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Pyrrole carboxamide introduction in the total synthesis of pyrrole-imidazole alkaloids

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Abstract

In this review various strategies for the incorporation of the signature pyrrole carboxamide moiety in the total syntheses of pyrrole-imidazole alkaloids (PIA) are discussed. These so-called oroidin alkaloids have a broad range of biological activities and display interesting skeletal diversity and complexity. These alkaloids are sponge-derived secondary metabolites and thus far more than 200 members of the PIA family have been isolated over the past few decades. Methods range from classical amide bond forming processes to non-traditional bond formation including the *de novo* synthesis of the pyrrole itself.

Keywords

Amide coupling, Heterocycles, Oroidin Alkaloids, Total synthesis, Pyrrole surrogates, Thio acid mediated amidation, Pyrrole hydantoin derivatives, Dibromopyrrole carboxylic acid, Anhydrides, Pd-Catalyzed Methods

Authors

Apsara K. Herath obtained her B.Sc. (2010) from the University of Peradeniya, Sri Lanka and Ph.D (2018) from the University of Texas at Arlington under the supervision of Professor Carl J. Lovely, where she explored new synthetic strategies toward total synthesis of oroidin alkaloids. After graduation she joined with Array Biopharma and now is continuing her independent career as a senior research scientist in Pfizer R & D in Boulder, Colorado.

Carl J. Lovely obtained his B.Sc. (1987) and Ph.D. (1990) from the University of Birmingham, United Kingdom with Professor W. Brian Jennings. After postdoctoral appointments in Germany and the US, he started his independent career as an assistant professor at the University of Texas at Arlington in 1996. He was promoted to full professor in 2008 and became associate chair in 2015. His research focuses on synthetic heterocyclic chemistry and its application to the total synthesis of natural products.

Introduction

Marine sponges are a rich source of secondary metabolites with highly diverse structures and a broad range of potential pharmacological properties.[1] During the last three decades one family, the pyrrole imidazole alkaloids (PIA) or the oroidin alkaloids, has received significant attention from the synthetic community.[2] This interest has been spurred by a combination of the challenges presented by the unusual functionality and novel structural frameworks to the current state of the art in synthesis coupled with the biological potential of these alkaloids.[3]

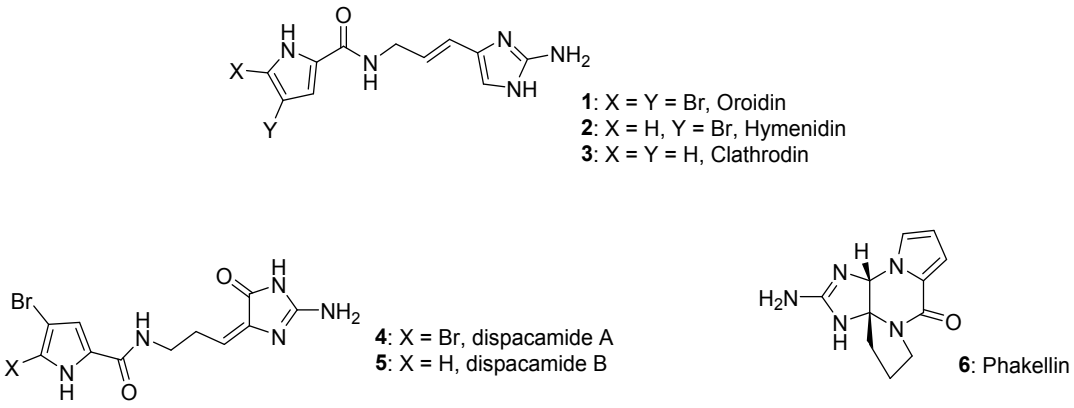


Figure 1 - Monomeric PIAs

Oroidin (**1**), hymenidin (**2**) and clathrodin (**3**) are considered to be the parent members of the group and have been assumed to serve as the biosynthetic building blocks for the more complex family members.[4-7] Each of these parent systems contains an imidazolylpropenyl amine which is acylated by a pyrrolecarbonyl moiety; the difference between them is simply the bromination level of the pyrrole. The broader family results from the cyclization, oxidation or oligomerization of any of these basic derivatives.[8] As a result, there are many examples of monomeric congeners (Figure 2), dimeric congeners and even tetrameric congeners; the variance in bromination of the pyrrole moiety has resulted in the isolation of members that only differ in the bromination level of the pyrroles but which otherwise possess the same basic frameworks. The challenges that these nitrogen rich and highly polar molecules present to contemporary synthetic methods are many which in turn has inevitably attracted the attention of synthetic chemists around the world. As a result of these efforts highly innovative methods have emerged for the construction of several members of the oroidin alkaloids. Inventive synthetic routes have been explored and reported for the total synthesis of a wide variety of these PIAs, including these parent systems.[9-10] While the introduction of the pyrrole carboxamide may be viewed as a trivial undertaking, chemoselectivity issues and introduction of an amino group present challenges requiring the development of alternative synthetic methods.

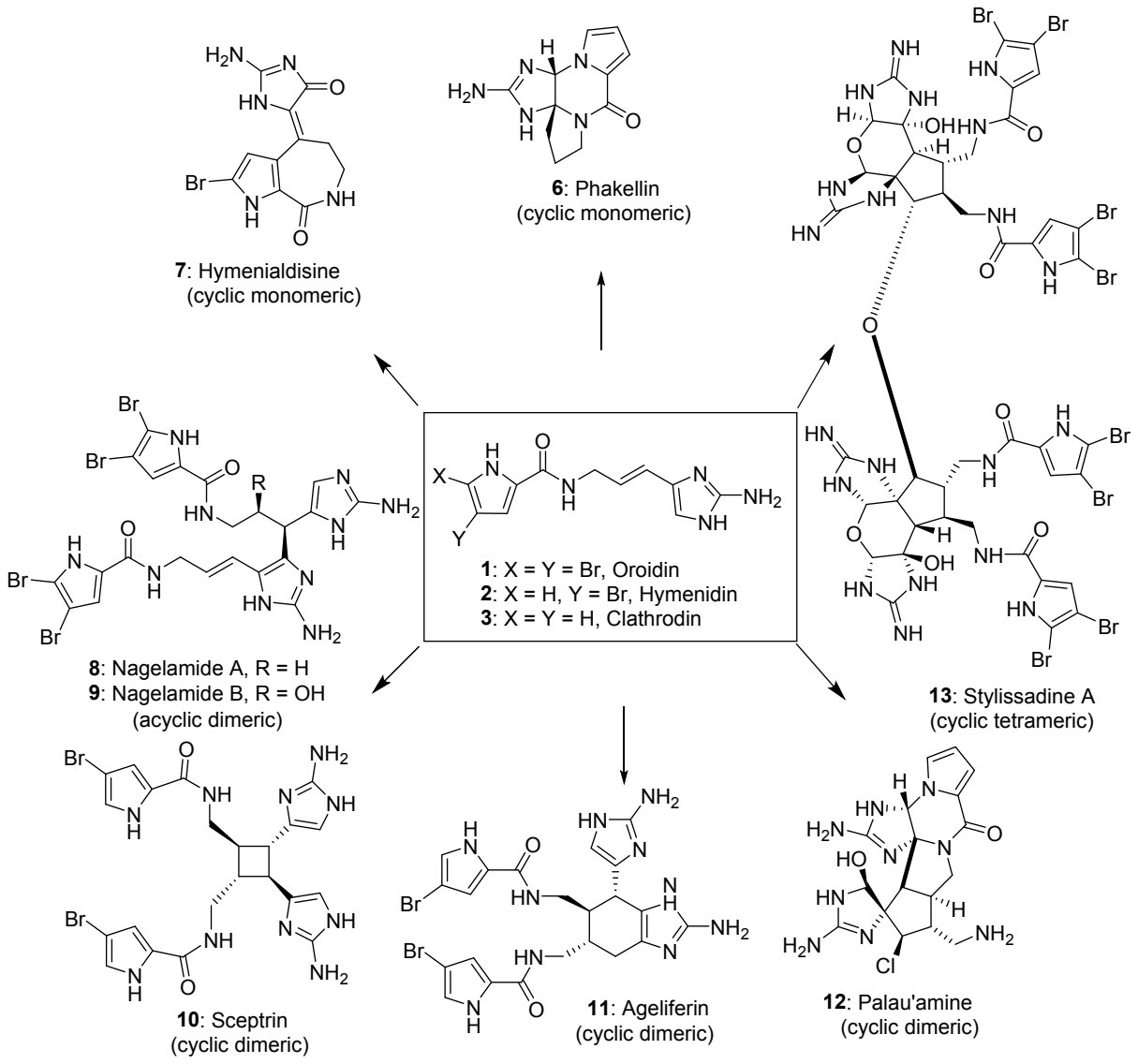
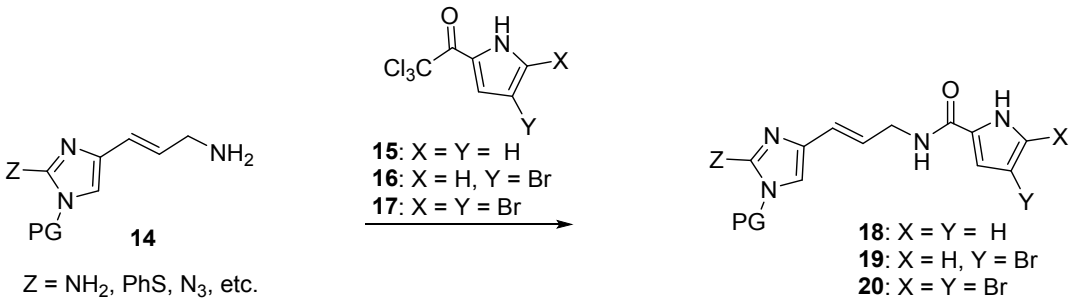


Figure 2 - Some members the of oroidin family

The Lindel group have reviewed different approaches for the synthesis of PIAs first in 2003,[11] which was expanded initially in 2005[12] and most recently, in 2017,[13] published a book chapter concerning the chemistry and biology of PIAs. This current review contains a summary of relevant examples from these prior reviews in addition to more recent work which has been reported after 2017.

