THE TOTAL SYNTHESIS OF PYRROLE-CONTAINING AND RELATED MARINE NATURAL PRODUCTS

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Abstract. *The pyrrolic framework is a ubiquitous motif encountered in both terrestrially- and marine-derived natural products. This review delineates various methods for the synthesis and manipulation of pyrrole and its derivatives as means for effecting the total synthesis of a diverse range of biologically active systems isolated from marine organisms. The examples presented here derive from the authors' longstanding activities in the area.*

Contents

1. Introduction

The five-membered and electron-rich aromatic heterocycle 1*H*-pyrrole **1** (Figure 1) is a motif encountered in numerous natural products, in medicinal chemistry, in materials science and in supramolecular chemistry.[1] So, for example, it is not only the key structural feature in the pigments of life[2] but also a central component in many secondary metabolites derived from both terrestrial and marine organisms. Representative examples in the latter category include (–)-agelastatin A **2**,[3] a potent anti-cancer agent, isoheptylprodigiosin **3**,[4] an anti-microbial agent, and (+)-heronapyrrole C **4**,[5] a rare example of a naturally-occurring 2-nitropyrrole and one that acts on Gram-positive bacteria without exerting cytotoxic effects against healthy mammalian cell lines. On the other hand, atorvastatin **5** (also known as Lipator®),[6] a statin medication used to prevent cardiovascular disease, tolmetin **6**,[7] a non-steroidal anti-inflammatory agent and premazepam **7**,[8] a compound that exerts anxiolytic and sedative effects in humans, are examples of synthetically-derived entities that embody the title ring system. Compounds **5** and **6** are clinically deployed drugs.

Interest in pyrrole-containing systems is ongoing not only because of their capacities to serve as scaffolds for drug development[9] but also because natural products that embody them continue to be identified as compounds with notable biological activities and so possessing therapeutic potential.[10] This situation reflects the continuing relevance of natural products more generally as precursors to or inspirations for new drug entities[11] and with those derived from marine environments representing an increasingly important subset of such compounds.[12]

In an extended and ongoing campaign being conducted within our laboratories, we have been focused on developing new methods for the assembly of biologically active and pyrrole-containing natural products, especially ones derived from the marine environment. Herein we delineate our activities in the area as a means of demonstrating the remarkable diversity of chemical transformations that can be used to manipulate pyrroles. In addition, some new methods for the assembly of this heterocycle are also presented so as to emphasize the seemingly endless ways in which it can be constructed.

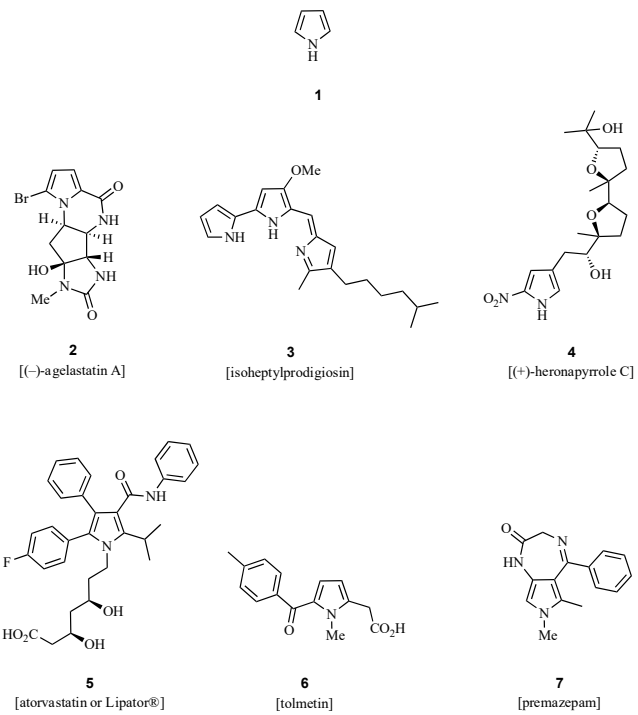


Figure 1. The structure of parent pyrrole **1** together examples of natural products **2**-**4**, and medicinal agents **5**-**7** incorporating this ring system.

2. The longamides and related brominated pyrrole-2-carboxamides

Certain sponges, especially those of the genus *Agelas* encountered on the world's tropical reefs, produce pyrrole-2-carboxamides including many that are brominated at C4 and/or C5 of the heterocyclic ring.[13] Representative examples of such metabolites include agelastatin A **2** (Figure 1) and, as shown in Figure 2, longamide **8**, longamide B **9**, the corresponding methyl ester **10**, hanishin **11** and dispyrin **12**.[14] Many of these display intriguing biological effects including anti-bacterial ones and/or are cytotoxic toward certain cancer cell lines.

Such features prompted us to develop syntheses of compounds **8**-**11** and the approach used in obtaining them is shown in Scheme 1.[15] Thus, parent pyrrole **1** was acylated at C2 using trichloromethyl chloroformate (diphosgene) as the electrophile and the product ketone **13** then subjected to two-fold and completely regioselective halogenation using molecular bromine in acetic acid. Dibromide **14** so formed was reacted in a haloform-type process with aminoacetaldehyde dimethyl acetal **15** and the ensuing amide **16** was converted into longamide **8** through acid-catalyzed acetal hydrolysis. This final product is in equilibrium with the open-chain aldehyde **17** as evidenced by the capacity of this system to participate in a Horner-Wadsworth-Emmons olefination reaction under standard conditions and so affording, presumably *via* an intramolecular hetero-Michael addition reaction involving the initially-formed acrylate **18**, longamide B methyl ester **10**, the structure of which was confirmed by single-crystal X-ray analysis. Saponification of this last compound followed by an acidic work-up gave the corresponding carboxylic acid, namely longamide B itself (*viz*. **9**) and esterification of this with ethanol in the presence of mineral acid then delivered hanishin **11**.

Clearly this approach to compounds **8**-**11** provides them in racemic form and in many instances the natural products themselves are also obtained as racemates or only in (partially) enantiomerically enriched form (and presumably because of the operation of retro hetero-Michael fragmentation/re-addition processes as shown in the equilibrium between isomers **18** and **10**). Nevertheless, the *S*-enantiomeric forms of these

compounds can be prepared from *L*-aspartic acid β-methyl ester *via* a lactamization pathway and thereby allowing for the absolute configurations of the optically active natural products to be established.[16] Other enantioselective syntheses have followed,[17] as have biological evaluations of these natural products as well as various non-natural analogues and so revealing that esters **10** and **11** exert some cytotoxic effects against human lung adenocarcinoma (A549) and human prostate cancer (PC3) cells.[18] Interestingly, the C-4 debromo-analogue of hanishin is slightly more active than the natural product.[18]

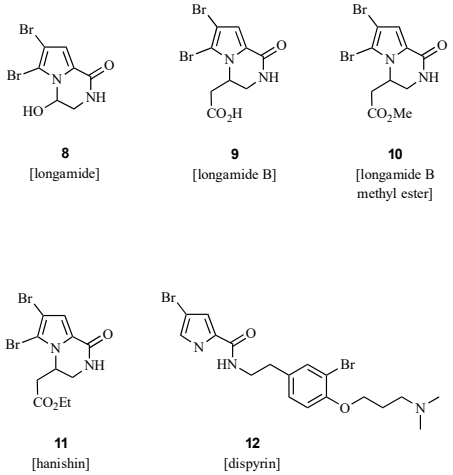
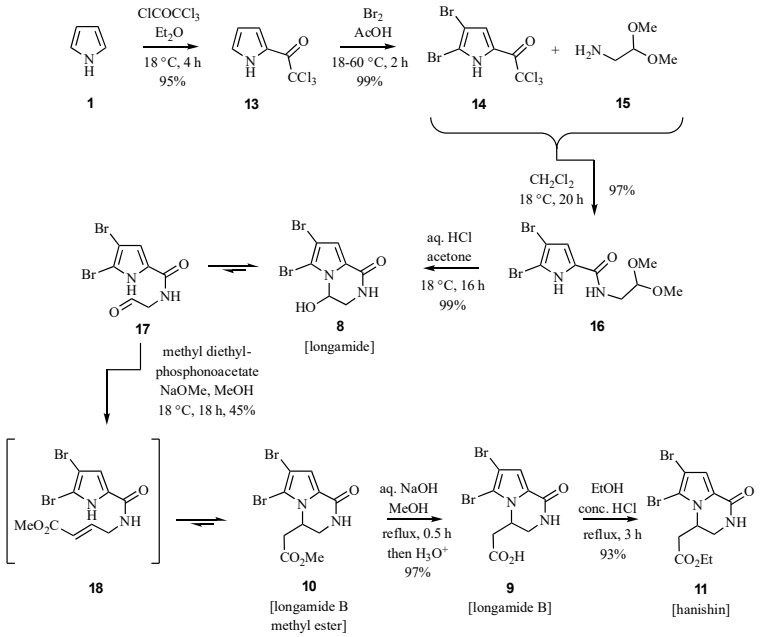


Figure 2. The structures of longamide **8**, longamide B **9**, the corresponding methyl ester **10**, hanishin **11** and dispyrin **12**.



