and deprotection of



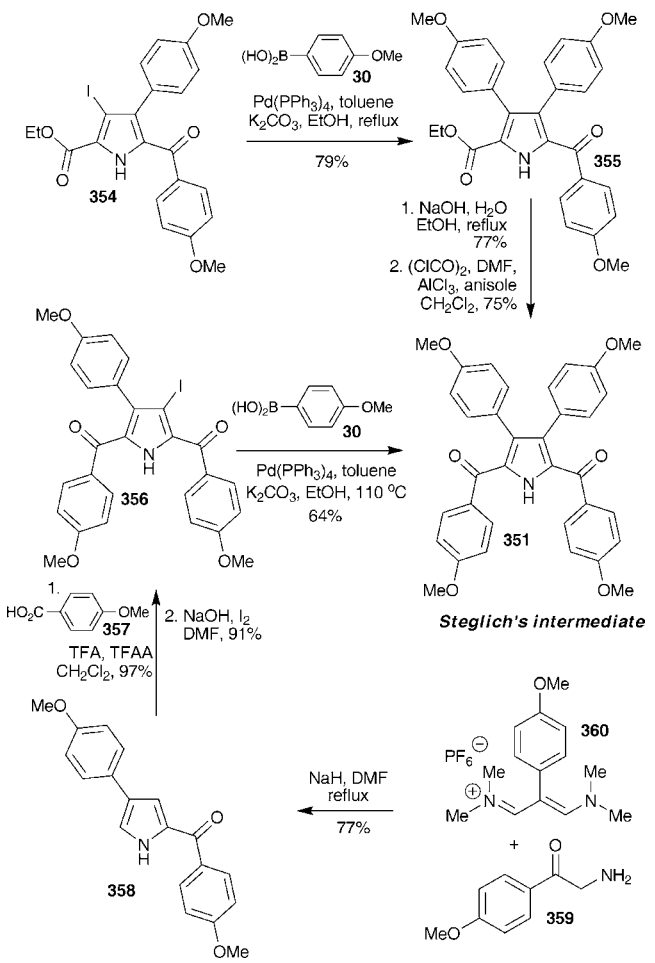
Scheme 55 Formal synthesis of permethyl storniamide A by Gupton that converges with Boger's intermediate.



Scheme 56 First synthesis of polycitone A and B by Steglich.

the phenols. As will be observed in the following sections, the ability to vary the substituents on the starting phenylpyruvic acid allows this strategy to be easily applied to other members of this natural product family.

Gupton developed two powerful methodologies for the construction of pyrroles: (i) the reaction of either β-chloroenals or chloropropenium salts with glycinate ester derivatives for the synthesis of 2,3,4-tri-substituted pyrroles (used for the synthesis of ningalin B (Scheme 79) and the formal synthesis of lukianol A (Scheme 81)); and (ii) the reaction of 2-arylvinamidinium hexafluorophosphates with α-aminocarbonyl compounds to form 2,4-disubstituted pyrroles, used for the formal synthesis of permethyl storniamide A (Scheme 55) and the total synthesis of rigidin (Scheme 69). Gupton's synthesis of Steglich's polycitone intermediate[136] (**351**, Scheme 56) made use of the second methodology for forming pyrroles and involved two variations (Scheme 57). The bottom route represents the more daring strategy, using the α-aminoketone **359** as the coupling partner with **360**. The desired pyrrole **358** was subjected to Friedel–Crafts acylation and iodination to afford **356**, which underwent Suzuki coupling with **30** to yield Steglich's intermediate **351**. Compound **351** was also prepared *via* a route (Scheme 57, top) that utilised the α-aminoglycinate ester to provide **355** (see synthesis of

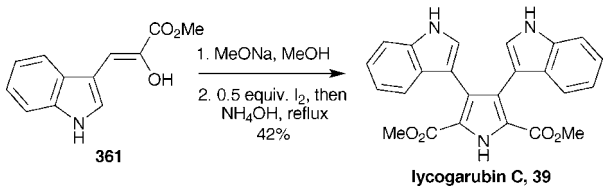


Scheme 57 Gupton's routes to Steglich's polycitone intermediate based on the coupling of amines and vinamidinium salts.

rigidin, Scheme 69[137] for preparation of this intermediate). Although the use of the glycinate ester was a viable route to the polycitones, additional steps were required compared to the α-aminoketone strategy.

3.1.7 Lycogalic acid and lycogarubin C. The Steglich laboratory was one of two groups that independently isolated lycogarubin C (**39**, Scheme 58) from slime molds.[138] Steglich proposed that **39** was likely formed biosynthetically from the oxidative dimerisation of indolylpyruvate **361**, with the resulting 1,4-dicarbonyl derivative condensing with ammonia to form the pyrrole-containing natural product. This hypothesis was put to practice (Scheme 58), with lycogarubin C being produced from simple materials in a single reaction pot.

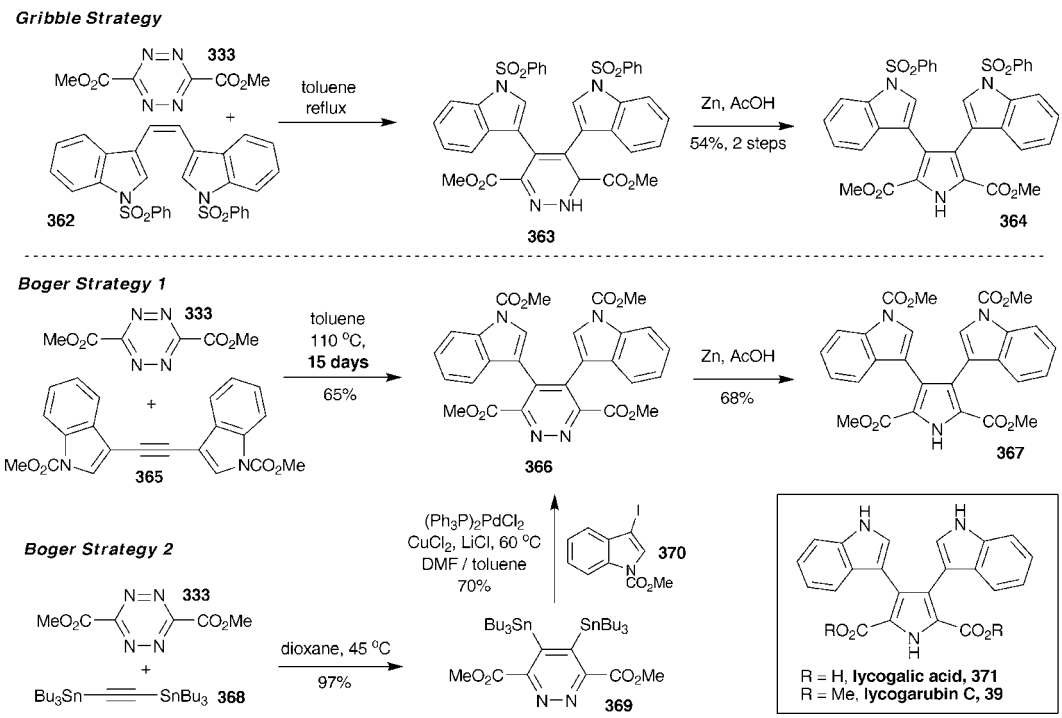
In early 2010 Boger[139] and Gribble[140] independently reported the total synthesis of lycogalic acid (**371**) and lycogarubin C (**39**) (Scheme 59). Both reports involved the Diels–Alder reaction of the tetrazine **333**, but the difference between the two arose in the nature of the dienophile. Gribble initially attempted to react **333** with the acetylene equivalent of **362**, but only observed starting material or decomposition. Gribble then successfully utilised the Diels–Alder strategy with the alkene **362** to obtain the non-aromatic product **363** which, under reducing conditions, was converted to the pyrrole **364**. Boger successfully employed the alkynyl dienophile **365**, but with the requirements for a very long reaction time and high temperature to reach acceptable conversion to **366**. Although the reaction of **333** and **365** allowed Boger to obtain the desired aromatic product **366**, an alternative strategy that involved the reaction of **333** and the bis-(tributyltin)alkyne **368** to form the diazine **369** was developed. This stannyldiazine was utilised in a Stille coupling with the iodoindole **370** to provide the common intermediate **366**, which was efficiently converted to **367**. Compounds **364** and **367** both served as precursors to lycogalic acid and lycogarubin C.



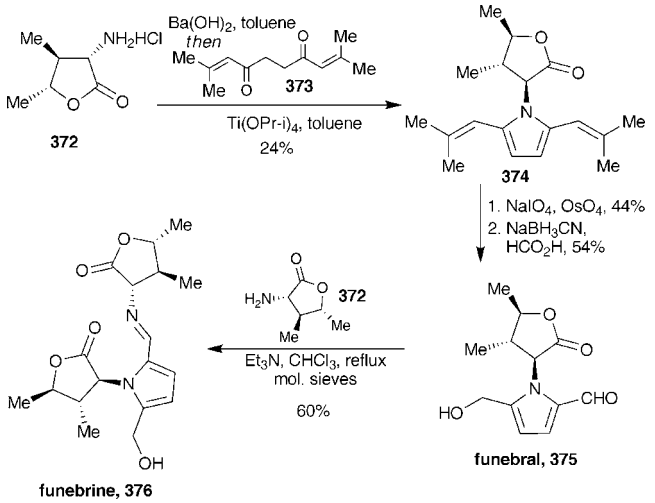
Scheme 58 First synthesis of lycogarubin C by Steglich.

3.2 *En route* pyrrole generation, simple pyrrolic moiety in natural product, racemic syntheses

3.2.1 Funebral and funebrine. The secondary metabolites funebrine (**376**) and funebral (**375**, Scheme 60), were isolated from the flowers of the large tree *Quararibea funebris* of south-eastern Mexico.[141,142] Quesne and Forsythe reported the total synthesis of these intriguing monopyrroles.[143,144] Their strategy involved the synthesis of the pyrrole **374** using the amino lactone **372** in a Paal–Knorr pyrrole synthesis with the diketone **373** in the presence of titanium isopropoxide, the latter used as a catalyst to coordinate the oxygen atoms of the diketone, maintain neutral conditions and simultaneously inhibit polymerisation. The pyrrole **374** contained the required critical substitution at both the 2- and 5-positions, primed for the completion of the total synthesis. This was a key feat, as when the amino lactone **372** was used to make a simple *N*-substituted pyrrole, formylation of *both* the 2- and 5-positions was unfeasible. Oxidative cleavage of the alkenes of **374**, and mono-reduction of the resulting dialdehyde gave funebral (**375**). Reaction of funebral with a second lactone unit (**372**), in the presence of triethylamine



Scheme 59 Subtle differences in reactivity due to the chosen protecting group in syntheses of lycogalic acid and lycogarubin C by Gribble and Boger.