It is not hyperbole to state that amide bonds play a pivotal role in life, since they serve as the primary backbone of proteins. Moreover, amide bonds are frequently utilized in drug design and in many synthetic materials including nylon, artificial silks, supported catalysts, hydrogels, and in biocompatible matrices.[14] A pharmaceutical survey which was performed in 2006[14-15] showed that, nearly 66% of drug candidates contain amide bonds and 25% of them are currently on the market as drugs.[14, 16] This present review is focused on the different strategies for the introduction of the pyrrolecarboxamide used in the synthesis of PIAs and analogs. Although the amide bond is frequently formed by classical methods through the acylation of amines through use of acyl chlorides, mixed anhydrides, etc., use of carboxylic acid surrogates (trichloroketones, thio acids), ligation conditions (Staudinger) and use of masked amides (hydantoins) have also been employed to install the amide moiety to PIA systems. The development of these alternative conditions has come in response to the synthetic difficulties encountered *en route* to various structural frameworks due to chemoselectivity or structural sensitivity issues which reinforces the idea that synthetic innovation is driven by novel structures.[17]

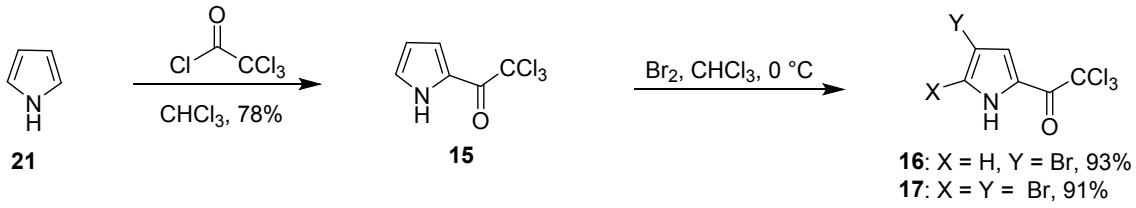
1. Amidation with trichloroacetyl pyrrole



Scheme 1 - General scheme for acylation with trichloroketones

The most commonly employed method for construction of the pyrrolecarboxamide bond is through a base-mediated reaction of an amine, e.g., **14** with the relevant pyrrole acid chloride surrogates **15-17** (Scheme 1). 2-(Trichloroacetyl)pyrroles are used as a common pyrrole acid chloride equivalent, since the -CCl_3 group acts as a good leaving group generating a neutral byproduct

and also it forms the amide bond smoothly in the presence of unprotected 2-aminoimidazoles without giving any other major side products.[18] Bailey and Johnson described the relevant activated acid synthesis as depicted in Scheme 2.[19] Bromination of pyrrole trichloroketone at low temperature provided either the monobromo ketone **16** or dibromo ketone **17** in excellent yields through control of stoichiometry. The precursor pyrrole trichloroketone **15** was obtained by heating of pyrrole with trichloroacetyl chloride.[20] Some classical examples of their use in total synthesis are given below for context. The acylation strategy with **15**-**17** (Scheme 1) has been employed in the total synthesis of many PIA natural products and below we discuss some examples of this chemistry which has been utilized in a range of settings from application to the synthesis of the simple to the more complex alkaloid systems.



21 **15**

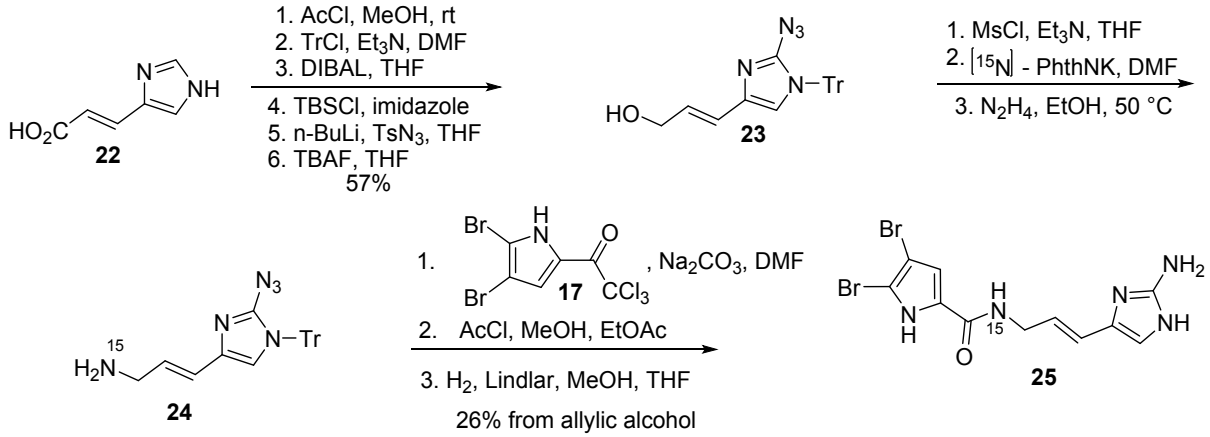
16: X = H, Y = Br, 93%
17: X = Y = Br, 91%

Scheme 2 - Synthesis of bromo trichloroketones

Several research groups have reported the total synthesis of the parent oroidin and closely related derivatives in last few decades.[21] These synthetic strategies used en route to these targets can be characterized into three general categories;[21] 1. Pd-catalyzed C-C bond formation with alkynes/alkenes 2. Methods involving olefination and 3. Approaches involving naturally occurring sources like urocanic acid and ornithine.

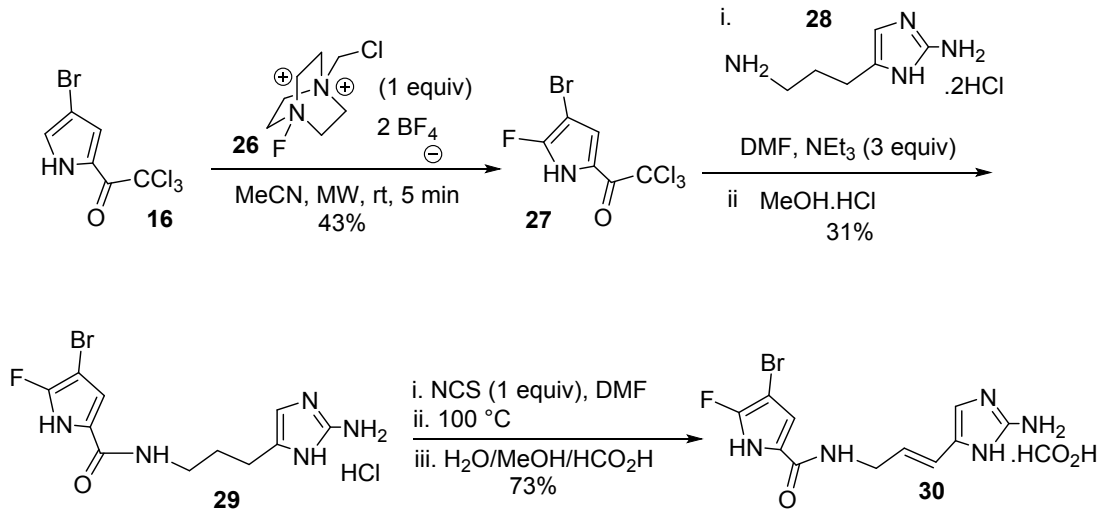
Romo *et al.* reported an interesting route to synthesize an ^{15}N-labelled oroidin from urocanic acid providing an isotopically labeled system which was used to follow the amide nitrogen of the molecule in biosynthetic investigations (Scheme 3).[22] Urocanic acid **22** was converted to the allylic alcohol **23** through a six-step sequence. Subsequent mesylation followed by nucleophilic

substitution with ^{15}N-labelled phthalimide and hydrazinolysis delivered the allylic amine **24**. The resulting amine was treated with pyrrole trichloroketone **17** to construct the amide linkage thus forming ^{15}N-oroidin (**25**) after azide reduction and deprotection.



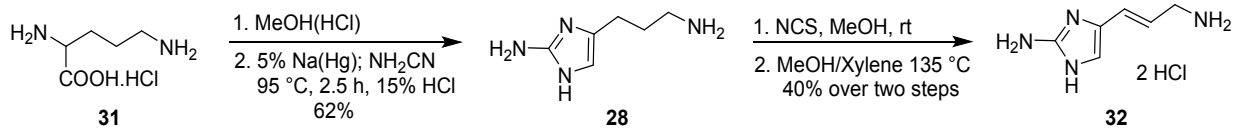
Scheme 3 - Synthesis of isotopically labeled oroidin by Romo

Lindel and co-workers reported a synthesis of fluorohymenidin (**30**) through the use of a fluorinated congener (Scheme 4).[23] The brominated trichloroketone **16** was reacted with the electrophilic fluorinating agent **26** under microwave irradiation to afford **27**. Treatment of primary amine **28** with bromofluoropyrrole ketone **27** effected the desired amide bond formation delivering. Chlorination of the pseudo benzylic position and dehydrochlorination then introduced the double bond to produce **30**.