Scheme 1. The first syntheses of natural products **8**-**11**.

3. The lamellarins and related compounds

The first members of the lamellarin class of natural product were described in 1985 by Clardy *et al.*[19] and a multitude of others have been reported in the interim.[10,20,21] These take two broad structural forms with the simpler ones embodying 3,4-diarylated pyrrole 2-carboxylic acid moieties as exemplified by lamellarins O **19** and Q **20**. The more complex ones are, in essence, ring-fused variants of the simpler ones and include lamellarins K **21** and W **22**. The significant cytotoxic, anti-viral and other biological effects displayed by members of the latter group, as well as certain related natural products, such as the lukianols (*e.g.* A/**23**), ningalins (*e.g.* B/**24**), polycitones (*e.g.* B/**25**) and storniamides (*e.g.* A/**26**), have prompted many efforts to develop routes to such compounds. These endeavors have been spurred on by the often very limited quantities of such materials available from the natural sources. Our initial efforts to prepare compounds such as lamellarin K built upon our straightforward and successful routes to its simpler congeners that we now describe (Figure 3).

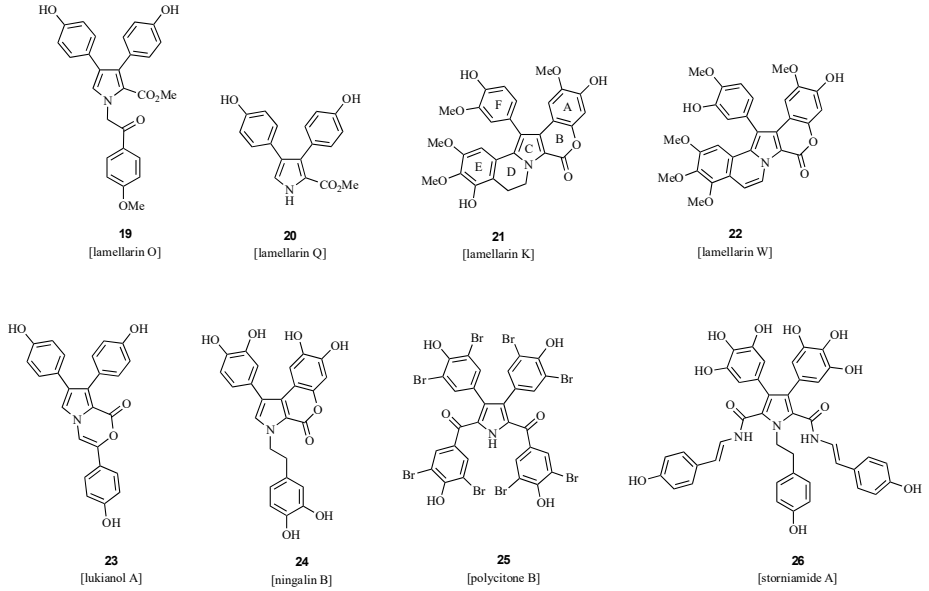
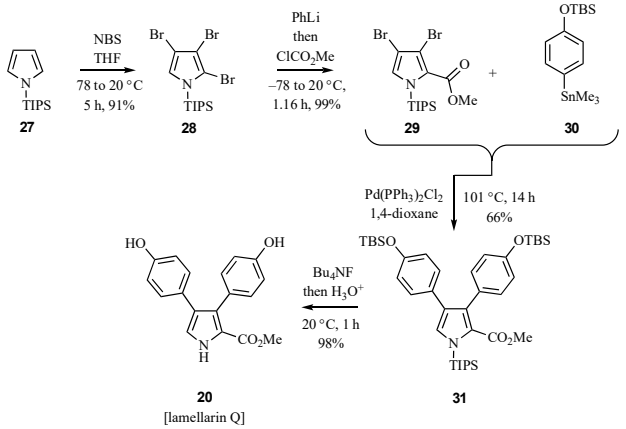


Figure 3. The structures of representative lamellarins **19**-**22** and the related natural products **23**-**26**.

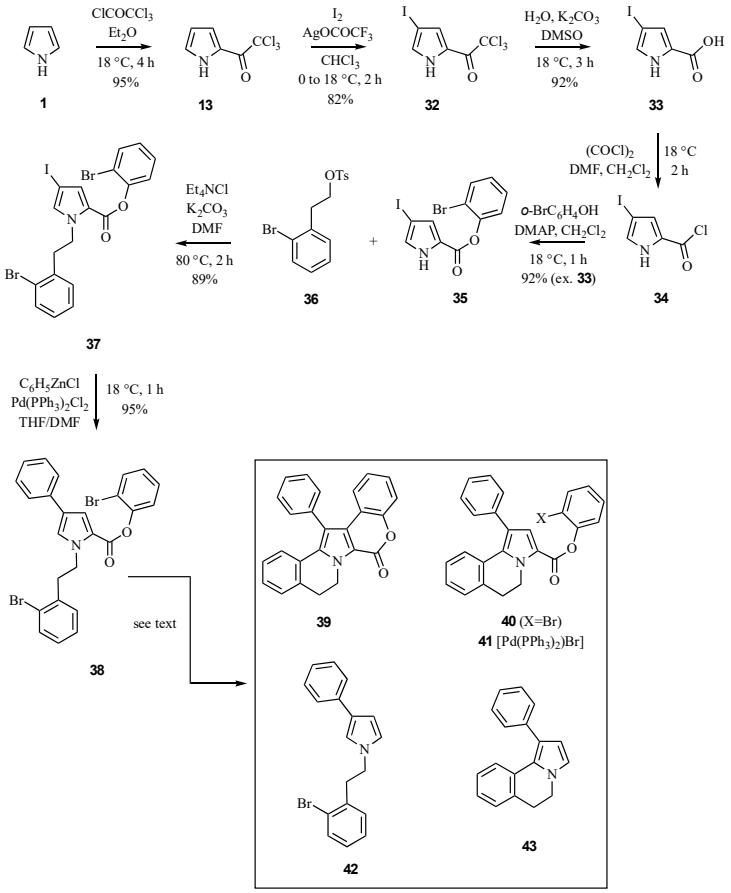
The synthetic route we established[22] to obtain lamellarin Q is shown in Scheme 2 and started with the three-fold bromination of *N*-TIPS-substituted pyrrole **27** followed by treatment of the resulting tribromide **28** with phenyllithium and trapping of the ensuing C-2 lithiated pyrrole with methyl chloroformate to give ester **29**. Stille cross-coupling of the last compound with two equivalents of arylstannane **30** then gave the 3,4-diarylated pyrrole **31** and treatment of this tetra-*n*-butylammonium fluoride afforded, *via* three-fold desilylation, lamellarin Q **20**.

Related sequences were used to prepare lamellarin O **19** and lukianol A **23**.[22]

Our attempts to employ related chemistry for the purposes of assembling the basic polycyclic framework associated with the more complex lamellarins such as **21** and **22** are shown in Scheme 3 and, once again, exploited the reaction of parent pyrrole **1** with diphosgene so as the form the trichloromethyl ketone **13**.[23] Regioselective mono-iodination of compound **13** with molecular iodine in the presence of silver trifluoroacetate afforded halide **32** that was subjected to the latter stages of a haloform-type reaction and so producing acid **33**.