Scheme 60 Quesne and Forsythe's total synthesis of funebral and funebrine.

and molecular sieves, provided the imine functionality required for funebrine (**376**).[143]

3.3 *En route* pyrrole generation, simple pyrrolic moiety in natural product, asymmetric syntheses

3.3.1 Funebral and funebrine. Ishibashi later completed an enantioselective synthesis of funebral and funebrine. These workers prepared the lactone **372** enantioselectively using a chiral auxiliary-directed intramolecular 1,3-dipolar cycloaddition (not depicted).[145] Completion of the asymmetric total synthesis of funebral and funebrine involved pyrrole formation and subsequent steps using the chemistry employed by Quesne and Forsythe.[143,144]

3.3.2 Deoxypyrrololine. Deoxypyrrololine (**380**, Scheme 61) bears three chiral amino acids as substituents on the pyrrole. It is believed to be produced in certain tissues of people suffering from osteoporosis, and has potential as a biochemical marker for this disease.[146] Adamczyk completed the total synthesis of this compound using the same methodology for pyrrole formation as was developed and employed for the synthesis of porphobilinogen (Scheme 48).[127,147] The protected diamino diacid **377** was reacted with benzyl isocyanoacetate in the presence of DBU to give the trisubstituted pyrrole **378**. Preparation of deoxypyrrololine required *N*-alkylation with **379**, followed by deprotection and decarboxylation.

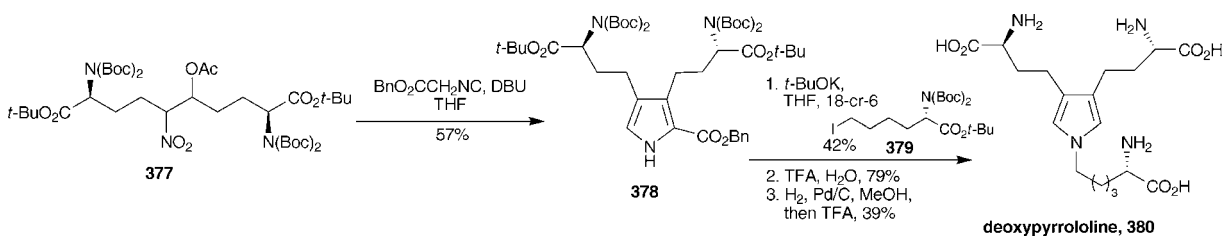
3.3.3 Coumermycin A_1. Interest in the synthesis of coumermycin A_1 (**388**) stems from the promise it shows in the battle against methicillin-resistant species of *Staphylococcus*. The Merck synthesis of coumermycin A_1[148] commenced with the sugar **381**, prepared by the degradation of commercially available novobiocin (Scheme 62). Pyrrole introduction proceeded *via* coupling of **381** with the anhydride **382** in the presence of a phosphine to yield **383**. After further elaboration, two equivalents of **384** were coupled with the pyrrole acid **385** (prepared *via* reaction of two equivalents of the isonitrile **387** with acetaldehyde to form **386**, and subsequent *tert*-butyl group removal) to form the natural product coumermycin A_1.

The first synthesis of coumermycin A_1 (**388**) was completed in 1965 at Hoffman La-Roche,[149] and commenced with **389**, a key component in the La-Roche novobiocin synthesis. Treatment of **389** with 2-methylpyrrole magnesium iodide (**390**) regioselectively opened the cyclic carbonate functionality to yield **391** (Scheme 63). After elaboration to **392**, two equivalents were coupled with the pyrrole bis-acid chloride **393** to yield coumermycin A_1, after acetate removal. Although the method by which the pyrrole bis-acid chloride was prepared is not documented in the report, this synthesis of coumermycin A_1 is included in this section as it is envisioned that it could be/was prepared from the pyrrole bis-acid **385**, which could be generated by a method akin to that used in Scheme 62. Yields were not reported.

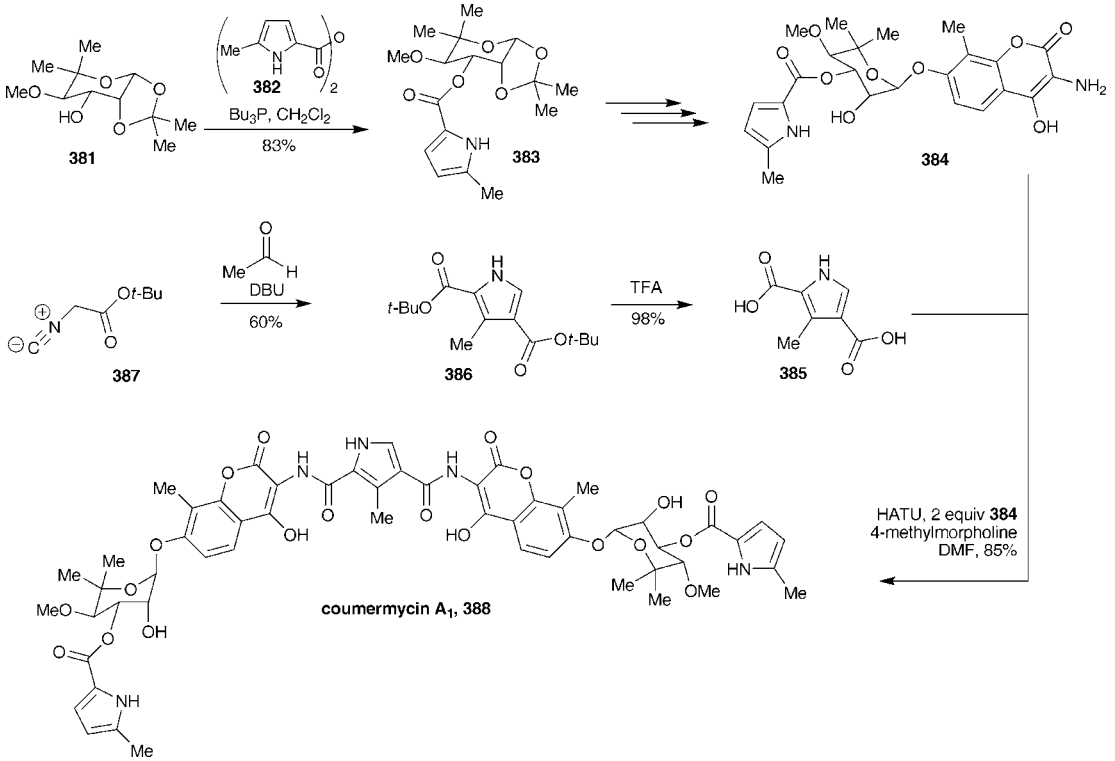
3.4 *En route* pyrrole generation, fused pyrrolic moiety in natural product, achiral

3.4.1 Methoxatin. Certain species of *Pseudomonas* bacteria can survive in media in which methanol is the only source of energy and cellular carbon.[150,151] These bacteria possess a methanol dehydrogenase that oxidises formaldehyde and methanol, and it is believed that methoxatin (**398**, Scheme 64) is the coenzyme that makes this oxidation possible. Methoxatin was first synthesised by Corey.[152] The indole **395** was prepared in several steps from 2-methoxy-5-nitroaniline. The addition of dimethyl 2-oxoglutaconate (**394**) under acidic conditions led to the formation of the third ring of methoxatin, courtesy of a Doebner–von Miller annulation, and oxidation of **396** gave the *ortho*-quinone **397**, which was converted to methoxatin in two steps.

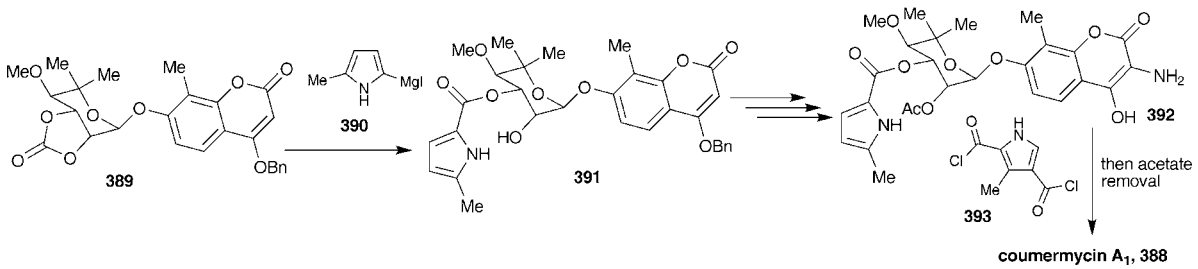
Weinreb also reported a total synthesis of methoxatin (Scheme 65). When **399**[153] was subjected to the Japp–Klingemann hydrazone synthesis with benzenediazonium fluoroborate in aqueous pyridine followed by reduction with sodium borohydride, the hydrazone **400** was produced. Hydrogenation of **400** gave the tricyclic triester **401**, and conversion of this intermediate to methoxatin required only oxidation and ester hydrolysis.



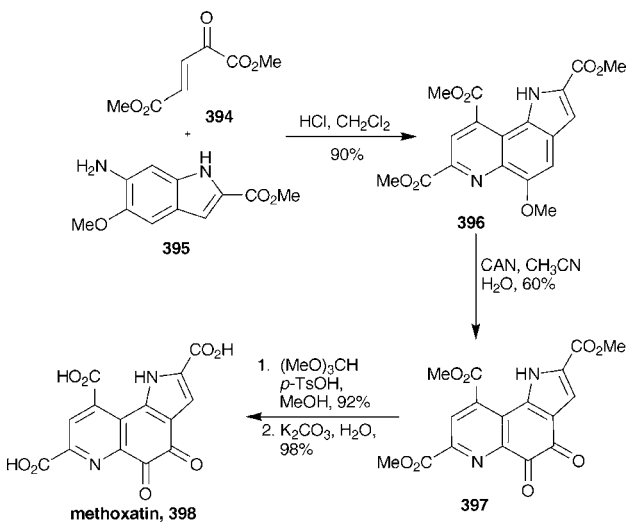
Scheme 61 Adamczyk's synthesis of deoxypyrrololine.



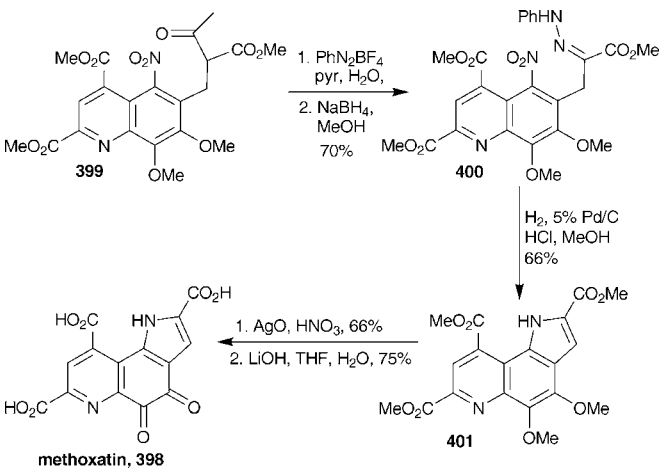
Scheme 62 Synthesis of coumermycin A_1 by Merck.



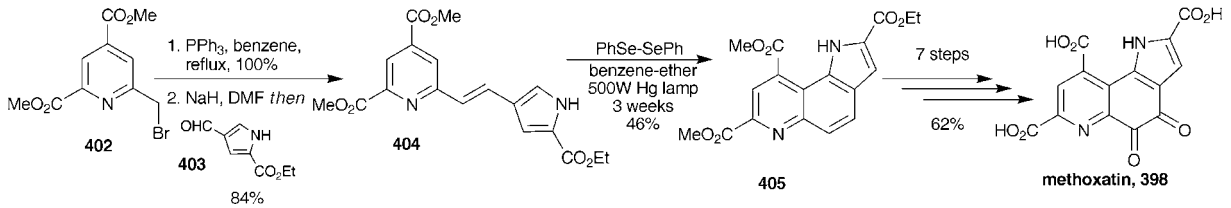
Scheme 63 The first synthesis of coumermycin A_1 by Hoffman La-Roche.