Scheme 4 - Synthesis of fluorohymenidin by Lindel

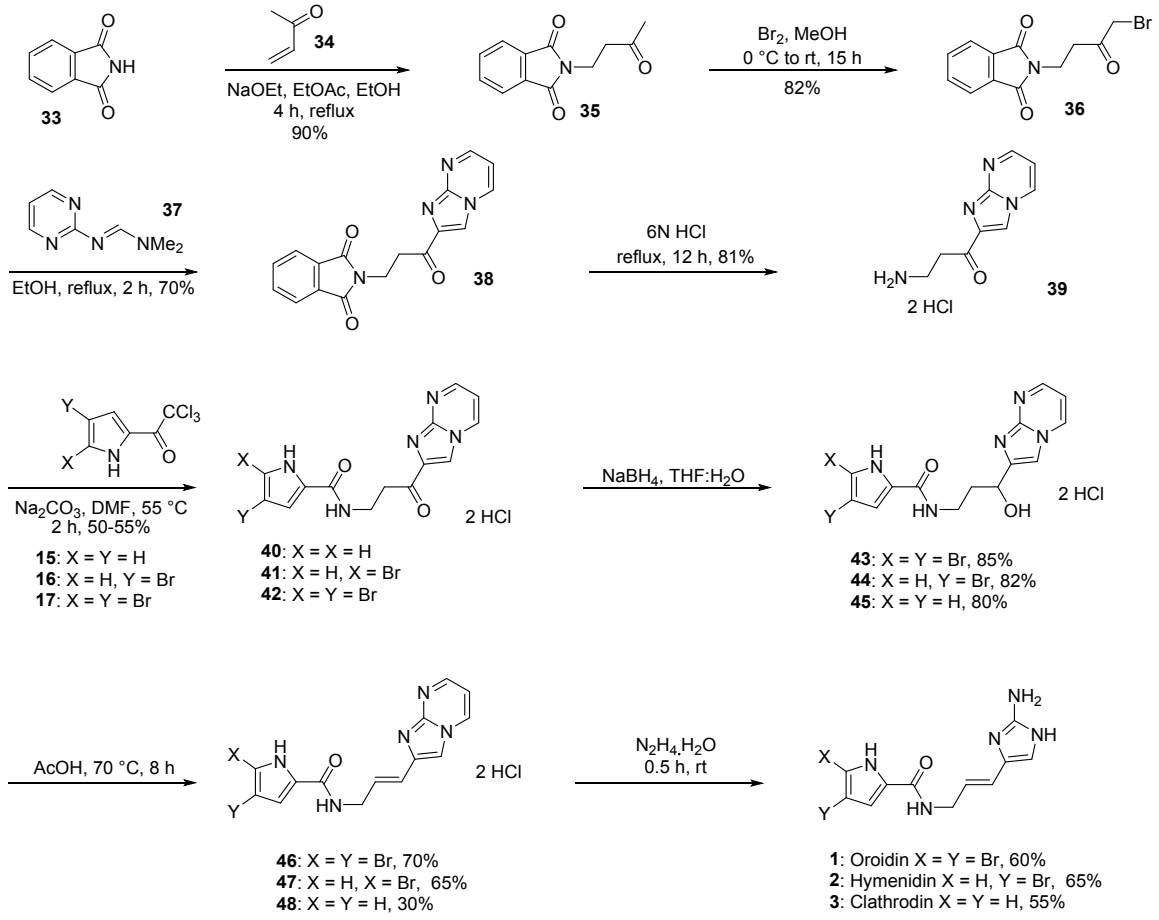
Olofson *et al*. described the synthesis of oroidin from ornithine (**31**) in 1998.[24] Ornithine methyl ester was reduced by an Akabori reaction (with sodium amalgam) followed by condensation with cyanamide and cyclization which provided compound **28**. Subsequent oxidation with NCS and elimination incorporated the unsaturation in **32**.



Scheme 5 - Synthesis of 4-(3-aminopropyl)-1-imidazol-2-amine by Olofson *et al.*

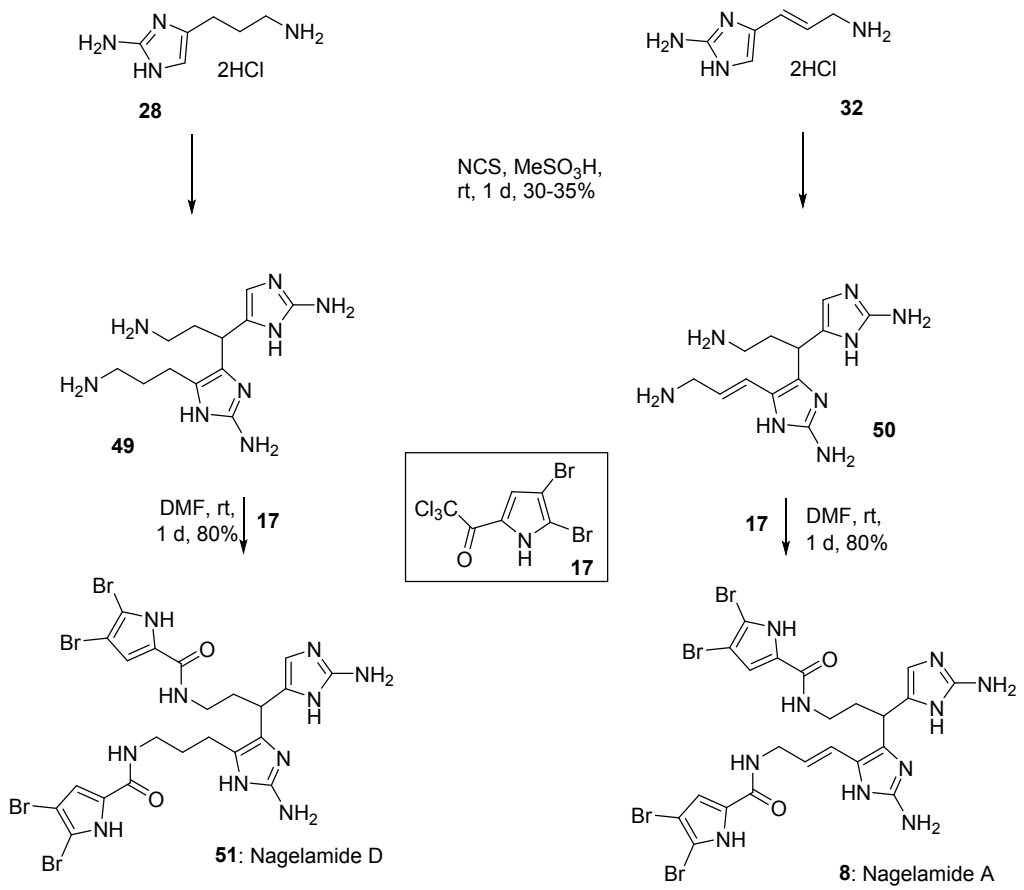
In 2013, Rasapalli and co-workers reported use of imidazo[1,2-*a*]pyrimidine **39** as a masked 2-aminoimidazole motif in the total synthesis of clathrodin, hymenidin and oroidin (**1**-**3**).[21] A Michael addition of phthalimide **33** to methyl vinyl ketone (**34**) was delivered the ketone **35** which was α-brominated to give α-bromoketone **36** (Scheme 6). *N*,*N*-Dimethyl-N′-2-pyrimidinyl-(*E*)-methanimidamide (**37**) and bromide **36** were condensed to furnish imidazo[1,2-*a*]pyrimidine **38**. Acidic hydrolysis of phthalimide **38** provided the primary amine **39** which upon treatment with pyrrole trichloroketone **15**-**17** delivered the amides **40-42**. Reduction of ketone to the

corresponding alcohols **43-45** followed by dehydration installed the unsaturation in the carbon linker. Deprotection of the masked amino imidazolyl group with hydrazine provided the oroidin, hymenidin and clathrodin (**1-3**) in moderate yield.

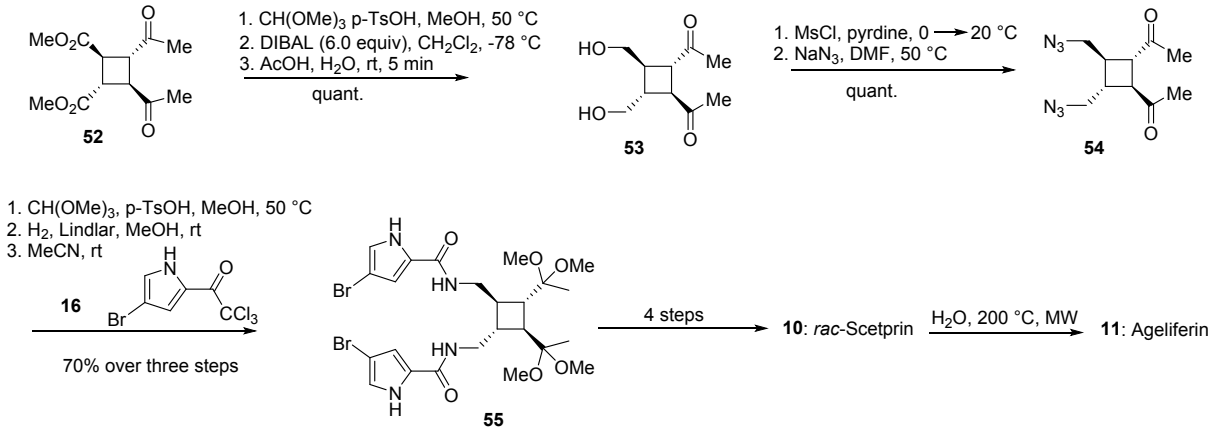


Scheme 6 - Oroidins via imidazo[1,2-*a*]pyrimidine by Rasapalli

In 2006, Horne's group reported the NCS mediated homodimerization of **28** and **32** can be employed to construct tetraamines **49** and **50** which upon treatment with trichlorocetylpyrrole **17** completed the total synthesis of nagelamide A (**8**) and nagelamide D (**51**) respectively as depicted in Scheme 7.[25]