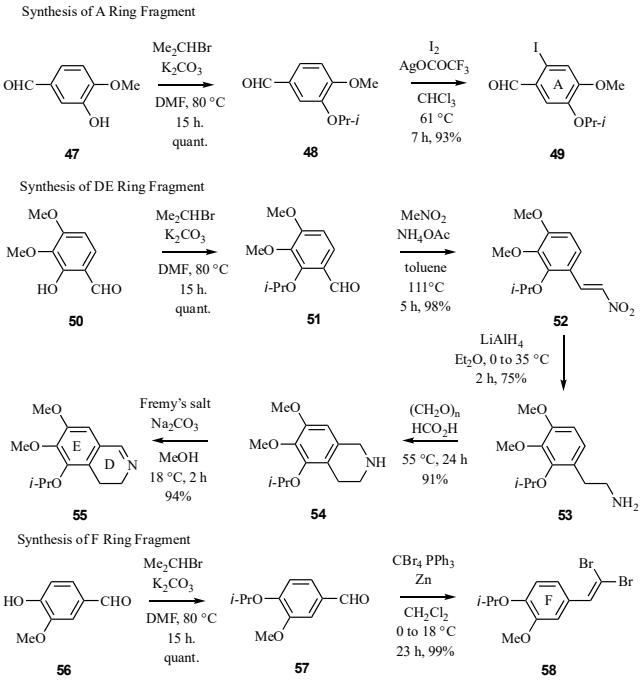
Scheme 2. Synthetic route to lamellarin Q.



Scheme 3. The two-fold, intramolecular Heck approach to the polycyclic framework of the more complex lamellarins.

The readily derived acid chloride **34** was reacted with *o*-bromophenol and the ensuing pyrrole ester **35** alkylated at nitrogen with tosylate **36** and thereby producing compound **37** that was itself subjected to a Negishi cross-coupling with *in situ* generated phenylzinc chloride to give the C4-arylated pyrrole **38**. The expectation (hope) was that this last compound would undergo a two-fold intramolecular Heck reaction and thereby form compound **39** that embodies the full polycyclic framework of the more complex lamellarins such as congener K **21**. In the event, on treating substrate **38** with $Pd(OAc)_2$ and NaOAc in the presence of PPh_3 at 135 °C then compound **39** was indeed obtained and its structure confirmed by single-crystal X-ray analysis. Unfortunately this product was only formed in 16% yield and as one component of a complex mixture. On attempting the same reaction at 110 °C then a chromatographically separable mixture of compounds **40** (17%) and **41** (8.5%) was obtained and the structure of the latter also confirmed by single-crystal X-ray analysis. Amongst various further efforts undertaken so as to effect the desired conversion in an efficient manner, substrate **38** was treated with the Hermann-Beller catalyst at elevated temperatures but now a 3:1 mixture of compounds **42** and **43** was obtained in 52% combined yield.

The disappointing outcomes just described together with the failure of efforts to implement a more biomimetic approach[24] that also sought to exploit the normally well-defined chemical reactivity of intact pyrroles prompted a reassessment of our strategy and led to one in which this heterocyclic ring system was constructed toward the end of the synthesis.[25] The highly effective and modular approach that emerged is exemplified by its application to the synthesis of lamellarin K **21**. The opening stages are shown in Scheme 4 and involved the assembly of the A-, DE- and F-ring fragments of the target.

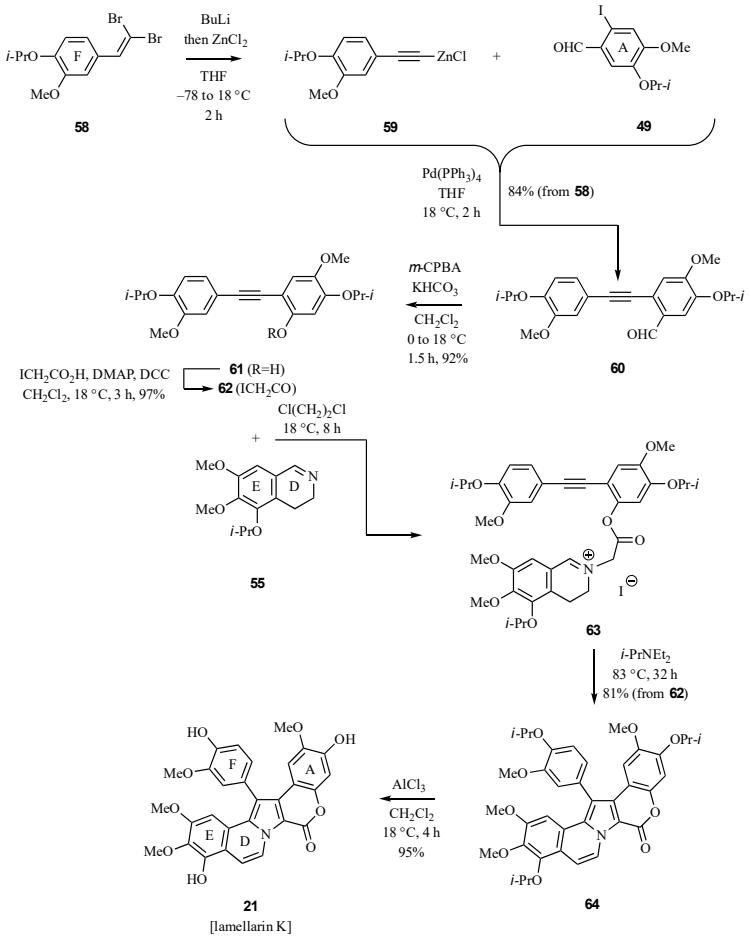


Scheme 4. The synthesis of three key ring-fragments required for the assembly of lamellarin K **21**.

The first of these fragments was prepared by the conversion of isovanillin **47** into the corresponding isopropyl ether **48** that was itself subjected to iodination using molecular iodine in the presence of silver trifluoroacetate and so providing halide **49**. Similarly, the synthesis of the DE-ring fragment started with the conversion of phenol **50** into the isopropyl ether **51** and the associated aldehyde residue of the latter was engaged in a Henry reaction that afforded the β-nitrostyrene **52**. Reduction of compound **52** with lithium aluminium hydride then gave the corresponding β-phenethylamine **53** that on subjection to a

Pictet-Spengler reaction with paraformaldehyde in the presence of formic acid gave the tetrahydroisoquinoline **54**, oxidation of which with Fremy's salt then provided the target dihydroisoquinoline **55**. The relevant F-ring fragment was formed over just two steps, the first of these involving the etherification of vanillin to provide compound **57**, the aldehyde residue of which was subjected to a Corey-Fuchs olefination reaction to give β,β-dibromostyrene **58**.

The assembly of the three key ring fragments prepared as described above is shown in Scheme 5 and started with treatment of dibromide **58** with *n*-BuLi (to effect a Fritsch-Buttenberg-Wiechell rearrangement) and the transmetalation of the resulting lithium acetylide with zinc chloride and so forming the zincate **59** that was engaged, *in situ*, in a Negisihi cross-coupling reaction with aryl iodide **49** to produce the tolan **60**.



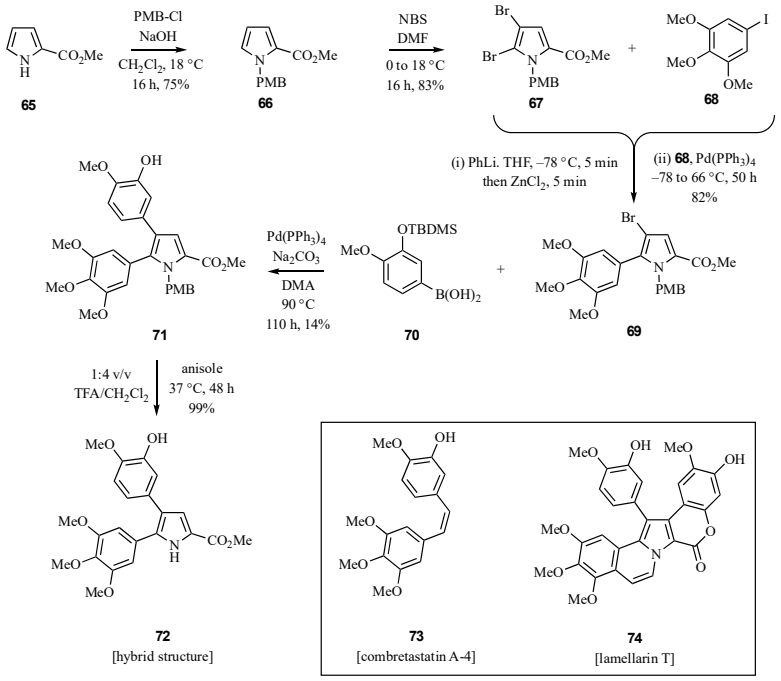
Scheme 5. Using an intramolecular azomethine ylide cycloaddition reaction for the late-stage assembly of the pyrrole ring associated with lamellarin K **21**.