Scheme 64 Corey's synthesis of methoxatin.



Scheme 65 Weinreb's total synthesis of methoxatin.

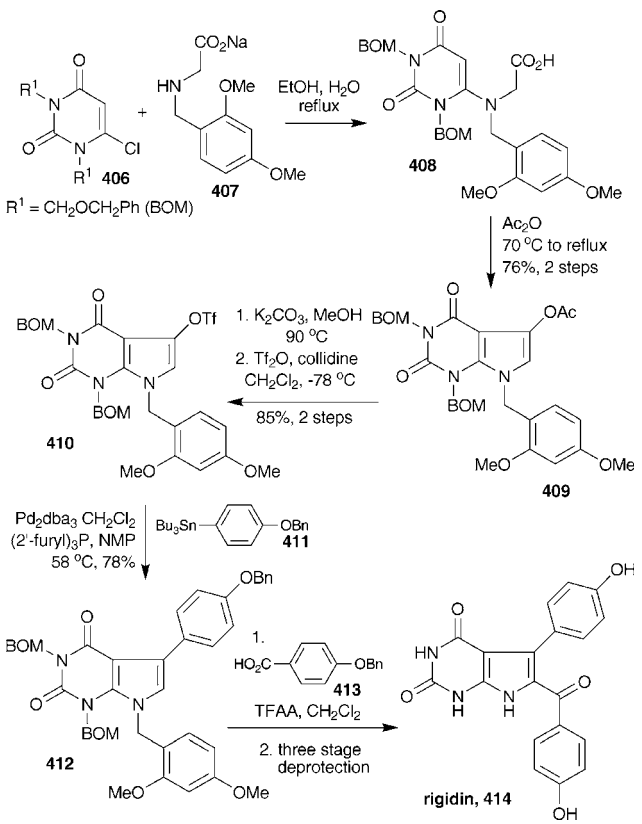


Scheme 66 Hendrickson's preparation of methoxatin.

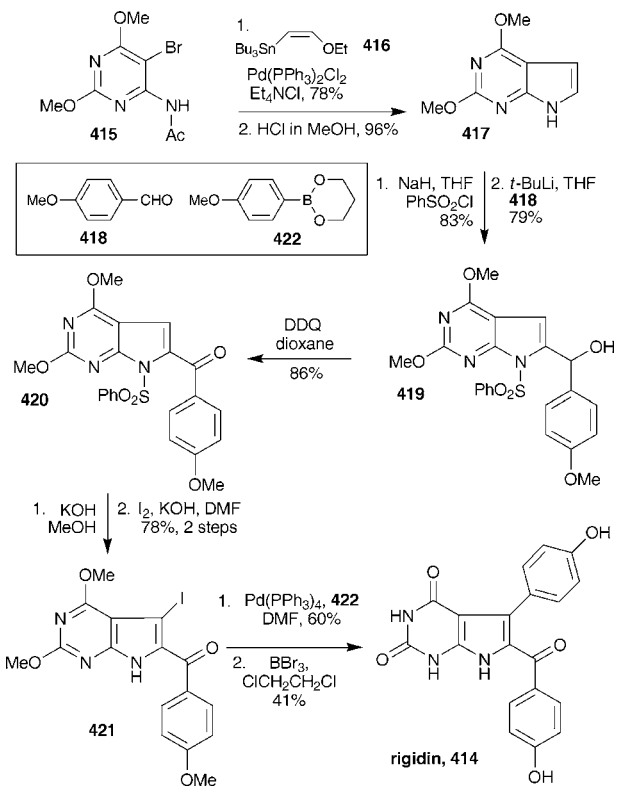
Hendrickson's preparation of methoxatin has the distinction of being convergent (Scheme 66).[154] The pyridyl bromide **402** underwent reaction with triphenylphosphine, followed by ylide formation and subsequent addition of the pyrrolic aldehyde **403** gave **404** without the need for *N*-protection of the pyrrole. Oxidative cyclisation was conducted under photochemical conditions in the presence of diphenyldiselenide to give **405** and thus complete the ring system of methoxatin, setting the stage for a lengthy end-game sequence to complete the total synthesis.

3.4.2 Rigidin. The first synthesis of rigidin (**414**) was reported by Edstrom, and built the pyrrole heterocycle onto a uracil scaffold (Scheme 67).[155] Reaction of the uracil **406** and the glycine derivative **407** produced the intermediate **408**, which upon heating in acetic anhydride was converted to the pyrrole **409**. Conversion of the acetate to the triflate **410** provided a handle for phenyl ring installation *via* a Stille reaction with **411** to produce **412**. The final aromatic ring was installed *via* a Friedel–Crafts acylation with the substituted benzoic acid **413**, leaving a step-wise deprotection strategy to complete the total synthesis.

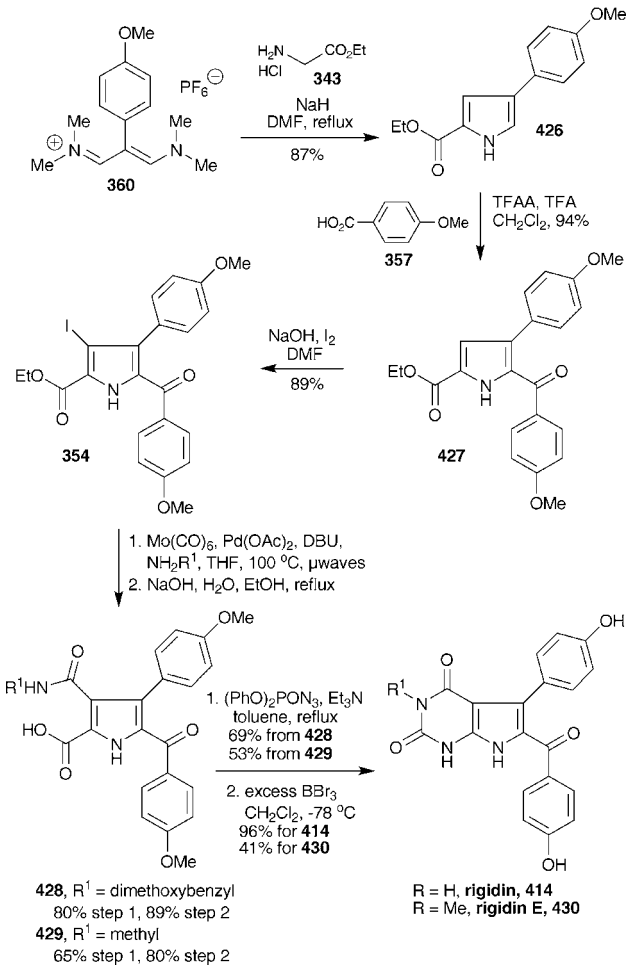
One year later, Sakamoto reported a synthesis of rigidin (**414**) that began with the Stille union of the highly functionalised pyrimidine **415** and the vinyl stannane **416**. Treatment of the product with methanolic acid furnished the pyrrolopyrimidine **417** (Scheme 68).[156,157] After benzenesulfonyl protection of the pseudo-pyrrolic nitrogen atom, the heterocycle was lithiated and quenched with anisaldehyde (**418**) to give the alcohol **419**. Reaction with DDQ induced benzylic oxidation to give **420**, from which the *N*-sulfonyl group was removed. The pyrrolopyrimidine was then iodinated to form **421**, a substrate that allowed for the formation of the final carbon–carbon bond. Treatment of **421** with $Pd(PPh_3)_4$ and the boronic ester **422** yielded the skeleton of the natural product, with BBr_3 treatment then removing the methyl ethers to complete the synthesis. It is noteworthy that although the pyrrole unit appears to be carried through the synthesis from an early stage, Sakamoto did not actually unveil it until the final step, *via* dearomatisation of the pyrimidine ring.



Scheme 67 First total synthesis of rigidin by Edstrom.



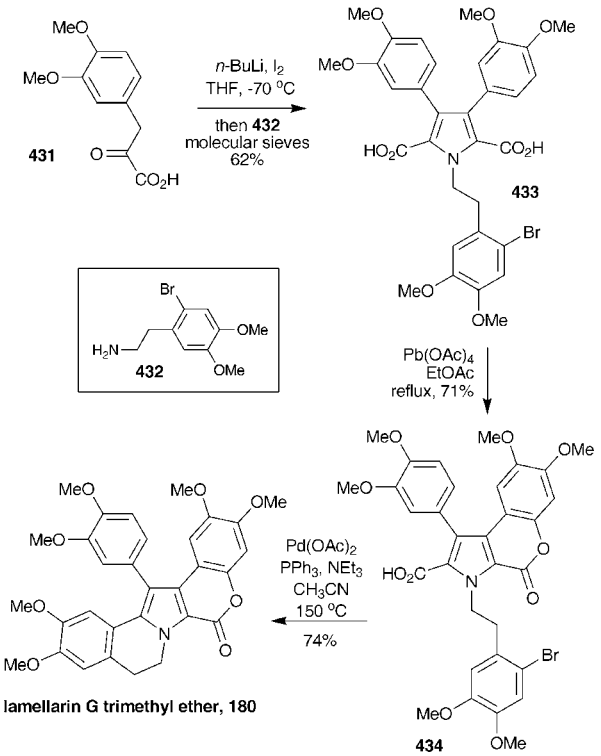
Scheme 68 Sakamoto's synthesis of rigidin.



Scheme 69 Gupton's synthesis of rigidin and rigidin E utilised the pyrrole as a scaffold for the construction of the uracil heterocycle.

Gupton also completed a synthesis of rigidin[137] (**414**) and rigidin E (**430**), and used a strategy contrary to the previous syntheses by Edstrom[155] and Sakamoto[156] (Scheme 67 and Scheme 68, respectively). Gupton's synthesis incorporated the pyrrole ring early and used it as a scaffold for appending the uracil ring (Scheme 69), while the previous syntheses built the pyrrole onto a pyrimidine core. Using his vinamidinium salt methodology for the synthesis of 2,4-substituted pyrroles, Gupton reacted **360** with glycine ethyl ester (**343**) in the presence of base to form the pyrrole **426**. Subsequent electrophilic aromatic substitution utilising **357**, and then iodination, produced **354**, a common intermediate in Gupton's synthesis of polycitones A and B (Scheme 57).[136] A divergent synthesis of both rigidin and rigidin E utilised a microwave-assisted aminocarbonylation reaction, trapping with either methylamine, for rigidin E, or dimethoxybenzylamine, for rigidin. Curtius rearrangement of the free acids (**428** and **429**) with intramolecular capture of the resulting isocyanate by the amide nitrogen atom formed the uracil ring of the natural product, and deprotection completed the total syntheses.