Scheme 7 - Total synthesis of nagelamide A and D by Horne *et al.*

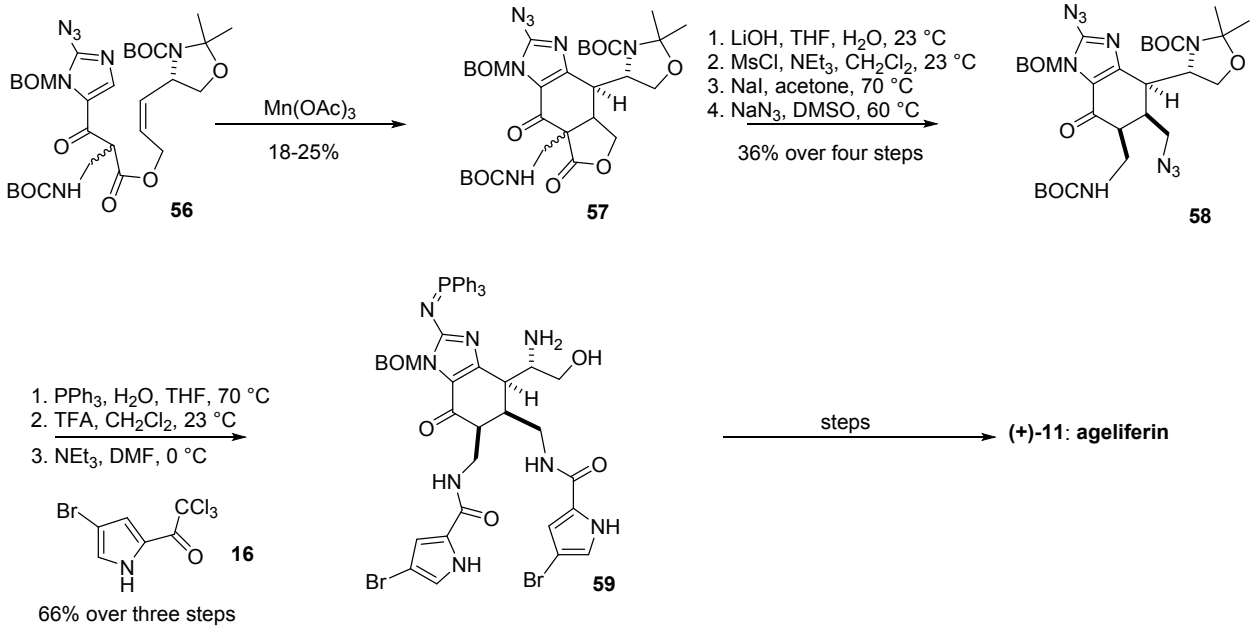


Scheme 8 - Total synthesis of ageliferin by Baran

The total syntheses of sceptrin (**10**) and ageliferin (**11**) were reported by Baran *et al.* and are depicted in Scheme 8.[26] Cyclobutane ester **52** was reduced to the corresponding alcohol **53**

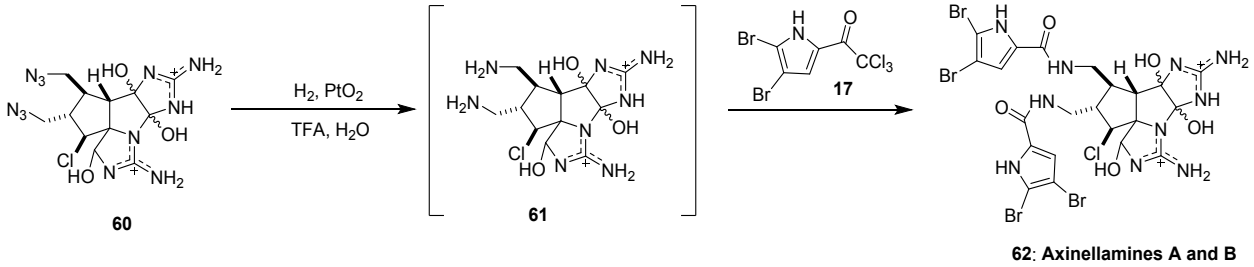
followed by bismesylation and conversion to the diazide **54** (Scheme 8). The resulting diazide was reduced by catalytic hydrogenation to the corresponding diamine with Lindlar catalyst, the pyrrole carboxamides were installed on the amines via the pyrrole trichloroketone **16**. The 2-aminoimidazole moieties were installed through a 4-step sequence and *rac*-sceptrin (**10**) was obtained, subsequent microwave heating of **10** resulted in ring expansion and the formation of *rac*-ageliferin (**11**) via rearrangement.

Chen *et al*. used a Mn(III)-mediated single electron transfer reaction to effect cyclization to the tetrahydrobenzimidazole **56** *en* route to a total synthesis of (+)-ageliferin (**11**) (Scheme 9).[27] The azides at C2 and in the alkyl chain were treated with PPh_3 and hydrolyzed via a net Staudinger reaction (Scheme 9). Interestingly, the triphenylphosphine imide of the 2-aminoimidazole exhibited unexpected stability to hydrolysis, so effectively it acted as a good protecting group for the C2-amine. The resulting primary amines were then acylated with the pyrrole trichloroketone **16** to give **59** which was converted to (+)-ageliferin (**11**) after several additional steps.



Scheme 9 - Total synthesis of ageliferin by Chen

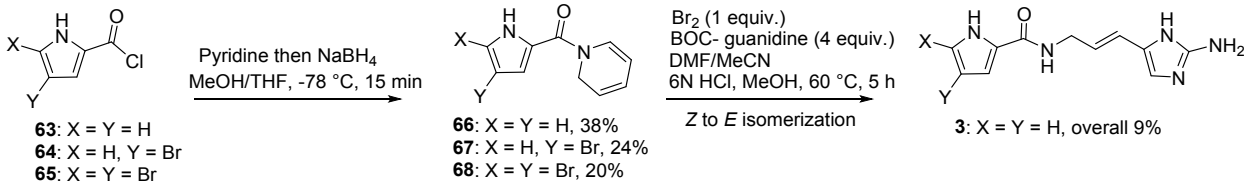
In 2011, Baran and co-workers reported the first total synthesis of *rac*-axinellamines (Scheme 10).[28] PtO_2 mediated hydrogenation of bis azide **60** resulted in reduction to the corresponding tetraamine **61**. Subsequent treatment with 2,3-dibromo-5-trichloroacetylpyrrole (**17**) furnished axinellamines A and B.



Scheme 10 - Synthesis of axinellamines by Baran

2. Amidation with Acid Chlorides

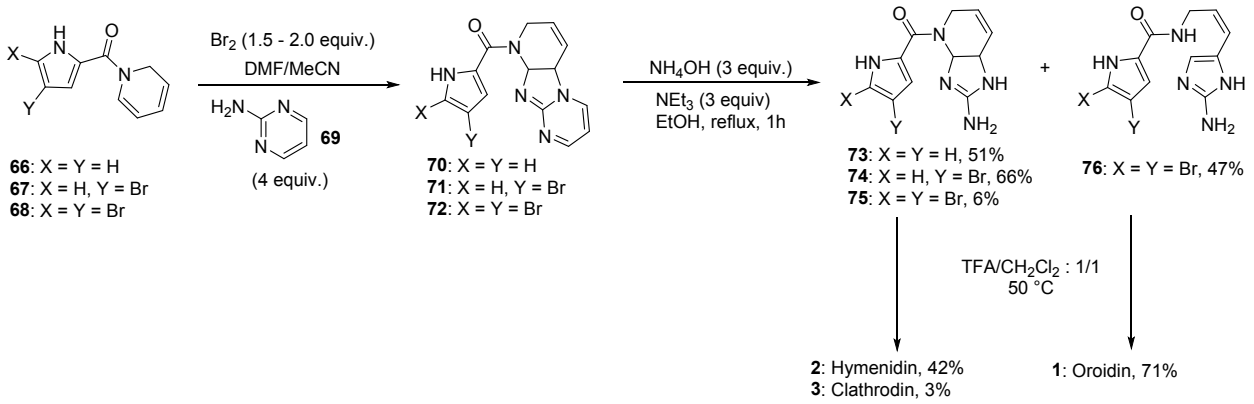
Al-Mourabit *et al*. reported installation of the pyrrole carboxamide in oroidin derivatives based on the intermediacy of the corresponding *N*-acyl pyridinium salts.[29] The N-acyl intermediates **66-68** were prepared by reaction of the corresponding pyrrole acid chloride **63-65** with pyridine and followed by reduction with $NaBH_4$. Nucleophilic addition of the BOC protected guanidine to **66** formed a bicyclic compound and aminal opening resulted in the formation of clathrodin (**3**) (Scheme 11).