Subjection of compound **60** to a Dakin oxidation reaction using *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of potassium bicarbonate gave, *via* cleavage of the initially generated formate, the phenol **61** that was esterified using α-iodoacetic acid and so providing ester **62**. The last compound was used to *N*-alkylate the dihydroisoquinoline **55** and the ensuing salt **63** deprotonated *in situ* with Hünig's base and

the resulting azomethine ylide subjected, by heating, to an intramolecular [3+2] cycloaddition reaction with the pendant tolan triple bond. The anticipated dihydropyrrole was not observed because of its ready oxidation to the corresponding pyrrole **64**, the *tris*-isopropyl ether of lamellarin K. In the final step of the reaction sequence compound **64** was treated with $AlCl_3$ in dichloromethane at ambient temperatures and so delivering target **21**.

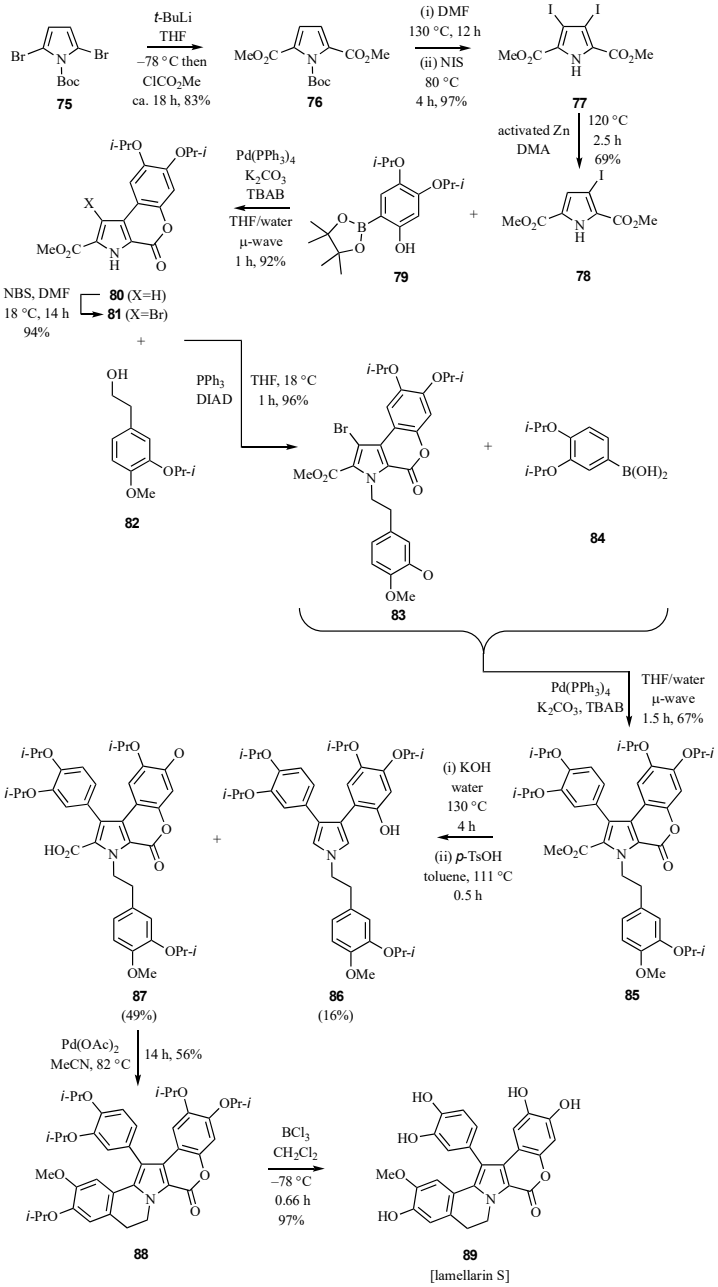
The modular and relatively convergent nature of this reaction sequence allows it to be carried out at multigram scale. As such it sustained major and extended efforts to develop this compound as a therapeutic agent. Furthermore, this approach was readily extended to the preparation of lamellarins T, U and W.[25] It has also been adapted to the solid phase and so allowing for the construction of lamellarin libraries.[26]

The structural similarities between certain of the lamellarins (*e.g.* congener T) and the tubulin binding agent combretastatin A-4 prompted us[27] to develop syntheses of hybrids of these systems as exemplified in Scheme 6. The illustrated reaction sequence began with the protection of the pyrrole nitrogen within compound **65** as the corresponding *p*-methoxybenzyl or PMB derivative and so affording compound **66**. Two-fold and regioselective dihalogenation of the last compound using NBS afforded compound **67** that on lithiation using phenyl lithium followed by transmetalation with zinc chloride gave the corresponding zincate that participated in a regioselective Negishi cross-coupling with aryl iodide **68** to give product **69**. This, in turn, engaged in a Suzuki cross-coupling with aryl boronic acid **70** and thus delivering the biarylated pyrrole **71**. The PMB group associated with the latter was cleaved with aqueous TFA using added anisole to trap the benzylic cation formed during this process. The target compound **72** so formed was subjected to single-crystal X-ray analysis. Biological evaluation of compound **72** (and various of its analogues produced by related means) established that it possessed similar anti-mitotic properties to the "parent" compounds **73** and **74**. This outcome suggests that the pyrrole and ester residues within hybrid **72** could be used for prodrug formation and/or targeted drug delivery purposes.[27]



Scheme 6. Synthesis of the combretastatin A-4/lamellarin T hybrid **72**.

A rather different strategy to that shown in Scheme 5, and involving manipulation of an intact pyrrole, was used to prepare the pentacyclic lamellarin S (Scheme 7).[28]



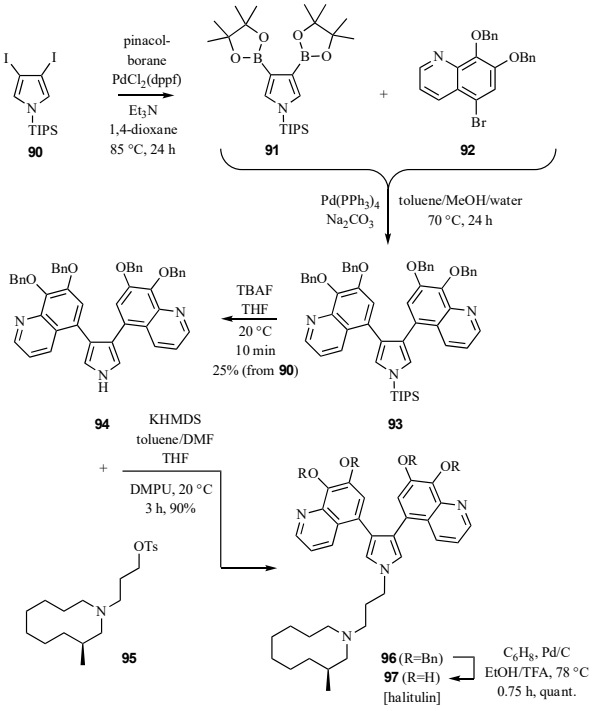
Scheme 7. A total synthesis of lamellarin S **89**.

Thus, as revealed immediately above and following protocols established by Fürstner and co-workers,[29] the readily available dibrominated and *N*-Boc protected pyrrole **75** was treated sequentially with *t*-BuLi then methyl chloroformate to give the bis-ester **76**. Heating this last compound in hot DMF to effect cleavage of the Boc group and reacting the product so-formed with excess *N*-iodosuccinimide (NIS)

afforded di-iodide **77** and this could be reduced with activated zinc to the corresponding mono-iodide **78** that itself engaged in a Suzuki-Miyaura cross-coupling with the arylboronate **79** and thus producing, after an *in situ* lactonization of the initially formed product, the tricyclic system **80**. Bromination of this last compound using NBS gave halide **81**, the ring-nitrogen of which served as a nucleophile in a Mitsunobu reaction with the β-phenethyl alcohol **82** and so providing the fully substituted pyrrole **83**. In a second Suzuki-Miyaura cross-coupling reaction compound **83** was reacted with the boronic acid **84** under standard conditions and thereby producing compound **85** that now embodies most of the key structural elements of the final target. In the first of the four remaining steps required to complete the synthesis, ester **85** was treated with potassium hydroxide and the saponification mixture so formed was then subjected to acidic work-up. This process not only cleaved the methyl ester of the substrate but also opened the associated lactone ring with these events also being followed by some decarboxylation. In order to re-establish the lactone residue the crude reaction product was treated with catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH) in toluene and by such means a chromatographically separable mixture of compounds **86** and **87** was obtained with the latter predominating. Treatment of product **87** with $Pd(OAc)_2$ in refluxing acetonitrile resulted in a decarboxylative and intramolecular Heck reaction to give the pentacyclic system **88** and on exposing this to BCl_3 then five-fold *iso*-propyl ether cleavage took place to give lamellarin S **89**, the spectral data for which matched those recorded on the natural product.