3.4.3 Lamellarins, ningalins A and B, and lukianol A. The first synthesis of lamellarin G trimethyl ether (**180**, Scheme 70) by

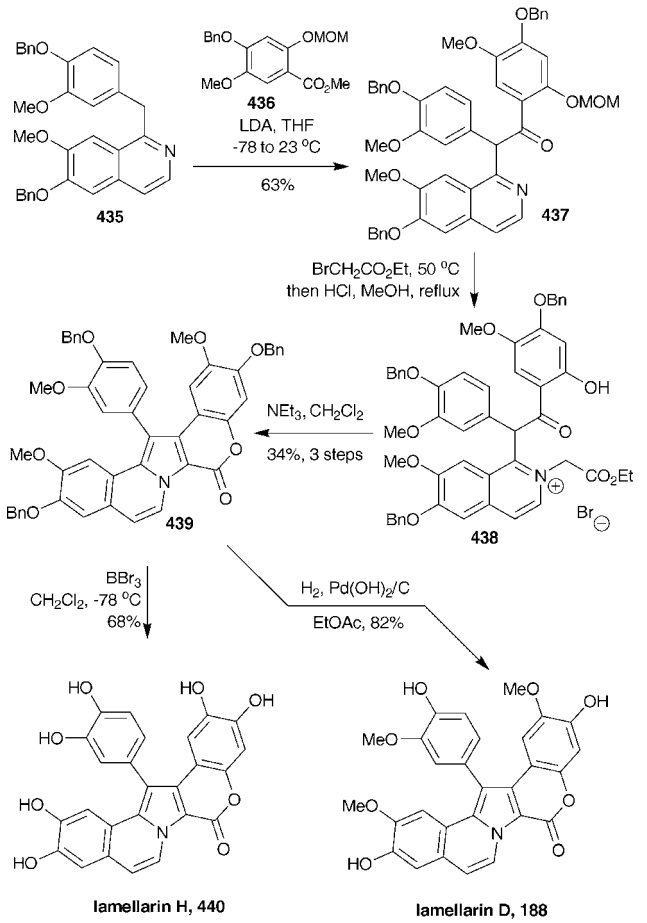


Scheme 70 Highly efficient biosynthetic synthesis of lamellarin G trimethyl ether by Steglich.

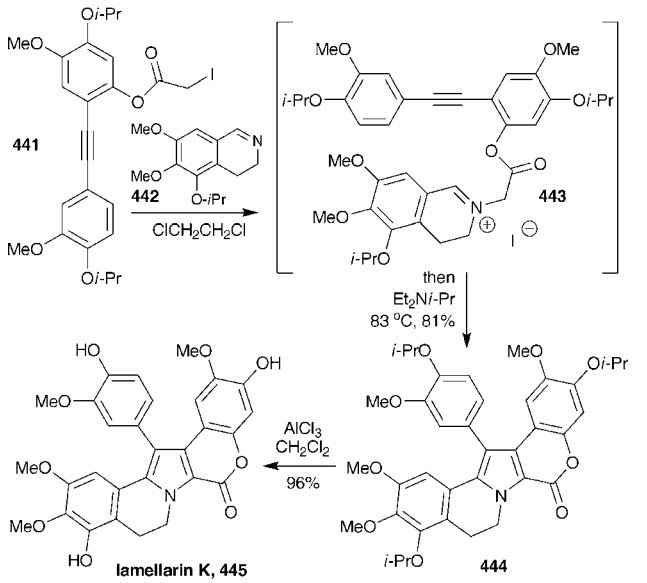
Steglich is an excellent example of how syntheses based on biosynthetic hypotheses can display a high degree of efficiency.[158] Similar to his strategy for the synthesis of lycogarubin C (Scheme 58),[138] oxidative coupling of the pyruvic acid **431** produced the corresponding 1,4-diketone (not depicted), and subsequent condensation with the substituted phenylethylamine **432** produced the *N*-alkyl pyrrole **433** (Scheme 70). Treatment of **433** with one equivalent of $Pb(OAc)_4$ led to a highly regioselective oxidation of the aromatic ring to give the phenol, which underwent lactonisation to provide **434**. Exposure of **434** to typical Heck conditions induced extrusion of CO_2 from the Pd(II) intermediate, and reductive elimination produced lamellarin G trimethyl ether. The brevity (three steps) of this synthesis sets the bar against which subsequent syntheses of this molecule will be measured.

Ishibashi published syntheses of lamellarins D (**188**) and H (**440**) which utilised an ylide to form both the requisite pyrrole and lactone rings in a single step (Scheme 71).[159] The benzyl lithium anion of **435** was produced upon exposure to LDA, and reaction with the benzoate **436** yielded **437**. *N*-Alkylation of **437** with ethyl bromoacetate, and subsequent exposure to acid to remove the MOM-group, produced the isoquinoline salt **438**. The key step involved addition of triethylamine to provide the ylide, which underwent condensation and aromatisation to form the pyrrole. Subsequent lactonisation provided the protected version (**439**) of the natural products. Global deprotection with BBr_3 yielded lamellarin H (**440**), and selective benzyl group removal led to lamellarin D (**188**), demonstrating the practicality of orthogonal protection in the starting materials.

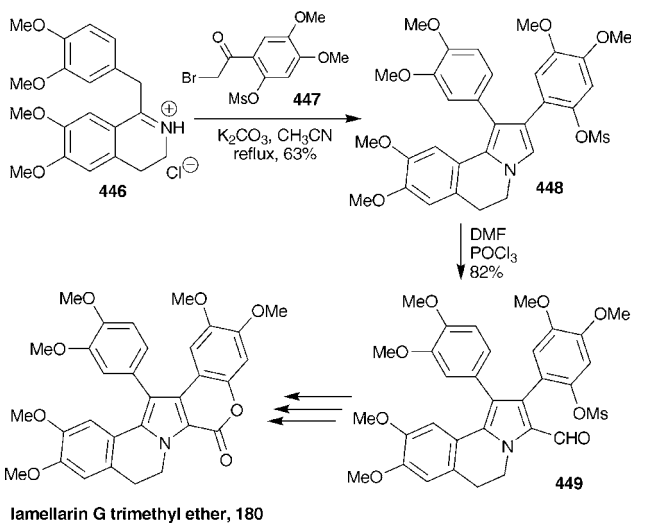
Banwell also utilised an azomethine ylide in his synthesis of lamellarin K (**445**), although the context of its use was unique



Scheme 71 Syntheis of lamellarins D and H by Ishibashi that utilised ylide-induced pyrrole formation.



Scheme 72 Utilisation of a 1,3-dipolar cycloaddition by Banwell for the synthesis of lamellarin K.



Scheme 73 Ruchirawat's synthesis of lamellarin G trimethyl ether that utilised a Knorr-type condensation.

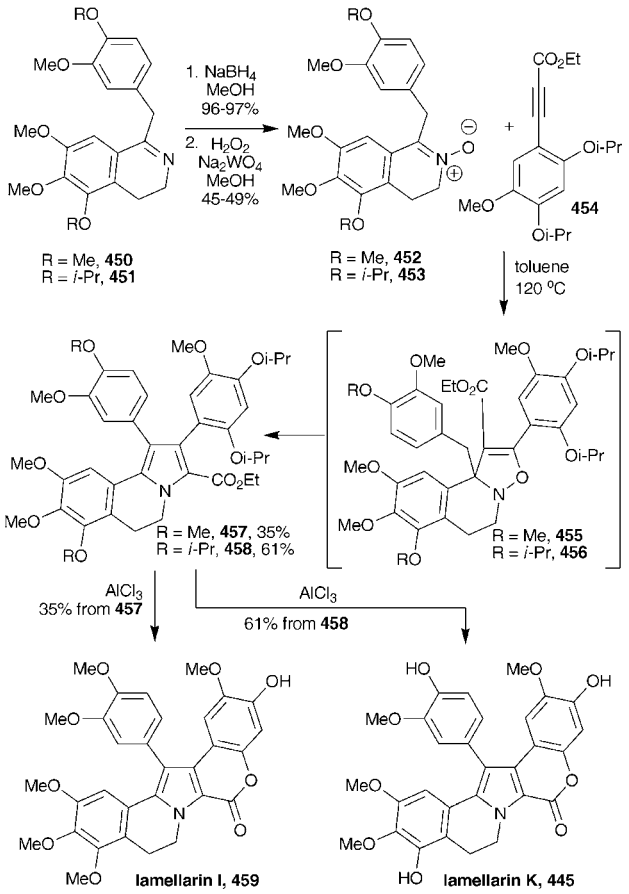
(Scheme 72).[160] Alkylation of the dihydroisoquinoline **442** with the α-iodoacetate **441** led to the imminum salt **443**, which was not isolated. Addition of Hünig's base to the reaction vessel, with an increase in temperature, led to formation of the azomethine imine. Subsequent cycloaddition with the alkyne formed the dihydropyrrole, which aromatised *in situ* to yield **444**. Selective removal of the isopropyl protecting groups *via* treatment with $AlCl_3$ produced lamellarin K. A strategy very similar to that of Banwell was utilised by Álvarez for the solid-phase synthesis of lamellarins U and L (not depicted).[161]

Ruchirawat prepared lamellarin G trimethyl ether (**180**) *via* a route that used a derivative of the Knorr pyrrole synthesis to form the desired heterocycle (Scheme 73).[162] Reaction of the dihydroisoquinoline salt **446** with the α-bromoketone **447** led to the corresponding iminium ion, which presumably underwent an intramolecular reaction of the enamine and ketone with loss of water to form the pyrrole **448**. Vilsmeier formylation gave **449**, *en route* to the natural product.

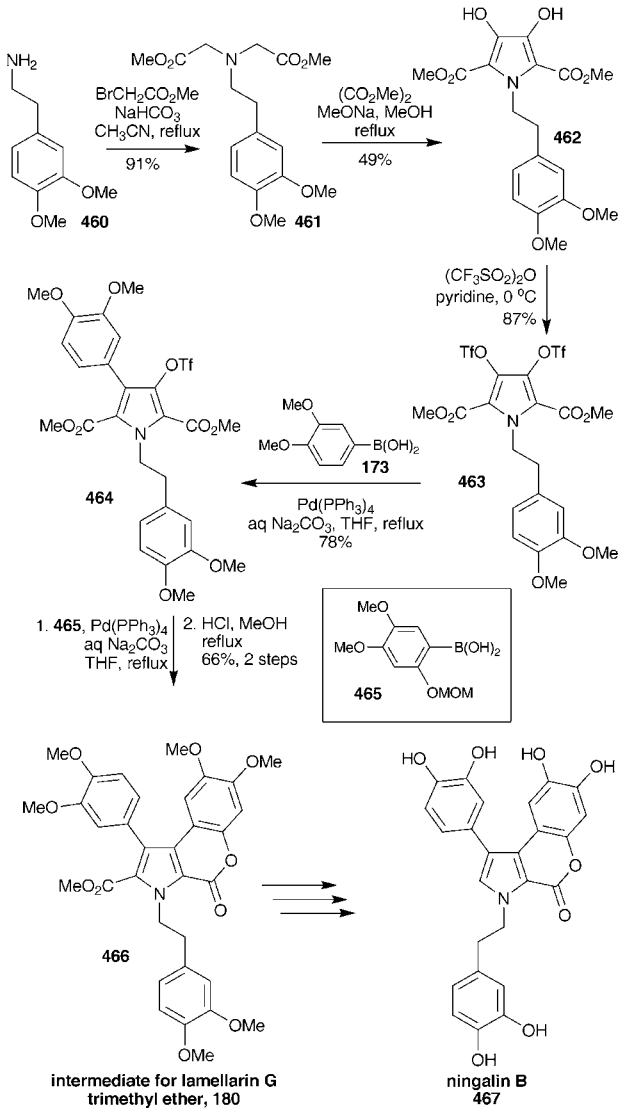
Guitián's syntheses of lamellarins I (**459**) and K (**445**) are based on the fact that pyrroles can be formed from the rearrangement of isoxazolines that contain a R–CH_2– substituent at the 3-position (Scheme 74).[163] The required isoxazoline intermediates (**455** and **456**) were prepared *via* the reaction of nitrones (**452** and **453**) with the alkyne **454**, to ultimately give the desired pyrroles (**457** and **458**, respectively) after rearrangement.[164] Selective removal of the isopropyl groups then led to the natural products.