Scheme 11 - Clathrodin by Al-Mourabit *et al.*

Treatment of **67-68** with Br_2 and a protected guanidine derivative did not result in the formation of the corresponding bicyclic intermediate, in contrast to **66** which led to the formation of clathrodin (**3**) as depicted above (Scheme 11). The bromopyrrole groups seemed to accelerate

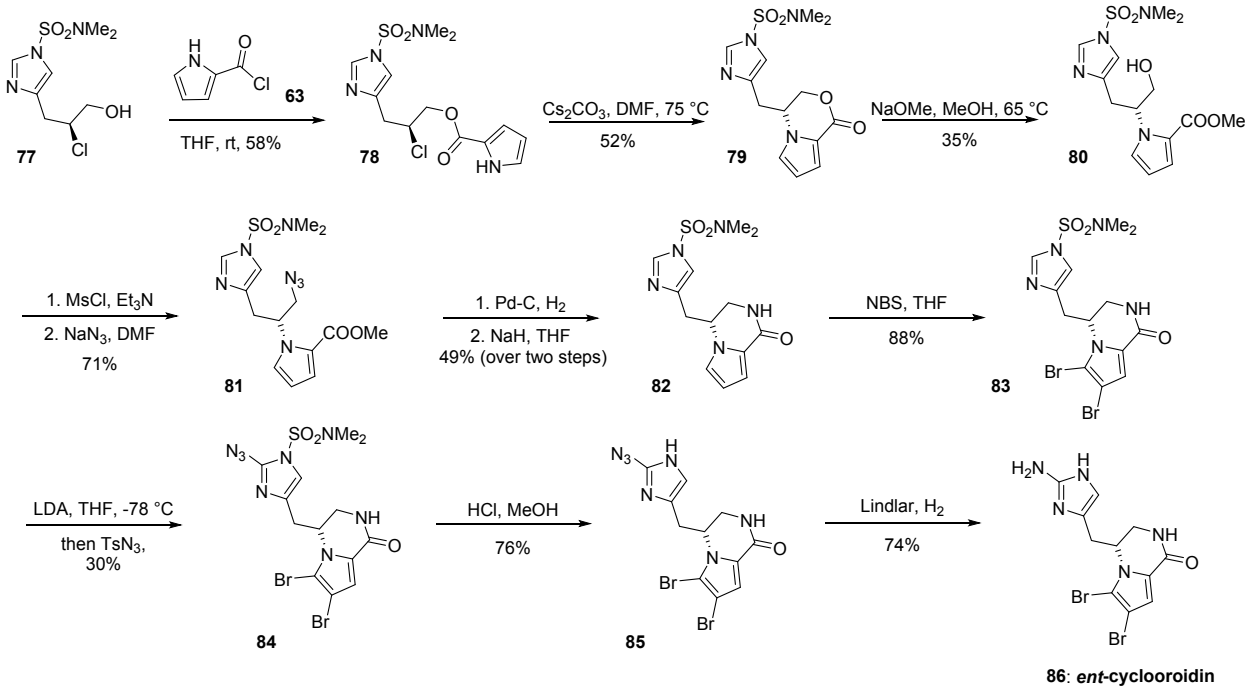
intramolecular nucleophilic attack of the nitrogen of pyrrole ring with the bromonium ion rather than intermolecular addition on the protected guanidine. Accordingly, the more nucleophilic, 2-aminopyrimidine (Scheme 12) was used as the surrogate for protected guanidine to overcome this problem. Accordingly, treatment of 2-aminopyrimidine delivered tricyclic compounds **70-72** which following reaction with ammonium hydroxide afforded the 2-aminoimidazolyl intermediates **73-75**. Further treatment with TFA triggered a *Z*- to *E*-isomerization and formation of the desired oroidin and derivatives (**1**-**3**).



Scheme 12 - Approach to oroidins by Al-Mourabit *et al.*

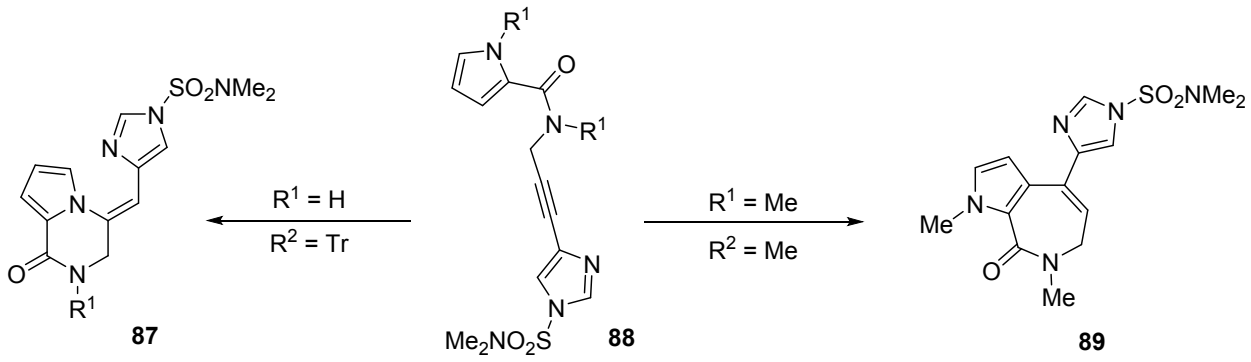
In 2010, our group an reported an asymmetric total synthesis of *ent*-cyclooroidin (**86**) and used pyrrole acyl chloride as the pyrrole source (Scheme 13).[30] Chlorohydrin **77** was prepared from histidine and reacted with the pyrrole acid chloride **63** to give the corresponding ester **78**. Base-mediated intramolecular cyclization provided the lactone **79**. Ring opening of lactone was achieved by *trans* esterification with NaOMe resulting in the formation of methyl ester **80**. Activation of the alcohol as the mesylate was followed by substitution to provide the azide **81**. Reduction of the azide to the corresponding primary amine, followed by deprotonation and intramolecular amidation delivered the piperazine derivative **82**. Dibromination of pyrrole was achieved with NBS to give **83** and lithiation of C2 in the imidazole ring followed by azidation yielded the C2 azide **84**. The DMAS (dimethylaminosulfonyl) group was removed under mild

acidic conditions and reduction of the C2 azide to the amine with Lindlar catalyst and hydrogen completed the total synthesis of cyclooroidin (**86**).



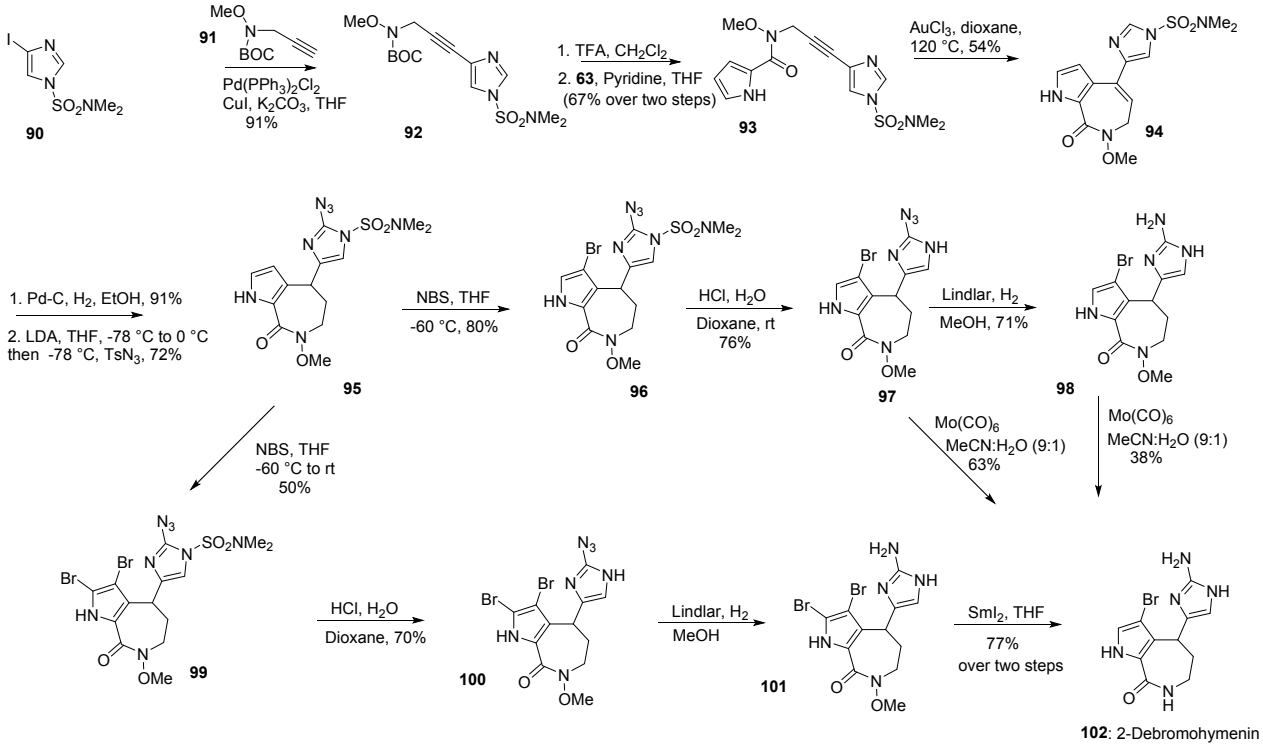
Scheme 13- Total synthesis of *ent*-cyclooroidin by Lovely

In 2011, our group found that imidazolyl propargylamine derivatives can be used synthesize oroidin related amides.[31] A collection of diverse heterocyclic scaffolds, which resemble oroidin alkaloids, were synthesized using various transition metal catalyzed processes (Scheme 14).