4. Halitulin

The alkaloid halitulin (Scheme 8), a strongly cytotoxic compound isolated from a South African sponge,[30] embodies two distinct structural elements, a pyrrole core bearing two oxygenated quinolone residues at C3 and C4 together with an methylazacyclodecane unit linked, *via* a propylene chain, to N1 (of the pyrrole). The fragment incorporating the saturated nitrogen heterocycle is almost certainly biogenetically related to the co-occurring 1,5-diazacyclotetradecane named haliclorensin.[30]



Scheme 8. A total synthesis of halitulin **97**.

As a culmination of various earlier efforts to establish a synthesis of halitulin,[31] our group and that of Steglich in Münich combined forces to develop the route shown in Scheme 8.[32] So, the readily available C3,C4 di-iodinated pyrrole **90** was subjected to a two-fold Miyaura borylation reaction and the product *bis*-boronate **91** then engaged in a double-barrelled cross-coupling reaction with C5-brominated quinolone **92** obtained by a new route.[32] Desilylation of product **93** gave the *N*-deprotected pyrrole **94** that was alkylated with the enantiomerically pure tosylate **95**, a compound that had been obtained in homochiral form by using, *inter alia*, ring-closing metathesis (RCM) protocols. By such means halitulin tetra-benzyl ether **96** was obtained and the associated protecting groups could be cleaved using transfer hydrogenolysis techniques and so providing halitulin **97** itself and thereby establishing that the natural product possesses the *S*-configuration at the methyl-bearing carbon of the azacyclodecane residue.

5. The discoipyrroles

In 2013 MacMillan and co-workers described the isolation of discoipyrroles A-D **98-101**, respectively, (Figure 4) from the marine-derived *Bacillus hunanensis* strain SNA-048.[33] These represent the first examples of compounds, natural or otherwise, embodying (in the cases of congeners A, B and D) a 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core. The first three of these compounds were isolated as racemates and the last as a *ca*. 1:1 mixture of diastereoisomers. All four compounds proved to be strong inhibitors of the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts. As such they have considerable therapeutic potential in certain settings.

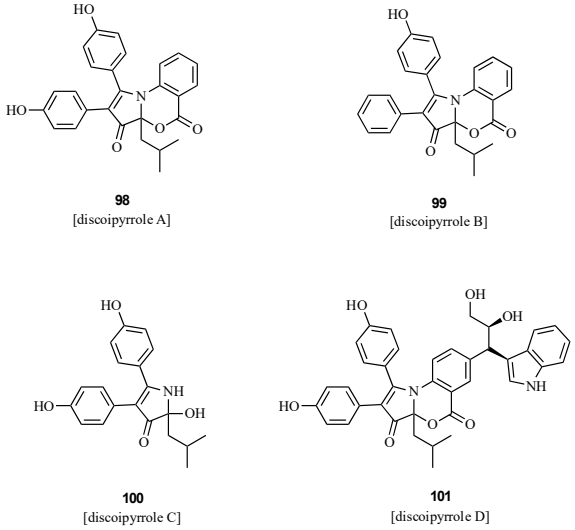
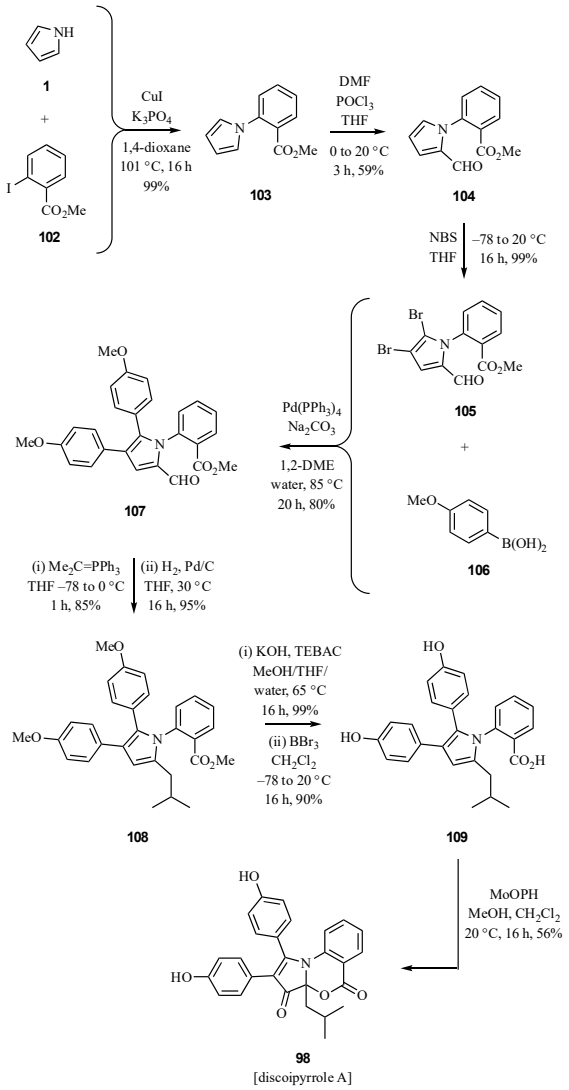


Figure 4. The structures of the currently known members **98-101** of the discoipyrrole class of marine natural product.

Given their notable biological properties and structural resemblance to certain of the lamellarin-type natural products we sought to use our knowledge of pyrrole chemistry to achieve potentially modular syntheses of the discoipyrroles. In particular, we imagined that the basic frameworks of these could be assembled around a pyrrole nucleus and that some sort of late-stage oxidative cyclization process could be used to create the signature 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-dione core of them.

The successful implementation of such an approach[34] is shown in Scheme 9 and began, in the case of discoipyrrole A **98**, with the *N*-arylation of parent pyrrole **1** with methyl *o*-iodobenzoate **102** and so affording compound **103** that was subjected to a regio- and chemo-selective Vilsmeier-Haack formylation reaction to produce the pyrrole 2-carboxaldehyde **104**. Controlled bromination of the last compound using NBS then gave dibromide **105** that was subjected to a two-fold Suzuki-Miyaura cross-coupling reaction

with the arylboronic acid **106** and thus affording the tri-arylated pyrrole **107**. Wittig olefination of the aldehydic residue within compound **107** and hydrogenation of the resulting alkene then gave the *iso*-butylated derivative **108** that was subjected to sequential saponification of the ester residue and two-fold demethylation of the anisole sub-units and thus affording the diphenolic carboxylic acid **109**. In the final and pivotal step of the reaction sequence, the tetra-substituted pyrrole **109** was subjected to reaction with freshly prepared oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) and thereby effecting an oxidative cyclization reaction of the desired form and so generating discoipyrrole A **98**.



Scheme 9. A total synthesis of discoipyrrole A **98**.