Using a strategy similar to that used for the formal synthesis of permethyl storniamide A (**42**, Scheme 54), Iwao synthesised lamellarin G trimethyl ether (**180**) and ningalin B (**467**).[133] By carefully controlling the reaction stoichiometry, a mono-Suzuki coupling was performed between the boronic acid **173** and the bis-triflate **463** (Scheme 75). This strategy enabled a subsequent Suzuki coupling between **464** and **465** to introduce a differently substituted aryl ring. Treatment with HCl allowed for MOM deprotection and the unsymmetrical formation of the lactone found in the key intermediate **466**.

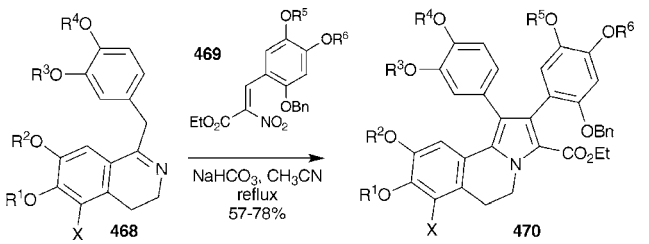
Ruchirawat developed a general method that allowed for the preparation of twenty-eight natural and unnatural lamellarins.[165]



Scheme 74 Synthesis of lamellarins I and K by Guitián that utilised an isoxazoline–pyrrole rearrangement.



Scheme 75 Use of a Hinsberg-type pyrrole synthesis by Iwao for the preparation of lamellarin G trimethyl ether and ningalin B.



Scheme 76 The Michael addition–ring closure strategy used by Ruchirawat to prepare 28 lamellarins.

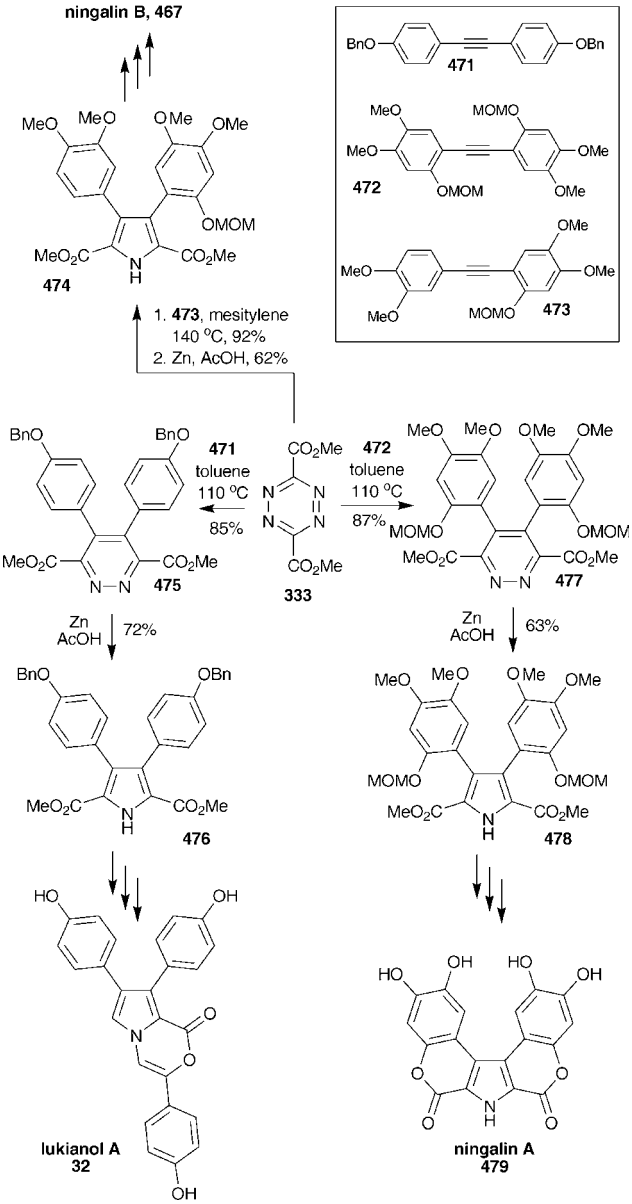
A strategy was utilised that, as the key step, formed the pyrrole *via* the convergent union of two diversely functionalised sub-units. Thus, reaction of a dihydroisoquinoline of the general structure **468** with a functionalised Michael acceptor of the general structure **469** led to a Michael addition–cyclisation event under basic conditions (Scheme 76). Both saturated and the corresponding unsaturated lamellarins were then prepared from **470**.

In syntheses of ningalins A and B, and lukianol A, Boger utilised the highly effective Diels–Alder reaction of the tetrazine **333** with a variety of functionalised tolans (**471**, **472** and **473**) to form the corresponding functionalised diazines after retro-Diels–Alder reactions to expel nitrogen (Scheme 77).[22,166] Treatment of these diazines with Zn/AcOH led to a reductive ring contraction to provide the pyrroles **476**, **474** and **478**, which were elaborated to the appropriate natural product.

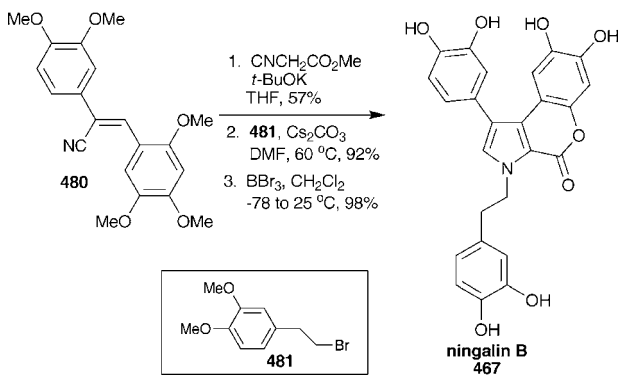
Bullington utilised the [3 + 2] cycloaddition of methyl isocyanoacetate with α,β-unsaturated nitriles to form pyrroles with aromatic substituents at the 3- and 4-positions (Scheme 78).[167] Thus, utilisation of the unsaturated nitrile **480** led to the pyrrolic framework, which was alkylated with **481**. Global deprotection *via* treatment with BBr_3 induced lactonisation and formation of ningalin B.

Gupton utilised an imine formation–conjugate addition strategy between the β-chloroenal **482** and the aminoacid derivative **483** to form the 1,2,3,4-tetrasubstituted pyrrole (Scheme 79) found within ningalin B (**467**).[168] The resulting pyrrole contained the *N*-alkyl substitutent, eliminating the subsequent alkylation step that is vital to many syntheses of these natural products. Upon ester hydrolysis **484** was produced, and this acid was converted to ningalin B (**467**) *via* treatment with lead tetraacetate, and global deprotection.

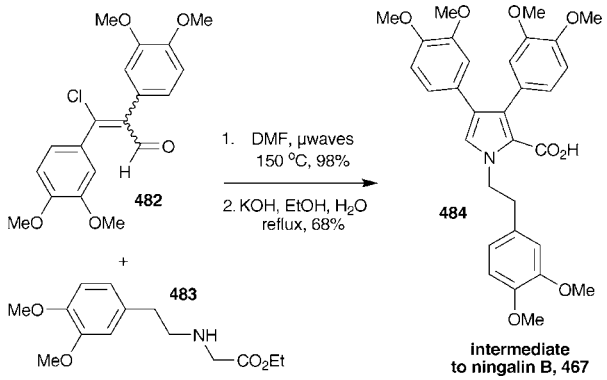
The synthesis of lukianiol A (**32**) by Fürstner (Scheme 80) utilised a new pyrrole synthesis based on the low-valent



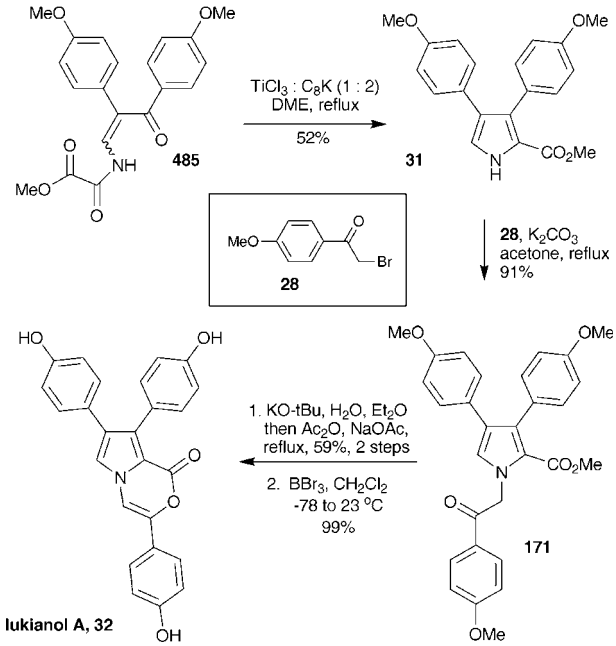
Scheme 77 Boger's tetrazine–tolan cycloaddition strategy allowed access to multiple natural products.



Scheme 78 Bullington's synthesis of ningalin B.



Scheme 79 Gupton's preparation of an intermediate that was converted to ningalin B.

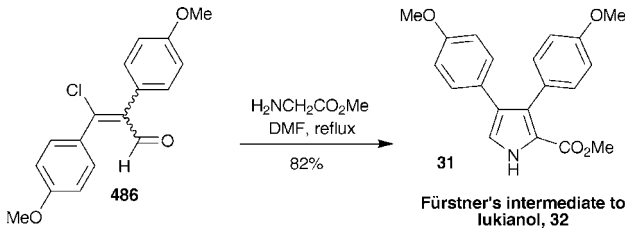


Scheme 80 Fürstner's 1995 synthesis of lukianol A.

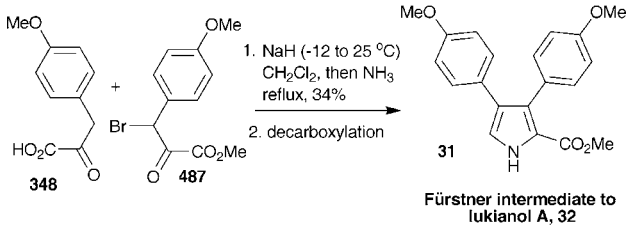
titanium-induced rearrangement of an amido-enone.[19] Subjection of **485** to preformed Ti-graphite led to the chemoselective reductive coupling of the ketone and amide carbon atoms to produce the trisubstituted pyrrole **31**. Alkylation of **31** with **28** yielded **171**, which underwent base-induced cyclisation and global deprotection to produce the natural product.