Scheme 14 - Propargyl-imidazole for oroidin analogs by Lovely

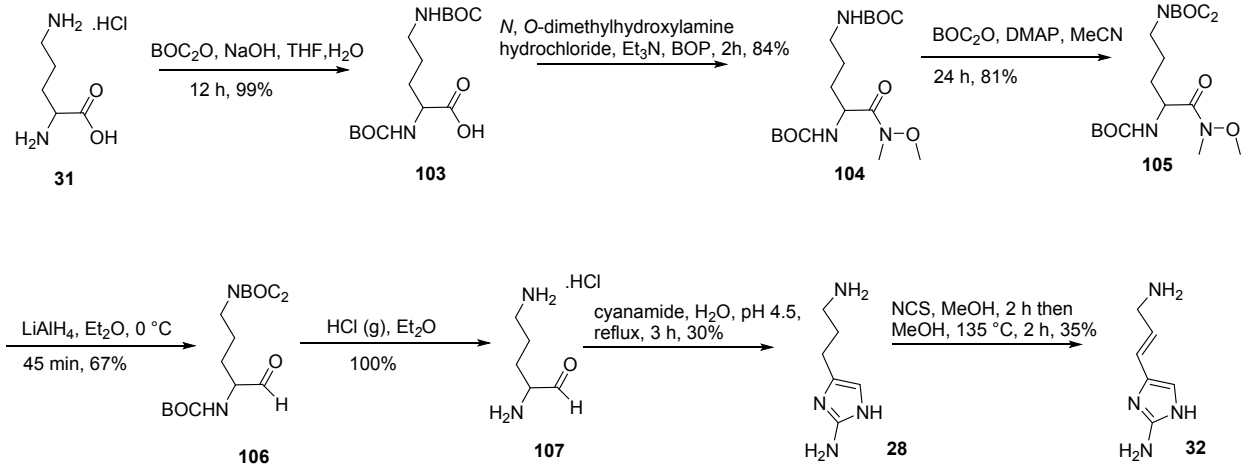
Building off these findings, the total synthesis 2-debromohymenin (**102**) from alkyne **91** and pyrrole acid chloride **63** was described recently (Scheme 15).[32] **92** was prepared by a Sonogashira reaction between terminal alkyne **91** and the haloimidazole **90**. The pyrroloazepinone core **94** was synthesized by an intramolecular gold-catalyzed hydroarylation of alkyne **98**. Reduction of the double bond in the azepinone core followed by azidation through metalation and trapping with tosyl azide delivered **95**. Different bromination conditions led to the formation of monobromo pyrrole and dibromo pyrrole intermediates **96** and **99**. Removal of the DMAS protecting group by treatment with HCl followed by azide reduction resulted in the formation of the C2-amino group in the imidazole moiety in **98** and **101**. N-OMe cleavage was achieved under two different conditions; $Mo(CO)_6$ gave 2-debromohymenin (**102**). Attempts were made to remove the N-OMe group in the dibrominated intermediate **101** under similar conditions, but this failed. Alternative reductants were evaluated of which SmI_2 removed the OMe group but with partial debromination of the pyrrole ring thus also affording 2-derbromohymenin (**102**).



Scheme 15 - Total synthesis of 2-Debromohymenin by Lovely

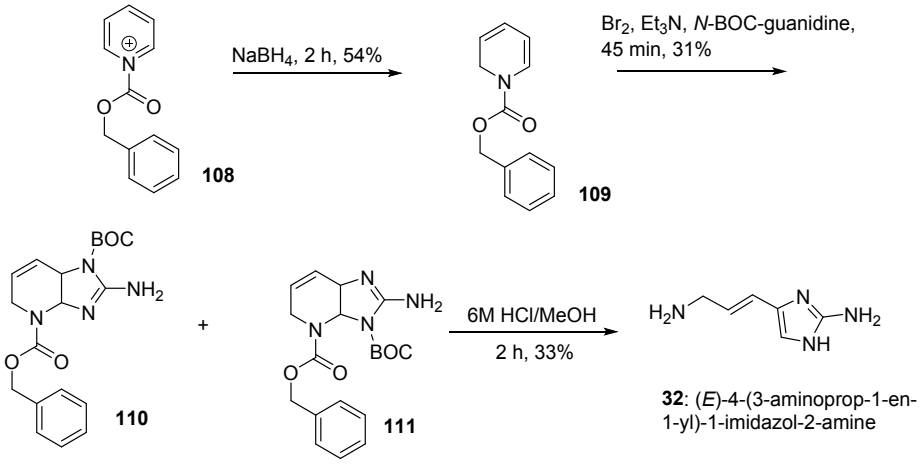
3. Amidation with activated carboxylic acids (Mixed Anhydrides)

Zula *et al*. reported an environment-friendly method to synthesize 4-(3-aminopropyl)-1-imidazol-2-amine (**32**) from ornithine (**31**) avoiding the use of sodium amalgam (see Scheme 5).[33] In this route, ornithine (**31**) was converted first to dicarbamate **103** followed by formation of the Weinreb amide **104**. Bis carbamation of the ϒ-amine facilitated the reduction of Weinerb amide to the corresponding aldehyde **106**. Deprotection of the BOC groups followed by cyclization provided the same intermediate **28** as the Horne group reported and incorporation of unsaturation was accomplished in an analogous way as reported previously (see Scheme 5). Conversion to oroidin was completed through use of a mixed anhydride (see Scheme 18).



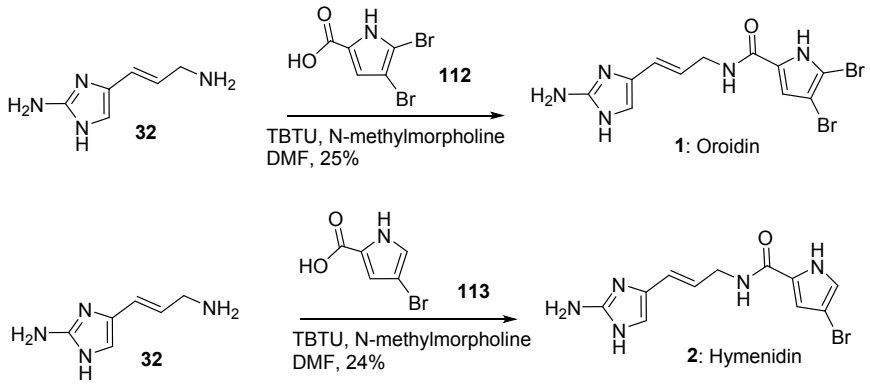
Scheme 16 - Synthesis of 4-(3-aminopropyl)-1-imidazol-2-amine by Zula *et al*.

Zula *et al*. further reported an alternate synthesis of (*E*)-4-(3-aminoprop-1-en-1-yl)-1-imidazol-2-amine (**32**) through an acyl-1,2-dihydropyridine intermediate (**111**) as described by Al-Mourabit and co-workers (Scheme 12).[33] Pyridine was acylated by benzyl chloroformate and then reduced with $NaBH_4$. Reaction with bromine and guanidine provided two bicyclic regioisomeric imidazopyridines **110** and **111**. Acid hydrolysis of these isomers led to ring opening and Cbz removal ultimately affording (*E*)-4-(3-aminoprop-1-en-1-yl)-1-imidazol-2-amine (**32**).



Scheme 17 - synthesis of (E)-4-(3-aminoprop-1-en-1-yl)-1-imidazol-2-amine by Zula *et al.*

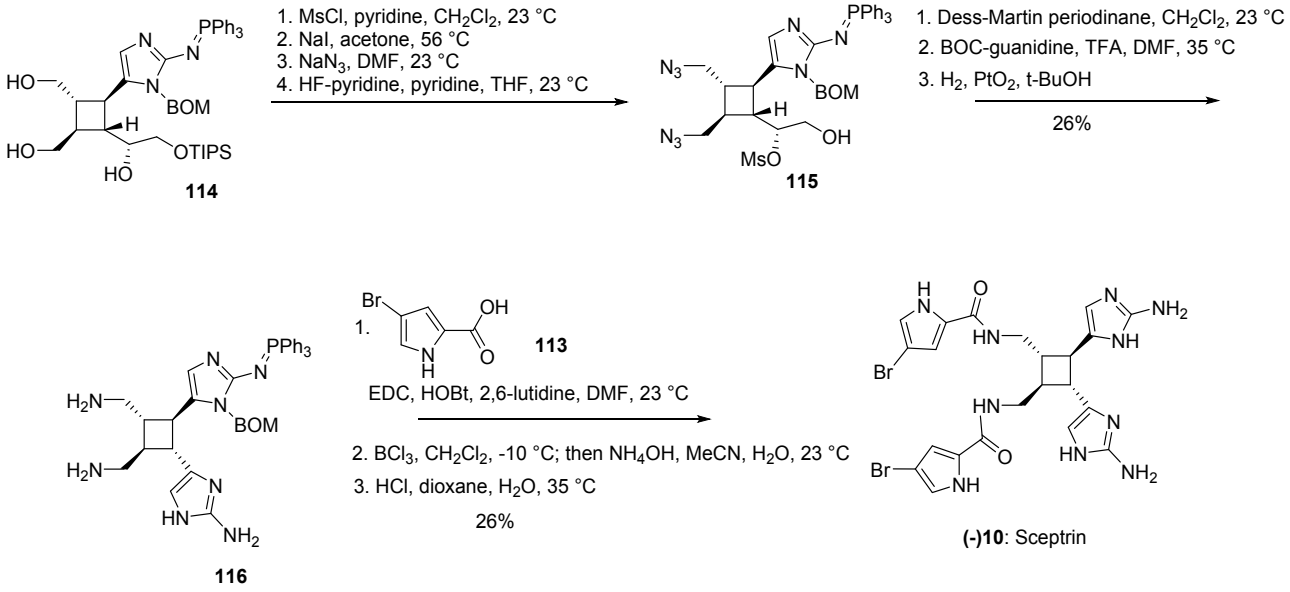
Subsequent treatment of **32** with 2-pyrrole carboxylic acid in the presence of a coupling reagent, TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate) gave oroidin (**1**) and hymenidin (**2**) in moderate yields (Scheme 18). However, interestingly attempts to install the amide with the corresponding pyrrole trichloroketone **15-17** generated only a low yield of the desired targets.



Scheme 18- Use of acid activators

Chen *et al*. reported a slightly different strategy to install the pyrrole carboxamide group in a total synthesis of sceptrin (**10**).[34] In their synthesis, cyclobutane **114** was converted to the correspond diazide via the trimesylate (Scheme 19). The desired bisazide **115** was reduced to the

corresponding diamine **116** by PtO_2/H_2 and coupled with pyrrole carboxylic acid through an EDC coupling. Removal of protecting groups completed the total synthesis of (-)-sceptrin (**10**).