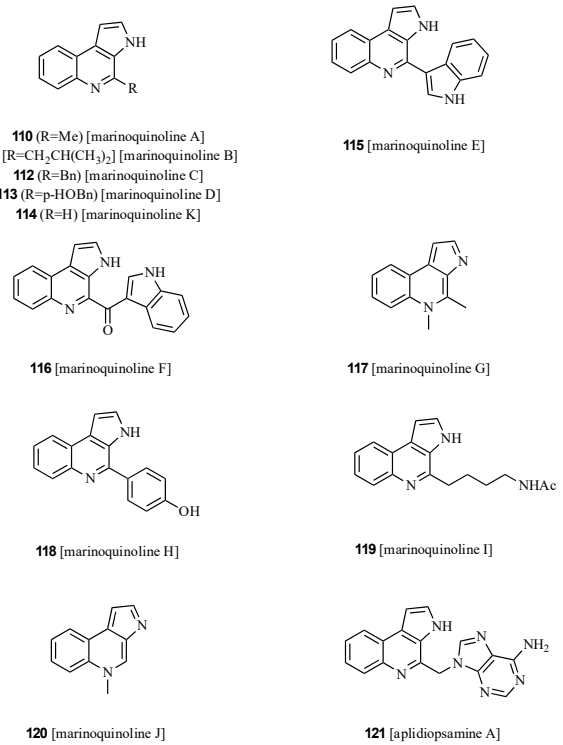
An analogous reaction sequence that exploits the capacity to engage dibromide **105** in regio-controlled mono-arylation reactions under Suzuki-Miyaura conditions was used to prepare discoipyrrole B **99** with the structure of this natural product being confirmed by single-crystal X-ray analysis. Subjecting an

analogue of compound **109** lacking an *N*-aryl group to reaction with MoOPH provided a means for preparing discoipyrrole C[35] and further emphasizing the functional group tolerance of this reagent.

The synthesis of the most structurally complex of the discoipyrroles, *viz*. congener D **101**, was also achieved by the same strategy and involved a mid-stage, MoOPH-promoted oxidative cyclization reaction and carrying forward the resulting 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-dione-containing compound in a series of further manipulations that demonstrates the robustness of this framework. The synthetic material was obtained as a 1:1 mixture of diastereoisomers and the derived spectral data proved an excellent match with those recorded on the natural product.[36]

6. The marinoquinolines

Marinoquinoline A **102**, the first member of a family of marine natural products bearing this name and that now numbers eleven (Figure 5), was obtained from a gliding bacterium associated with seaweed found in Southern Thailand.[37] Subsequently, Müller[38] then Fenical[39] obtained the remaining members of the class, *viz*. **103**-**112**, from various bacterial sources, including marine ones, while the structurally related aplidiopsamine A **113** was isolated by Carroll and co-workers from an ascidian collected in temperate Australian waters.[40] All of these compounds embody the 3*H*-pyrrolo[2,3-*c*]quinolone core (see structure **106**) as a key if not the key structural feature and various of them exert notable biological effects including anti-bacterial ones and/or a capacity to inhibit certain enzymes including acetylcholinesterase (AChE)[37] or PDE4.[41]



110 (R=Me) [marinoquinoline A]
111 [R=$CH_2CH(CH_3)_2$] [marinoquinoline B]
112 (R=Bn) [marinoquinoline C]
113 (R=p-HOBn) [marinoquinoline D]
114 (R=H) [marinoquinoline K]

115 [marinoquinoline E]

116 [marinoquinoline F]

117 [marinoquinoline G]

118 [marinoquinoline H]

119 [marinoquinoline I]

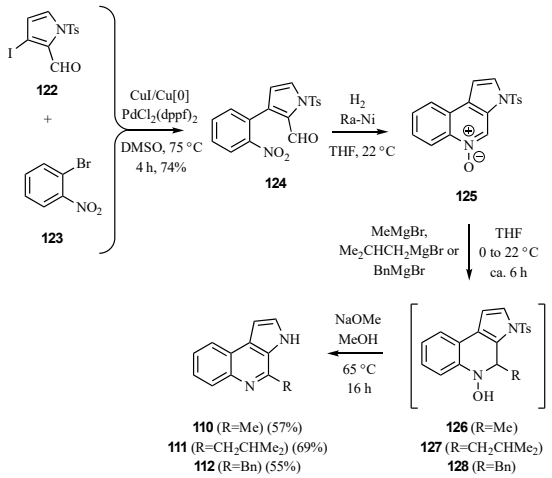
120 [marinoquinoline J]

121 [aplidiopsamine A]

Figure 5. The structures of the currently known members **110**-**120** of the marinoquinoline class of marine natural product and the structurally related aplidiopsamine A **121**.

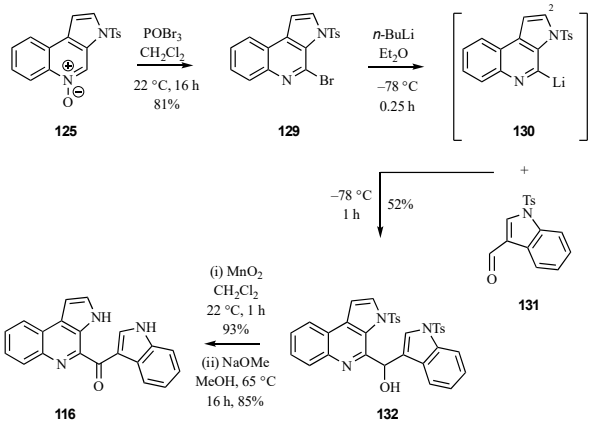
Both the structural features and biological profiles of these compounds attracted our attention and prompted us to develop syntheses of them.[42] A central feature of our approach was the deployment of a palladium-catalyzed Ullmann cross-coupling/reductive cyclization protocol that has served us well in

earlier work.[43] So, for example, the palladium-catalyzed Ullmann cross coupling of the C3-iodinated pyrrole **114** (Scheme 10), prepared by the method of Ghosez,[44] with *o*-bromonitrobenzene **115** afforded the anticipated C3-arylated pyrrole **116**. Reductive cyclization of the last compound using dihydrogen in the presence of Raney nickel afforded the isoquinoline-type *N*-oxide **117** that was accompanied by varying quantities of the corresponding deoxygenated (over reduced) material but that could be converted back into target **117** by oxidation with *m*-chloroperbenzoic acid. Through its reaction with the relevant Grignard reagent, compound **117** could be converted into the adducts **118**-**120** each of which was re-aromatized, and the associated sulfonamide residue cleaved, using sodium methoxide to give marinoquinolines A-C **102**-**104**, respectively. The structures of each of these was confirmed by single-crystal X-ray analysis.



Scheme 10. Total syntheses of marinoquinolines A **110**, B **111** and C **112**.

In a variation on this approach (Scheme 11),[42] the *N*-oxide **117** could be converted, on reaction with $POBr_3$, into bromide **123** that was itself subjected to a lithium-for-halogen exchange reaction using *n*-BuLi and the lithio-species **122** so formed treated, *in situ*, with the readily accessible indole-3-carboxaldehyde **123** and thus forming the anticipated adduct **124**. This was accompanied by a chromatographically separable regio-isomer arising from migration of the lithium atom to C2 within precursor **122**.



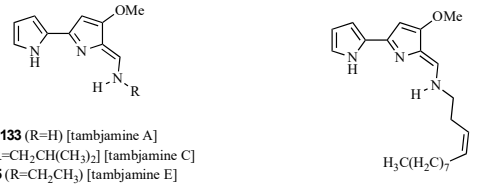
Scheme 11. A synthesis of marinoquinoline F **116**.

Oxidation of alcohol **124** with activated manganese dioxide and base-promoted cleavage of the sulfonamide residue within the product ketone then gave marinoquinoline F **108**, the structure of which was also confirmed by single-crystal X-ray analysis.

Syntheses of marinoquinolines **105-106** as well as aplidiopsamine A **113** were accomplished by related means and all the synthetically-derived samples of the natural products so-prepared were evaluated as inhibitors of acetylcholineesterase (AChE). The *iso*-butylated compound **103** (marinoquinoline B) proved to be the most active with an IC_{50} value of 3.6 (±1.8) μM.[42] This compares with an IC_{50} value of 0.6 μM reported[37] for the clinically deployed alkaloid galanthamine.