A variation of the strategy used by Gupton for the synthesis of ningalin B[168] was also utilised to prepare a key intermediate in Fürstner's synthesis of lukianol A (**32**).[19] β-Chloroenal **486** served as a three-carbon building block, and its reaction with glycine methyl ester led to Fürstner's intermediate **31** (Scheme 81). The mechanism of this transformation was postulated to proceed through condensation to the imine, cyclisation of the glycine α-carbon onto the eneimine, and subsequent aromatisation *via* dehydrohalogenation.

A modification of the phenylpyruvate dimerisation methodology used by Steglich allowed for the efficient synthesis of unsymmetrical 2,3,4,5-tetrasubstituted pyrroles.[135,138,158] Instead



Scheme 81 Gupton's synthesis of Fürstner's lukianol A intermediate.



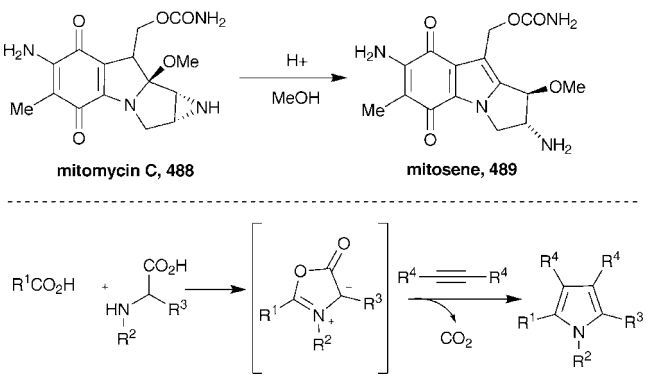
Scheme 82 Synthesis of lukianol A by Steglich based on the formation of unsymmetrical 2,3,4,5-tetrasubstituted pyrroles.

of homo-coupling phenylpyruvate derivatives such as **348** under oxidative conditions, installation of the halogen functionality onto one of the reactive partners prior to coupling allowed for the use of differentially substituted pyruvates.[169] The base-catalyzed union of **348** and **487**, and then treatment with ammonia led to the pyrrole mono-acid mono-ester (Scheme 82). The differentiation of the carbonyl functionalities allowed for mono-decarboxylation to produce **31**, a key intermediate in Fürstner's synthesis of lamellarin O and lukianol A.[19]

For additional syntheses of lukianol A that are included in sections discussing methodologies that produce a family of natural products, see Boger's preparation of ningalin A and B (Scheme 77).

3.5 *En route* pyrrole generation, fused pyrrolic moiety in natural product, racemic syntheses

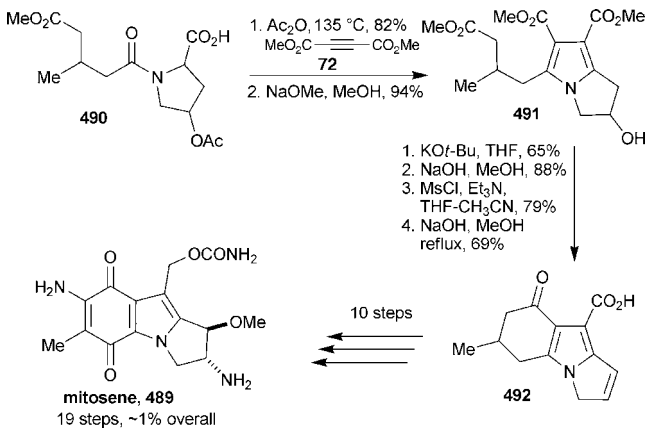
3.5.1 Mitosene. Mitosene (**489**, Scheme 83), a natural product isolated from *Streptomyces caespitosus* and *Streptomyces lavendulae*,[170] exhibits significant antitumor activity and is a chemical degradation product of mitomycin C (**488**, Scheme 83).[170,171] Under acidic conditions the hemiaminal group of mitomycin is cleaved and the aziridine undergoes ring-opening (Scheme 83, top).



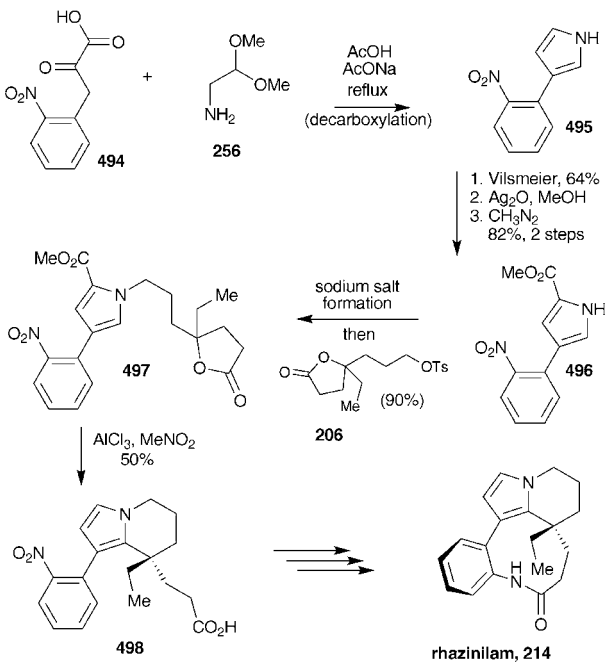
Scheme 83 Degradation of mitomycin C to mitosene and the Huisgen pyrrole synthesis.

Rebek reported the total synthesis of mitosene (Scheme 84),[171,172] addressing the construction of the pentasubstituted pyrrolic core *via* Huisgen chemistry (Scheme 83, bottom).[173] Thus, the proline derivative **490** was subjected to dimethyl acetylene dicarboxylate (**72**) in hot acetic anhydride to form the pyrrole ring, and gave **491** after hydrolysis of the acetyl group. Although the diastereoisomers of **491** could be separated, it was more practical to use the mixture in the total synthesis. Dieckmann cyclisation of **491** was followed by decarboxylation, mesylation of the secondary alcohol, and subsequent elimination gave the tricycle **492**. Ten steps were then required to obtain the natural product.

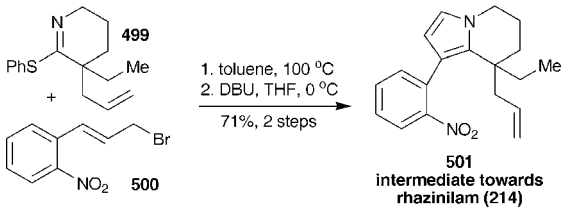
3.5.2 Rhazinilam. Rhazinilam (**214**) was prepared in 1973 by Smith (Scheme 85)[92] *via* the condensation of the α-ketoacid **494**



Scheme 84 Rebek's total synthesis of mitosene.



Scheme 85 Smith's 1973 total synthesis of rhazinilam.



Scheme 86 The pyrrole-forming strategy used by Magnus for the total synthesis of rhazinilam.

and aminoacetaldehyde dimethyl acetal (**256**) to form **495**, a compound that was previously used[174] to prepare pyrrolnitrin (**5**) analogs. Three steps were required to append the methyl ester to form **496**. *N*-Alkylation with the lactone-tosylate **206** gave **497**, which underwent Friedel–Crafts alkylation to form the fused core **498** of rhazinilam. Further manipulations converted **498** to the natural product.

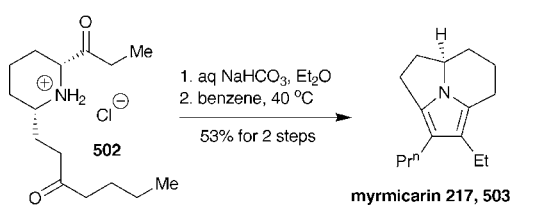
The total synthesis of rhazinilam (**214**) was completed by Magnus[175] twenty-eight years after the initial report by Smith (Scheme 85).[92] Utilising a pyrrole formation strategy similar to Sames' (Scheme 95)[106,107] Magnus coupled the thiophenyl iminoether **499** and 2-nitrocinnamyl bromide (**500**), with the crude product being treated with DBU to yield the key fused pyrrole core **501** (Scheme 86). Utilisation of the thiophenyl motif allowed for the formation of the requisite pyrrole without a subsequent oxidation event being required.

3.5.3 Myrmicarin 217. Schröder isolated the myrmicarin alkaloids from the poisonous secretions of a species of African ant, and also reported the first synthesis of a member of this family (Scheme 87).[176] The free-base of **502** led to tricyclic myrmicarin 217 (**503**) upon heating, *via* condensation to the enamine and then reaction of the enamine with the keto group to form the pyrrole of the natural product.

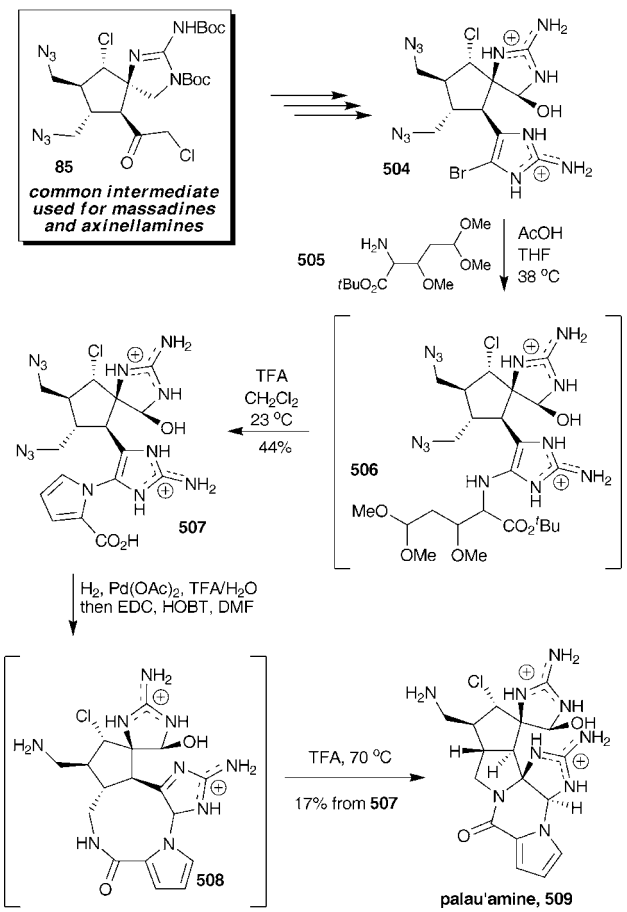
3.5.4 Palau'amine. Palau'amine (**509**) differs from the axinellamines and massadines (Scheme 13) in that the pyrrole moiety is incorporated into the molecular core rather than appended, and only one of the two primary amines is derivatised to the pyrrolic amide. Both of these discrepancies greatly increase the synthetic challenges associated with palau'amine, compared to the axinellamines and massadines. Although palau'amine was isolated in 1993 by Scheuer,[177] it was not until recently that the molecule succumbed to total synthesis. One reason for this delay was that the originally assigned structure was incorrect, and in 2007 three independent publications suggested that structural revisions should be considered.[178–180] Although based on extensive 2D NMR techniques, there were whispers of skepticism about the newly proposed structure due to the fact that it contained a highly strained *trans*-5,5-fused bicyclic ring system, which is very rare in other natural products.[181]

To complete the synthesis of palau'amine, Baran utilised a common precursor (**85**)[182] from both the axinellamine[45] and massadine[46] syntheses. After aminoimidazole introduction and deprotection, the aminoimidazole was brominated to provide **504**, a compound with a handle for introduction of the pyrrole unit (Scheme 88). Initially, a variety of metal-catalyzed cross-coupling reactions were investigated to form the key pyrrole–imidazole N–C bond within **507**, but all attempts met with limited success. The ambiphilic nature of the bromo-aminoimidazole was then utilised, and addition of the pyrrole surrogate **505**, followed by HBr elimination, yielded the intermediate **506** which, upon treatment with TFA, eliminated isobutene and three equivalents of methanol to form the pyrrole **507**. Azide reduction, selective amide formation to close the 9-membered macrocycle (**508**), and treatment with trifluoroacetic acid at elevated temperature was all that was then required to form the strained hexacyclic core, completing the first total synthesis of a molecule that has been studied by numerous groups for more than fifteen years.