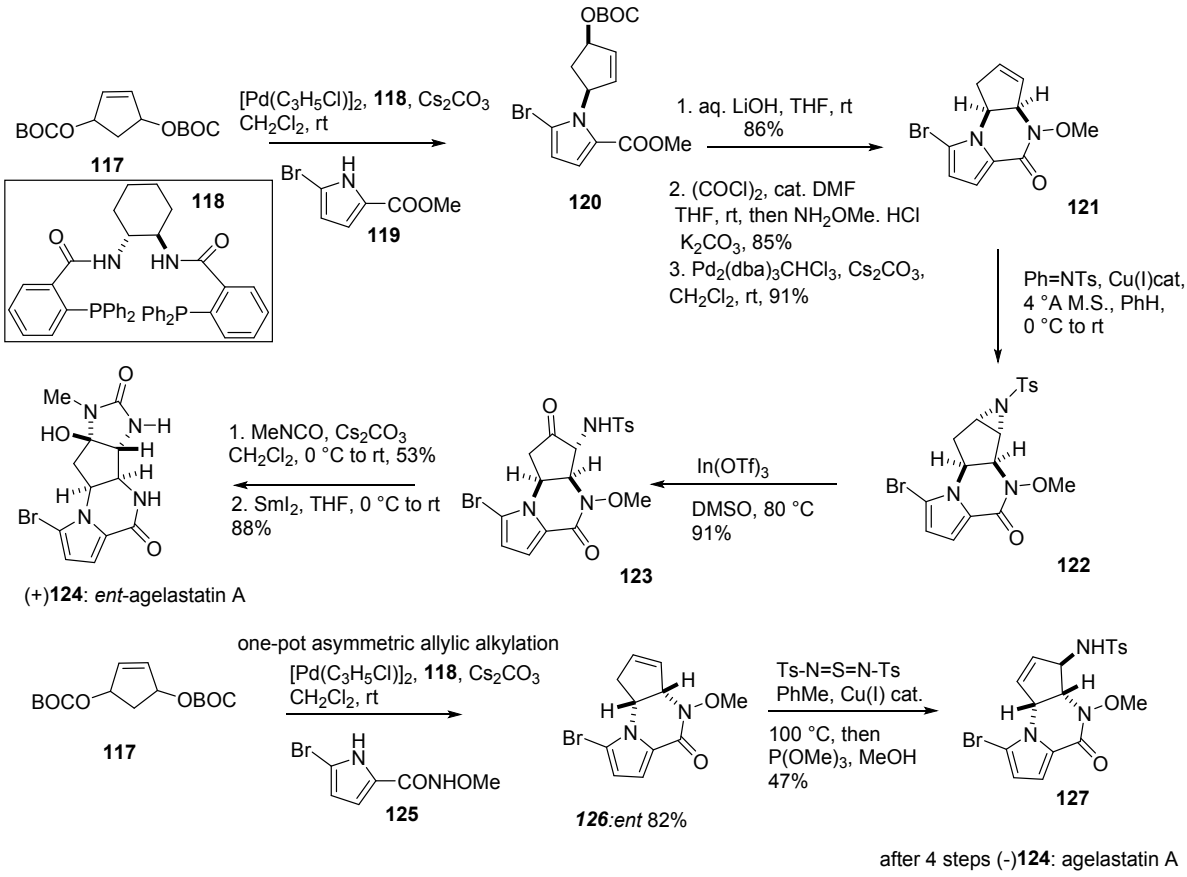


Scheme 19 - Total synthesis of sceptrin by Chen *et al*.

4. Amidation with Pd-Catalyzed Methods

In 2006, Trost and Dong reported the Pd-facilitated asymmetric allylic alkylation with pyrrole carboxamides as nucleophiles for total synthesis of agelastatin A (**124**) and its enantiomer (Scheme 20).[35] Two enantiomers were synthesized by switching the nucleophiles (**119** and **125**) under the alkylation conditions as shown below. The pyrrole moiety was installed by reacting carbonate **117** and ester **119** with the presence of the chiral, non-racemic ligand **118** thus alkylating the pyrrole nitrogen. Cyclopentene **121** was prepared by two steps via a second Pd-mediated allylic substitution (intramolecular) this time alkylating the amide nitrogen. Cyclopentanone **123** was obtained by Cu catalyzed aziridination followed by ring opening with DMSO in the presence of $In(OTf)_3$. The total synthesis of *ent*-agelastatin A (**124**) was completed

by further two steps as shown in Scheme 20. Pyrrole amide **125** underwent di-alkylation to provide piperazinone **127**, the most advanced intermediate in the synthesis of (-)-agelastatin A.



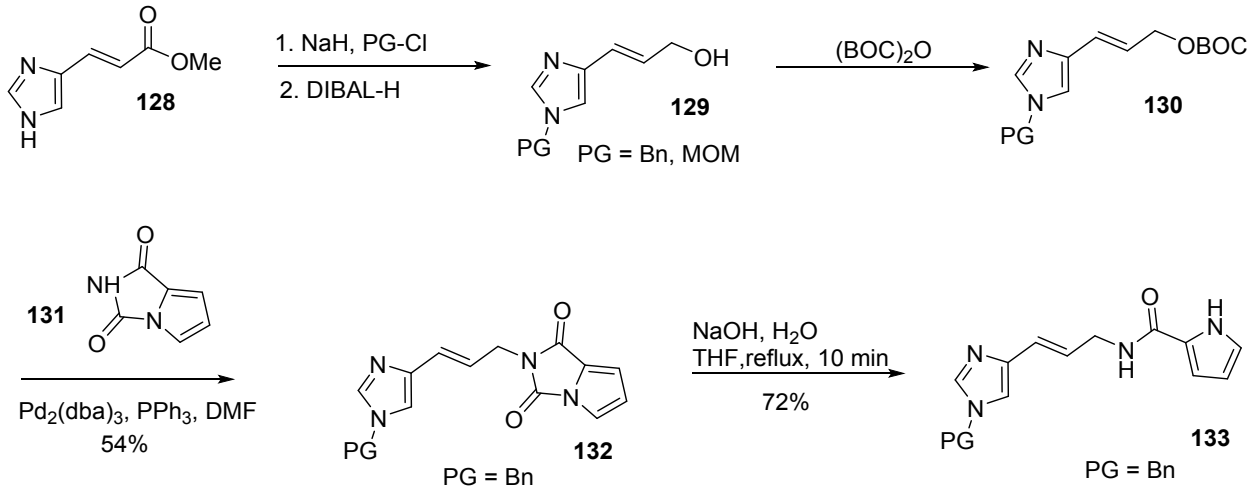
Scheme 20 - Trost's total synthesis of agelastatin A

5. Amidation with Pyrrole hydantoin derivatives

5.1: Tsuji-Trost conditions

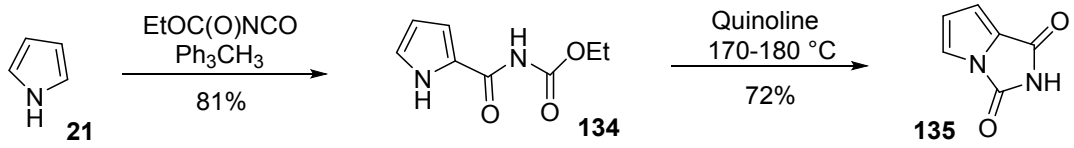
In 2006 our group demonstrated that pyrrole hydantoin derivatives can serve as surrogates of phthalimide in various contexts and thus can be utilized to install pyrrole carboxamides into oroidin systems more directly.[36] Urocanic acid was methylated and the methyl ester **128** was then protected. DIBAL reduction delivered the allylic alcohol **129** which upon treatment with BOC

carbonate resulted in the formation of the *t*-butyl allylic carbonate **130** (Scheme 21). Subsequent reaction with the hydantoin **131** under Tsuji-Trost conditions gave N-alkylation product **132** which upon basic hydrolysis furnishes the clathrodin analog **133** in good yield. The advantage to using the hydantoin is that the amine nitrogen is introduced directly and thus avoids the intermediacy of a polar amine and the need to incorporate it through additional synthetic transformations, thereby telescoping the sequence.



Scheme 21 - Clathrodin from hydantoin by Lovely

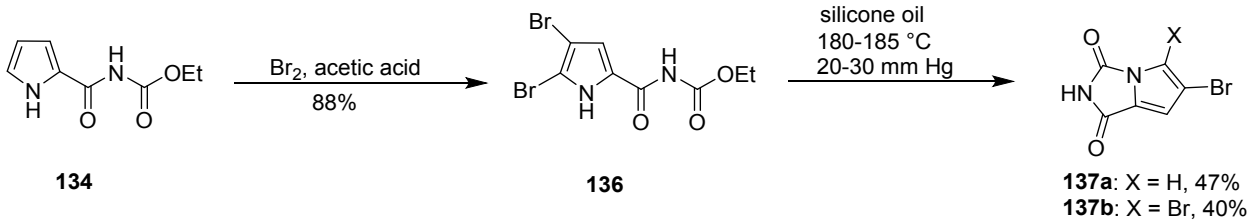
The hydantoin is readily prepared by thermolysis of *N*-ethoxycarbonylpyrrole-2-carboxamide (**134**) in quinoline, which itself was prepared from pyrrole on treatment with the isocyanate (Scheme 22).[37]