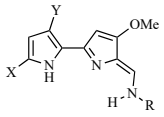
7. The tambjamines

The bipyrrolic group of alkaloids known as the tambjamines, and of which compounds **125-137** (Figure 6) are the currently known members, have been isolated from various marine and terrestrial organisms.[45] They are structurally related to the more well-known tripyrrolic prodigiosin family of alkaloids (see structure **3**) that are also obtained from both marine and terrestrial sources.[46,47]

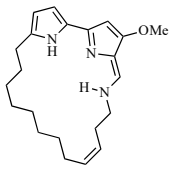


133 (R=H) [tambjamine A]
134 [R=$CH_2CH(CH_3)_2$] [tambjamine C]
135 (R=CH_2CH_3) [tambjamine E]
136 (CH_2CH_2Ph) [tambjamine F]
137 [R=$(CH_2)_{11}CH_3$] [BE-18591]

138 [tambjamine YP1]



139 (R=Y=H, X=Br) [tambjamine B]
140 (R=CH_2CH_3, X=Br, Y=H) [tambjamine G]
141 (R=$CH_2CH_2CH_3$, X=Br, Y=H) [tambjamine H]
142 [R=$CH_2CH(CH_3)_2$, X=Br, Y=H] [tambjamine I]
143 [R=$CH_2CH(CH_3)CH_2CH_3$, X=Br, Y=H] [tambjamine J]
144 [R=$CH_2CH(CH_3)_2$, X=H, Y=Br] [[tambjamine D]



145 [tambjamine MYP1]

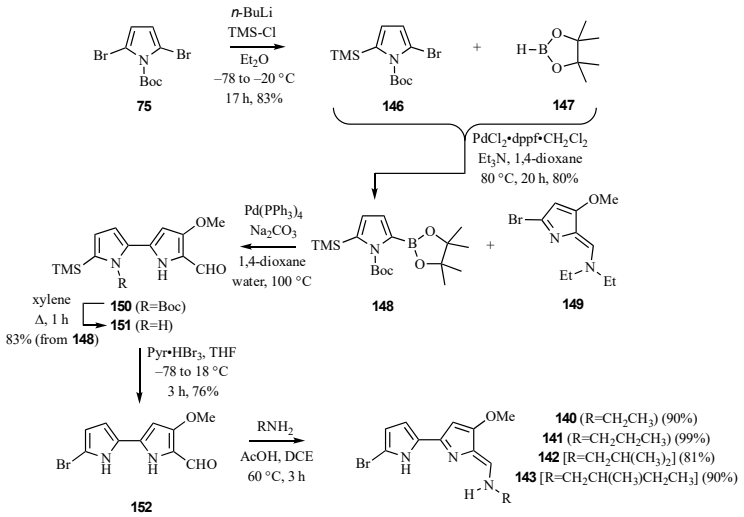
Figure 6. The currently known members **133-145** of the tambjamine class of natural product.

The simple synthetic protocol that we developed[48] for the preparation of various of the tambjamines is shown in Scheme 12 and starts with the conversion of the dibromide **75** into the monosilylated analogue **138** that could be coupled, under Miyaura-type conditions, with borane **139** to give the boronate **140**. This last compound was, in turn, engaged in Suzuki-Miyaura cross-coupling reaction with the brominated azafulvene **141** and so providing the bipyrrole **142**, the Boc group of which could be removed by thermal "cracking" to give compound **143**. Finally, an *ipso*-substitution reaction employing pyridinium bromide perbromide allowed for the regioselective formation of the key brominated bipyrrole **144**. Schiff-base condensations of this last compound with the relevant primary amine (RNH_2) then afforded the corresponding tambjamine, each of was isolated as the corresponding as the acetate salt. Sufficient quantities of such compounds could be acquired using this approach to facilitate comprehensive *in vitro*[49] and *in vivo*[50] biological evaluations of various of them. Perhaps most significantly, synthetically-derived and racemic tambjamine J **135** has been shown to strongly inhibit the growth of sarcoma 180 tumor cells implanted in mice.[50]

8. A new method for the synthesis of pyrroles

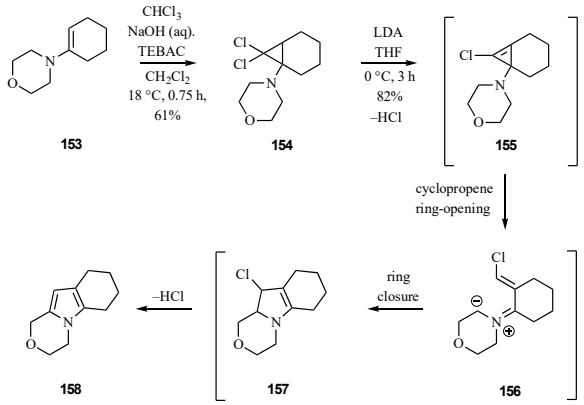
The foregoing commentary should serve to highlight the diversity of methods now available for the assembly of pyrroles as well as the manifold protocols available for effecting the regio-controlled substitution of this simple yet highly versatile ring system. Nevertheless, valuable new methods for its

assembly continue to emerge[51] and these will provide further techniques for their construction that help match the ever-expanding structural diversity of natural products embodying this remarkable heterocyclic ring system.[10,52]



Scheme 12. A synthetic route to tambjamines G-J **140-143**.

In connection with efforts to deploy *gem*-dihalocyclopropanes as building blocks in chemical synthesis,[53] we have developed a novel and simple (two-step) means for converting enamines into pyrroles. A representative example[54] is shown in Scheme 13 and involves, in the first step, treating the cyclohexanone morpholine enamine **145** with chloroform and sodium hydroxide in the presence of the phase transfer catalyst triethylbenzylammonium chloride (TEBAC). This dichlorocarbene-based addition process generates cyclopropane **146** and upon treatment of it with lithium di-isoproylamide (LDA) affords, probably *via* intermediates **147**, **148** and **149**,[55] the unusual bis-annulated pyrrole **150** in good yield. The exploitation of this very simple and potentially highly versatile protocol in the preparation of various pyrrole-containing marine natural products and/or their analogues represents an ongoing activity within our group.



Scheme 13. The conversion of enamine **153**, *via* cyclopropane **154**, into the annulated pyrrole **158**.

9. Conclusions

The distinctive, generally highly predictable and diverse reactivity patterns of pyrroles together with their frequent occurrence as key motifs within the structures of biologically active systems has clearly made for a fruitful union of synthetic and natural products chemistry. There is every reason to think that a productive relationship of this type will continue well into the future and such that both useful new synthetic strategies and medicinal agents will emerge. Superimposed on such expectations is the prospect that novel molecular probes and receptors as well as diagnostic tools based on these systems will result from ongoing efforts in the field of pyrrole synthesis.

Acknowledgements

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References

1. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th Ed., Blackwell Publishing, Chichester, UK. 2010, 295-324; (b) Domagala, A.; Jarosz, T.; Lapkowski, M. *Eur. J. Med. Chem*. **2015**, *100*, 176-187; (c) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. *RSC Adv*. **2015**, *5*, 15233-15266; (d) Kaur, R.; Rani, V.; Aboot, V.; Kapoor, Y.; Konar, D.; Kumar, K. *J. Pham. Chem. Chem. Sci.* **2017**, *1*, 17-32; (e) Dydio, P.; Lichosyt, D.; Jurczak, J. *Chem. Soc. Rev*. **2011**, *40*, 2971-2985.
2. Battersby, A. R. *Nat. Prod. Rep*. **2000**, *17*, 507-526.
3. See, for example, Movassaghi, M.; Siegel, D. S.; Han, S. *Chem. Sci*. **2010**, *1*, 561-566 and references cited therein.
4. Vitale, G. A.; Sciarretta, M.; Esposito, F. P.; January, G. G.; Giaccio, M.; Bunk, B.; Spöer, C.; Bajerski, F.; Power, D.; Festa, C.; Monti, M. C.; D'Auria, V.; de Pascale, D. *J. Nat. Prod*. **2020**, *83*, 1495-1504.
5. Ding, X.-B.; Furket, D. P.; Capon, R. J.; Brimble, M. A. *Org. Lett*. **2014**, *16*, 378-381 and references cited therein.
6. Endo, A. *Proc. Jpn. Acad., Ser. B*. **2010**, *86*, 484-493.
7. Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs*, **1978**, *15*, 429-450.
8. Zanolo, G.; Giachetti, M. C.; Canali, S.; Bernareggi, A.; Tarzia, G.; Assandri, A. *Eur. J. Drug Metab. Pharmacokin*. **1986**, *11*, 151-157.
9. Gholap, S. S. *Eur. J. Med. Chem*. **2016**, *110*, 13-31.
10. (a) Gupton, J. T. *Top. Heterocycl. Chem*. **2006**, *2*, 53-92; (b) Bailly, C. *Mar. Drugs*, **2015**, *13*, 1105-1123.
11. Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2020**, *83*, 770-803.
12. Liu, M.; El-Hossary, E. M.; Oelschlaeger, T. A.; Donia, M.; Quinn, R. J.; Abdelmohsen, U. R. *Lancer Infect. Dis*. **2019**, *19*, 237-45.
13. Zhang, H.; Dong, M.; Chen, J.; Wang, H.; Tenney, K.; Crews, P. *Mar. Drugs*, **2017**, *13*, 351-379.
14. Kennedy, J. P.; Brogan, J. T. Lindsley, C. W. *J. Nat. Prod*. **2008**, *71*, 1783-1786.
15. Banwell, M. G.; Bray, A. M.; Willis, A. C.; Wong, D. J. *New J. Chem*. **1999**, *23*, 687-690.
16. Patel, J.; Pelloux-Léon, N.; Minassian, F.; Vallée, Y. *J. Org. Chem*. **2005**, *70*, 9081-9084.
17. Trost, B. M.; Osipov, M.; Dong. G. *J. Am. Chem. Soc*. **2010**, *132*, 15800-15807.
18. Zhao, D.-G.; Ma, Y.-Y.; Peng, W.; Zhou, A.-Y.; Zhang, Y.; Ding, L.; Du, Z.; Zhang, K. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 6-8.
19. Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc*. **1985**, *107*, 5492-5495.
20. Pla, D.; Albericio, F.; Álvarez, M. *MedChemComm*. **2011**, *2*, 689-697.
21. Bracegirdle, J.; Robertson, L. P.; Hume, P. A.; Page, M. J.; Sharrock, A. V.; Ackerley, D. F.; Carroll, A. R.; Keyzers, R. A. *J. Nat. Prod*. **2019**, *82*, 2000-2008.
22. Banwell, M. G.; Flynn, B. L.; Hamel. E.; Hockless, D. C. R. *Chem. Commun*. **1997**, 207-208.
23. Banwell, M. G., Flynn, B. L., Hockless, D. C. R., Longmore, R. W.; Rae, A. D. *Aust. J. Chem.* **1999**, *52*, 755-765.