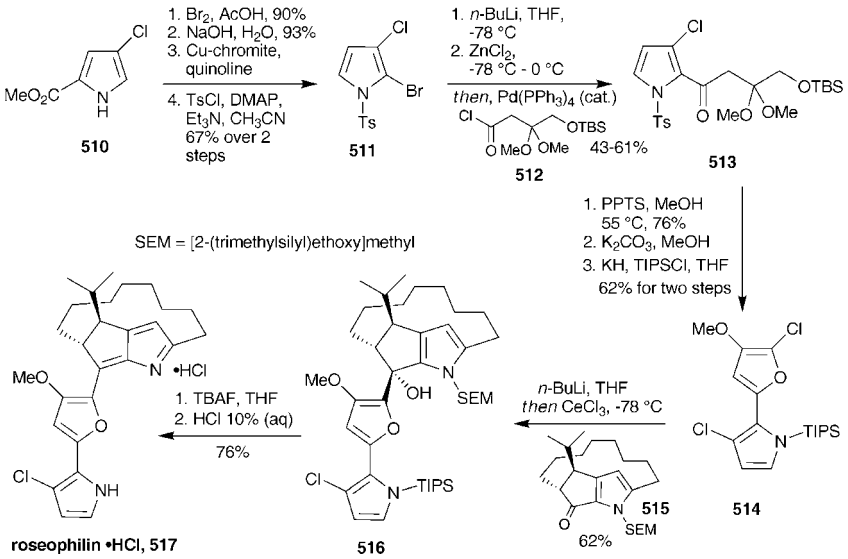
3.5.5 Roseophilin. Roseophilin (**517**, Scheme 89) is an antibiotic that was isolated from cultures of *Streptomyces*



Scheme 87 Schröder and Francke's synthesis of myrmicarin 217 featuring a double condensation to form the pyrrole.



Scheme 88 Baran's total synthesis of palau'amine *via* late-stage formation of the *trans*-5,5 core.



Scheme 89 The first total synthesis of roseophilin by Fürstner.

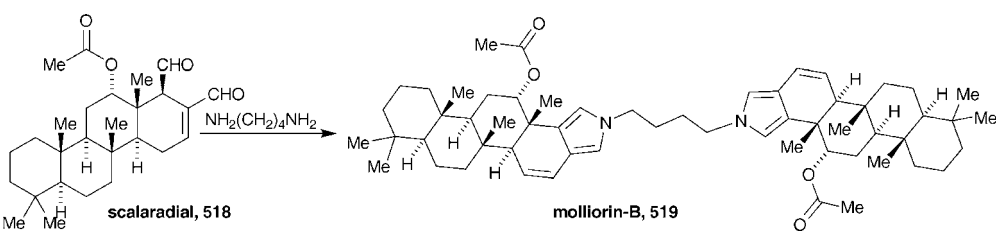
griseovirdis.[183] Akin to the prodigiosins, roseophilin features an *ansa*-bridged azafulvene macrocycle and a pendant pyrrole (A-ring). In roseophilin the macrocycle is attached to a pyrrolylfuran group, whilst in prodigiosin the macrocycle is attached to a pyrrole (prodigiosins are tripyrrolic).[3] The combination of biological activity and unusual chemical structure has made roseophilin a marquis target for total synthesis. Although the synthesis of the azafulvene moiety amidst the macrocyclic core naturally involves much synthetic pyrrole chemistry, the pyrrole that is manipulated in this regard is not retained in the natural product, and the related chemistry is thus omitted from this article. Much of this work has been previously reviewed,[3] and this portion of the review highlights only the introduction of the terminal pyrrolic ring.

Fürstner's total synthesis of roseophilin involved the preparation of the pyrrolylfuran **514** *via* a somewhat lengthy sequence beginning with the pyrrole **510** (Scheme 89).[184] Four steps rendered the tosylated pyrrole **511** a suitable substrate for metal–halogen exchange and formation of an organo-zinc intermediate. Subsequent palladium-mediated coupling with **512** generated **513**. Treating **513** with acid led to the formation of the furan ring. The tosyl group was exchanged for a TIPS group to complete the preparation of **514**. Transmetallation of **514** followed by the addition of the macrocycle **515**[185] gave **516** that underwent global deprotection and acidification to give the hydrochloride salt of roseophilin (**517**).

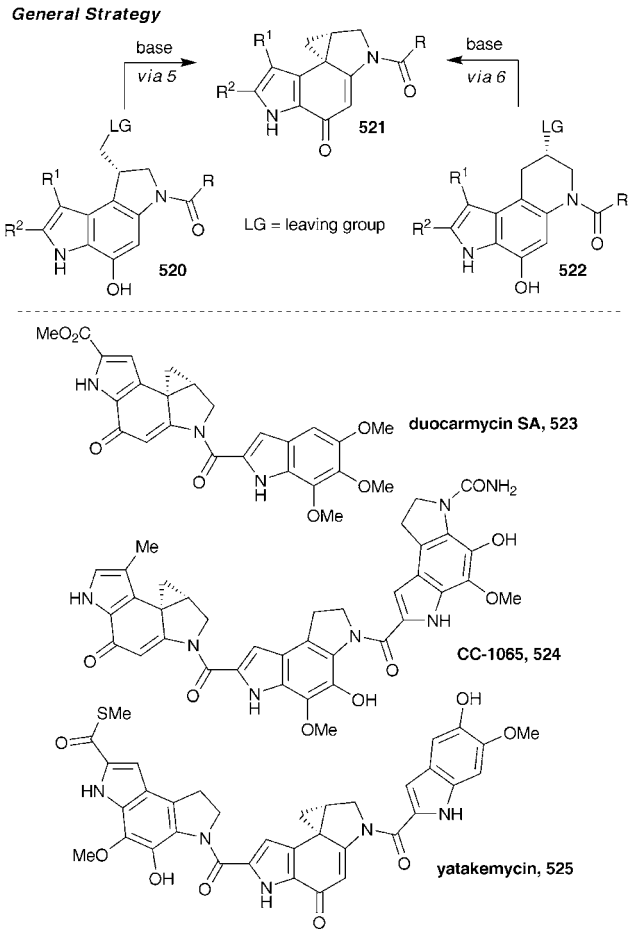
3.6 *En route* pyrrole generation, fused pyrrolic moiety in natural product, asymmetric syntheses

3.6.1 Molliorin-B. Molliorins are pyrroloterpenes isolated from marine sponges. Molliorin-B (**519**, Scheme 90) was synthesised by Cafieri *via* condensation of scalaradial (**518**) with 1,4-diaminobutane (yield unspecified), following a Paal–Knorr approach to this dimeric natural product.[186]

3.6.2 Duocarmycin SA, CC-1065 and yatakemycin. Duocarmycin SA (**523**), CC-1065 (**524**) and yatakemycin (**525**) are members of a class of antitumour compounds that alkylate double-stranded DNA in a sequence-selective manner (Scheme 91). The highly electrophilic cyclopropapyrroloindole (CPI) unit is responsible for the potent cytotoxicity (**521** represents the general structure). Although a number of creative and diverse strategies have been implemented for the total synthesis of each of these compounds, one of two methods has generally been utilised for the late-stage formation of the pyrrole *via* generation of the spiro-fused cyclopropane: (i) use of a five-membered dihydropyrrole; and (ii) use of a tetrahydropyridine. Boger was the first to complete the total synthesis of CC-1065,[187] duocarmycin SA[188,189] and yatakamycin[190–192] (Scheme 91), and introduced the pyrrole/CPI (**521**) *via* deprotonation of the phenol of the general structure **520** and displacement of a leaving group appended to a dihydropyrrole. Natsume first demonstrated the displacement of a leaving group attached to a tetrahydropyridine



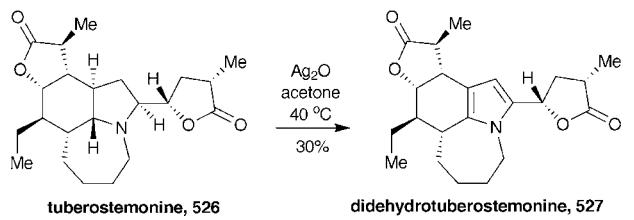
Scheme 90 Synthesis of molliorin-B by Cafieri.



Scheme 91 Duocarmycin SA, CC-1065 and yatakemycin natural products, and general strategies utilised to access the pyrrole heterocycle.

(general structure **522**) for formation of the pyrrole/CPI unit (**521**) in the racemic synthesis of duocarmycin SA (**523**).[193] Of the two strategies, this utilisation of the five-membered dihydropyrrole (**520**)[194,195] is more common than the approach using tetrahydropyridines (**522**)[196] for pyrrole/CPI formation during total synthesis of these compounds.

3.6.3 Didehydrotuberostemonine. During the synthesis of tuberostemonine (**526**, Scheme 92), it was discovered that decomposition of the natural product began to occur within hours, an outcome that made purification and spectral characterisation difficult.[197] The rapid decomposition was thought to be courtesy of facile oxidation of the pyrrolidine ring, and Wipf used this information to his advantage in the preparation of didehydrotuberostemonine (**527**, Scheme 92). Crude **526**, which

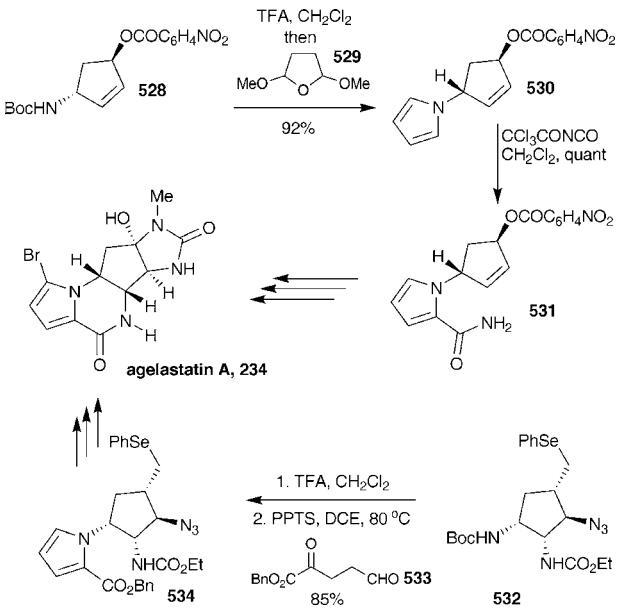


Scheme 92 Wipf's oxidation of tuberostemonine to didehydrotuberostemonine.