24. Axford, L. C.; Holden, K. E.; Hasse, K.; Banwell, M. G.; Steglich, W.; Wagler, J.; Willis, A. C. *Aust. J. Chem*. **2008**, *61*, 80-93.
25. Flynn, B. L.; Banwell, M. G. *Heterocycles*, **2012**, *84*, 1141-1170 and references cited therein.
26. Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett*. **2003**, *5*, 2959-2962.
27. Banwell, M. G.; Hamel, E.; Hockless, D. C. R.; Verdier-Pinard, P.; Willis, A. C.; Wong, D. J. *Bioorg. Med. Chem*. **2006**, *14*, 4627-4638.
28. Hasse, K.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem*. **2011**, 88-99.
29. Fürstner, A.; Krause, H.; Theil, O. R. *Tetrahedron* **2002**, *58*, 6373-6380.
30. Kashman, Y.; Koren-Goldshlager, G.; Garcia Gravalos, M. D.; Schleyer, M. *Tetrahedron Lett*. **1999**, *40*, 997-1000.
31. (a) Banwell, M. G., Bray, A. M., Edwards, A. J.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1347-1350; (b) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1340-1343.
32. Heinrich, M. R.; Steglich, W.; Banwell, M. G.; Kashman, Y. *Tetrahedron*, **2003**, *59*, 9239-9247.
33. Hu, Y.; Potts, M. B.; Colosimo, D.; Herrera-Herrera, M. L.; Legako, A. G.; Yousufuddin, M.; White, M. A.; MacMillan, J. B. *J. Am. Chem. Soc*. **2013**, *135*, 13387-13392.
34. Zhang, Y.; Banwell, M. G.; Carr, P. D.; Willis, A. C. *Org. Lett*. **2016**, *18*, 704-707.
35. Yan, Q.; Ma, X.; Banwell, M. G.; Ward, J. A. *J. Nat. Prod*. **2017**, *80*, 3305-3313.
36. Zhang, Y.; Banwell, M. G. *J. Org. Chem*. **2017**, *82*, 9328-9334.
37. Sangnoi, Y.; Sakulkeo, O.; Yuenyongsawad, S.; Kanjana-opas, A.; Ingkaninan, K.; Plubrukarn, A.; Suwanborirux, K. *Mar. Drugs* **2008**, 6, 578-586.
38. Okanya, P. W.; Mohr, K. I.; Gerth, K.; Jansen, R. Müller, R. *J. Nat. Prod*. **2011**, *74*, 603-608.
39. Choi, E. J.; Nam, S.-J.; Paul, L.; Beatty, D.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Chem. Biol*. **2015**, *22*, 1270-1279.
40. Carroll, A. R.; Duffy, S.; Avery, V. M. *J. Org. Chem*. **2010**, *75*, 8291-8294.
41. Panarese, J. D.; Lindsley, C. W. *Org. Lett*. **2012**, *14*, 5808-5810.
42. Bolte, B.; Bryan, C. S.; Sharp, P. S.; Sayyahi, S.; Rihouey, C.; Kendrick, A.; Lan, P.; Banwell, M. G.; Jackson, C. J.; Fraser, N. J.; Willis, A. C.; Ward, J. S. *J. Org. Chem*. **2020**, *85*, 650-663.
43. Khan, F.; Dlugosch, M.; Liu, X.; Banwell, M. G. *Acc. Chem. Res*. **2018**, *51*, 1784-1795.
44. Ghosez, L.; Franc, C.; Dennone, F.; Cuisnier, C.; Touillaux, R. *Can. J. Chem*. **2001**, *79*, 1827-1839.
45. Picott, K. J.; Deichert, J. A.; deKemp, E. M.; Schatte, G.; Sauriol, F.; Ross, A. C. *MedChemComm*. **2019**, *10*, 478-483 and references cited therein.
46. Hu, D. X.; Withall, D. M.; Challis, G. L.; Thomson, R. J. *Chem. Rev*. **2016**, *116*, 7818-7853
47. For recent reports on the isolation of prodiginines from marine sources see: (a) Vitale, G. A.; Sciarretta, M.; Esposito, F. P.; January, G. G.; Giaccio, M.; Bunk, B.; Spröer, C.; Bajerski, F.; Power, D.; Festa, C.; Monti, M. C.; D'Auria, M. V.; de Pascale, D. *J. Nat. Prod*. **2020**, *83*, 1495-1504; (b) Setiyono, E.; Adhiwibawa, M. A. S.; Indrawati, R.; Prihastyanti, M. N. U.; Shioi, Y.; Brotosudarmo, T. H. P. *ACS Omega*, **2020**, *5*, 4626-4635.
48. Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett*. **2007**, *9*, 5127-5130.
49. Pinkerton, D. M.; Banwell, M. G.; Garson, M. J.; Kumar, N.; de Moraes, M. O.; Cavalcanti, B. C.; Barros, F. W. A.; Pessoa, C. *Chem. Biodiversity* **2010**, *7*, 1311-1324.
50. Barros-Nepomuceno, F. W. A.; de Araújo Viana, D.; Pinheiro, D. P.; de Cássia Evangelista de Oliveira, F.; Ferreira, J. M.; de Queiroz, M. G. R.; Ma, X.; Cavalcanti, B. C.; Pessoa, C.; Banwell, M. G. submitted for publication.
51. See, for example, Luo, K.; Mao, S.; He, K.; Yu, X.; Pan, J.; Lin, J.; Shao, Z.; Jin, Y. *ACS Catal*. **2020**, *10*, 3733-3740.
52. See, for example, (a) Niehs, S. P.; Dose, B.; Scherlach, K.; Pidot, S. J.; Stinear, T. P.; Hertweck, C. *ACS Chem. Biol*. **2019**, *14*, 1811-1818; (b) Zhang, F.; Braun, D. R.; Chanana, S.; Rajski, S. R.; Bugni, T. S. *J. Nat. Prod*. **2019**, *82*, 3432-3439.
53. (a) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem.* **2005**, *9*, 1589-1600; (b) Banwell, M. G.; Gao, N. (Y.); Ma, X.; Petit, L.; White, L. V.; Schwartz, B. D.; Willis, A. C.; Cade, I. A. *Pure Appl. Chem.* **2012**, *84*, 1329-1339.

54. Bissember, A. C.; Phillis, A. T.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 5421-5424.
55. Sharp, P. S.; Mikusek, J.; Ho, J.; Krenske, E. H.; Banwell, M. G.; Coote, M. L.; Ward, J. S.; Willis, A. C. *J. Org. Chem*. **2018**, *83*, 13678-13690.