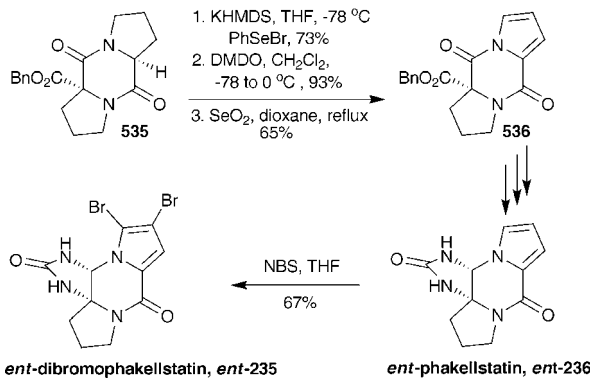
was already contaminated with decomposition products, was immediately treated with silver oxide in acetone to induce oxidation in a controlled manner, producing the markedly more stable natural product didehydrotuberostemonine (**527**).

3.6.4 Agelastatin. Only two of the syntheses of agelastatin A (**234**) covered in this review prepare the pyrrole *en route*. Tanaka (Scheme 93, top)[198,199] and Du Bois (Scheme 93, bottom)[200] both condensed a primary amine, unmasked *in situ* using TFA, with a 1,4-dicarbonyl compound or equivalent (**529** or **533**, respectively) to yield the cyclopentene or cyclopentane framework with an appended pyrrole (**530** or **534**, respectively).

3.6.5 Dibromophakellstatin. The first asymmetric synthesis of a member of the phakellin family by Romo is the only example featured in this review where the pyrrole was prepared *en route* (Scheme 94).[201] Compound **535** was prepared *via* the dimerisation of proline and subsequent desymmetrisation of the

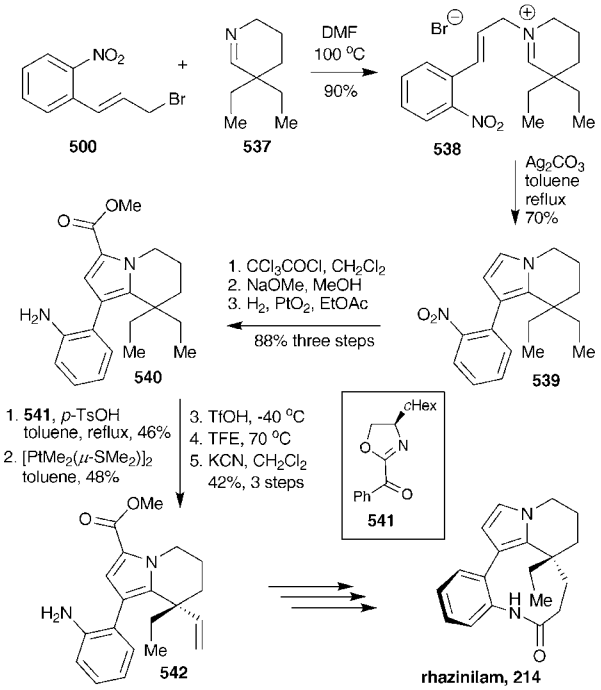


Scheme 93 Syntheses of agelastatin A by Tanaka (top) and Du Bois (bottom) that install the pyrrole ring *en route*.

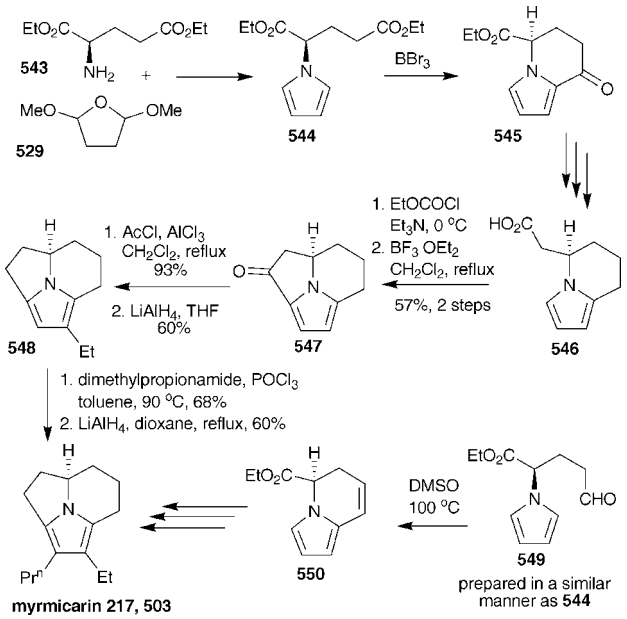


Scheme 94 First enantioselective synthesis of dibromophakellstatin by Romo, featuring desymmetrisation of a proline dimer and pyrrolidine oxidation to a pyrrole.

C_2-symmetric diketopiperazine *via* mono enolate acylation. Compound **535** was converted to the pyrrole in a three-step process entailing first selenide installation, then oxidation to the selenoxide with accompanied elimination to the dihydropyrrole, and finally oxidation to the pyrrole using selenium dioxide. Compound **536** was converted to *ent*-phakellstatin (*ent*-**236**), which was brominated to yield *ent*-dibromophakellstatin (*ent*-**235**).

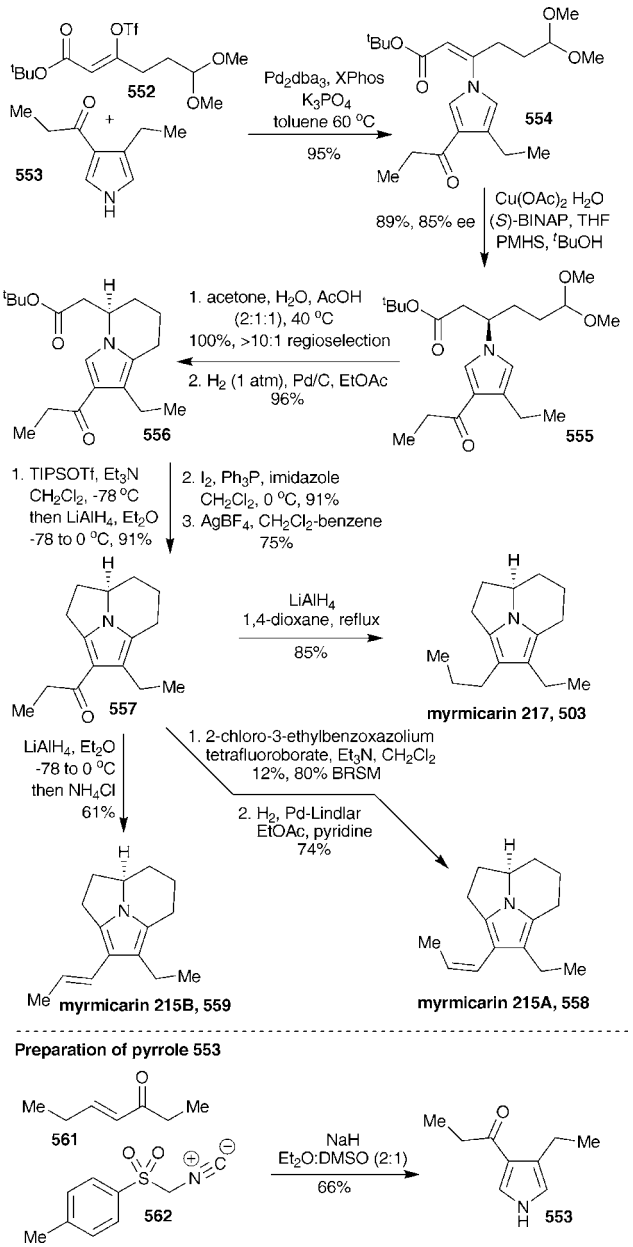


Scheme 95 Desymmetrisation of ethyl groups *via* a chiral platinum complex in Sames' synthesis of rhazinilam.



Scheme 96 The first asymmetric synthesis of myrmicarin 217 by Vallée (top), and modification to the synthesis reported by Lazzaroni (bottom).

3.6.6 Rhazinilam. Sames' preparation of rhazinilam (**214**, Scheme 95) is another excellent example of the use of C–H bond activation in total synthesis.[106,107] The coupling of 2-nitrocinnamyl bromide (**500**) and the imine **537**, followed by oxidative cyclisation induced with Ag_2CO_3, yielded the pyrrole **539** to which an ester was appended to decrease the sensitivity of the heterocycle towards reaction with electrophiles. The highlight of the synthesis was treatment of **540** with the chiral oxazolinyl ketone **541** to form an imine capable of coordinating dimethyl platinum. Activation of the platinum complex with triflic acid induced asymmetric dehydrogenation, yielding the alkene **542** with enantiomeric excesses ranging from 60 to 75%. This intermediate was then elaborated to rhazinilam.



Scheme 97 Synthesis of three tricyclic myrmicarin alkaloids from a common intermediate by Movassaghi.

3.6.7 Myrmicarin alkaloids. The first asymmetric synthesis of myrmicarin 217 (**503**) by Vallée[202] installed the pyrrole unit early, and utilised an amino acid derivative to set the chirality of the natural product (Scheme 96, top). Thus, condensation of the diethyl ester of D-glutamic acid (**543**) with tetrahydro-2,5-dimethoxyfuran (**529**) produced **544** which underwent a series of stepwise Friedel–Crafts type acylations and subsequent functional group manipulations to arrive at the natural product. Following the work of Vallée, Lazzaroni published a route that also started with **543**[203] (Scheme 96, bottom). The difference in the two strategies was that Lazzaroni utilised a dehydrative cyclisation of the aldehyde **549** to form the six-membered ring, instead of a Friedel–Crafts acylation.

Movassaghi's synthesis of myrmicarins 215A (**558**), 215B (**559**) and 217 (**503**)[204] installed the pyrrole using a palladium-mediated *N*-vinylation reaction between **553** and the vinyl triflate **552** to yield **554** (Scheme 97). Copper-catalyzed conjugate reduction of the enoate **554** utilising BINAP as the chiral influence and polymethylhydrosiloxane as the stoichiometric reductant installed the asymmetric center of **555** in 85% ee. After a series of cyclisation events, the common intermediate **557**, featuring the requisite tricyclic core, was in hand. Selective manipulations of the propylketone side chain of **557** rendered the myrmicarins 215A, 215B and 217.

4 Conclusions

This review has drawn together approaches for constructing pyrroles amidst the challenges and complexities of natural product frameworks. In closing we marvel at the many and varied ways by which synthetic chemists have incorporated the pyrrolic heterocycle into their strategies towards pyrrole-containing natural products. Many such routes draw upon somewhat traditional pyrrole chemistry, indeed strategies used for decades by porphyrin aficionados. Much of the more recent work delves into a new era for the synthesis of pyrroles, and all concomitantly exploit and wrestle with the exquisite reactivity of the pyrrolic moiety.

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