Scheme 22 - Synthesis of hydantoin

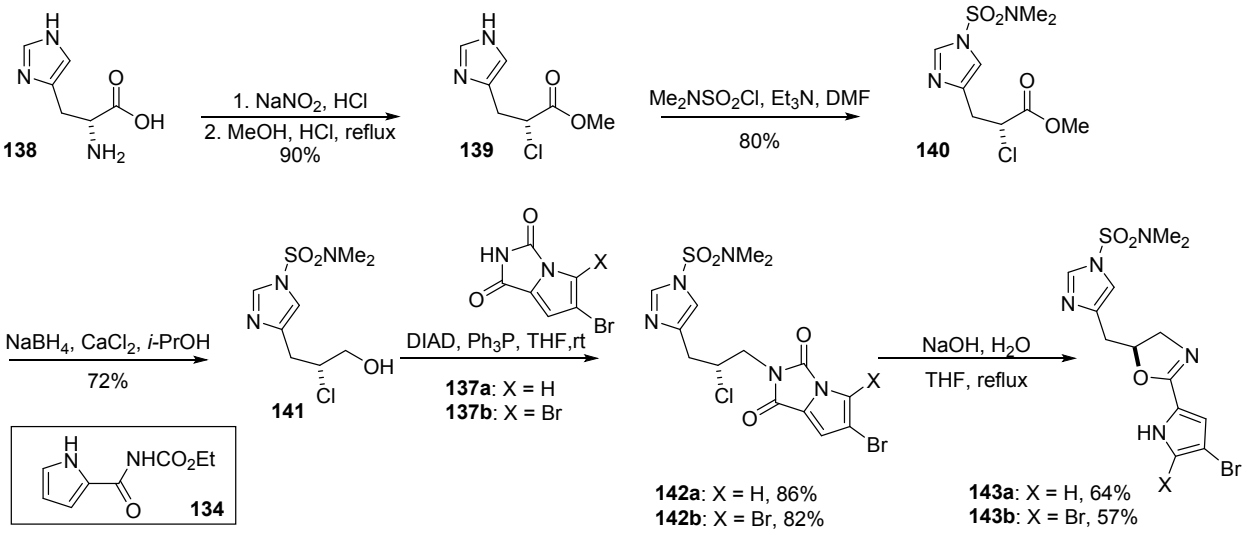
5.2: Mitsunobu conditions

Given this initial success with Tsuji-Trost chemistry with the parent hydantoin, other applications of this derivative were envisioned, in particular Mitsunobu-type reactions and whether extension to the brominated congeners could be performed. Ultimately it was discovered that the corresponding bromohydantoins **137a-b** could be prepared by the synthetic route depicted below (Scheme 23). Specifically, the intermediate **136** was mono or dibrominated and subsequent pyrolysis under slight vacuum to remove ethanol resulted the formation of the mono or dibromohydantoin in moderate yield.[38]

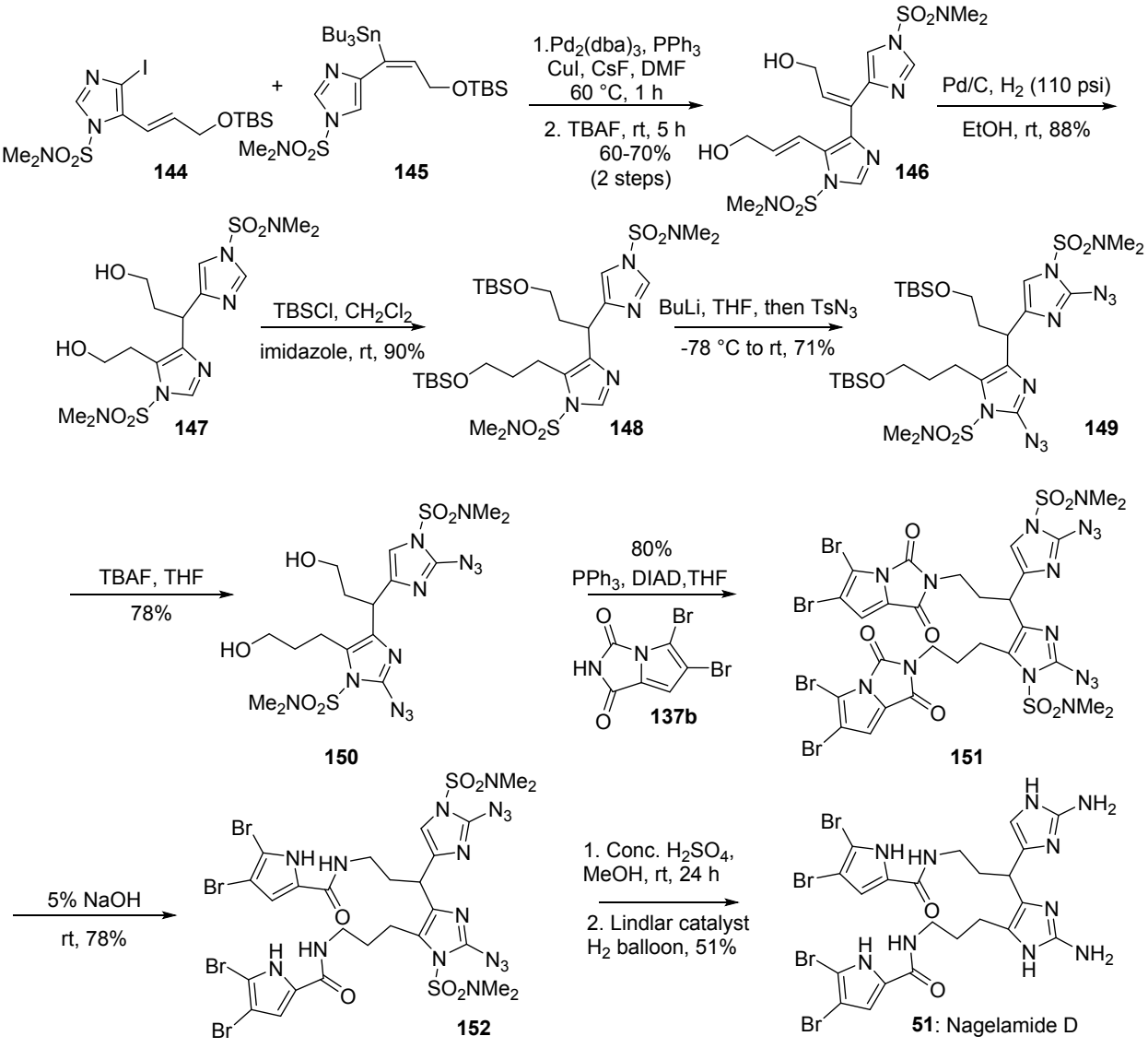


Scheme 23 - Synthesis of brominated hydantoins

In 2010 our group described an application of these reagents, reporting that the hydantoin group can be installed via a Mitsunobu reaction en route to the synthesis of the oxazoline moiety **143a-b** found in some oroidin dimers including nagelamide R and T.[39] Histidine (**138**) was converted to the corresponding α-chloro ester **139** by diazotization, in the presence of chloride ion and then the free imidazolic nitrogen was protected with a DMAS group (Scheme 24). The α-chloro ester **140** was reduced to the corresponding α-chloro alcohol **141**. Although an initial approach to install pyrrolecarboxamide through use of a known urethane **134** via the Mitsunobu reaction was unsuccessful, the hydantoins were considered superior nucleophiles in the Mitsunobu reaction as the masked pyrrole NH in the hydantoin avoided possible chemoselectivity issues. Subsequent NaOH mediated hydrolysis unmasked the pyrrole which underwent in situ cyclization to provide the desired oxazoline moiety **143a-b**.



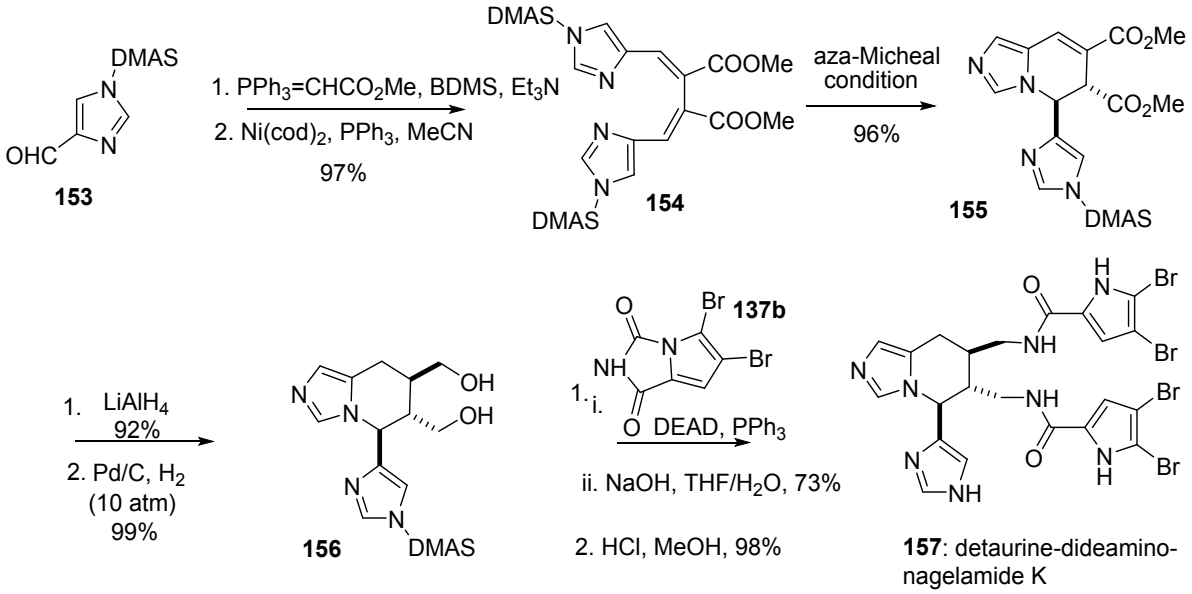
Scheme 24 - *en* route to the synthesis of the oxazoline moiety by Lovely



Scheme 25: Total synthesis of nagelamide D by Lovely

Also our group has used the dibromohydantoin **137b** unit as the nucleophile to install dibromopyrrole units via a double Mitsunobu reaction in the total synthesis of nagelamide D (**51**).[40-41] A Stille cross-coupling was used as the key reaction to connect the iodo **144** and the vinyl stannane **145** fragments to forge the bis vinylimidazole **146** (Scheme 25). Both **144** and **145** were prepared through elaboration of DMAS-protected iodoimidazole derivatives. Subsequent catalytic hydrogenation led to the saturation of the scaffold **147**. The diol was bis silylated to give **148** and then the C2 azides were introduced via metalation with BuLi with subsequent trapping

with TsN_3. A double Mitsunobu reaction with dibromohydantoin **137b** provided the framework **151** of nagelamide D after hydrolysis of the ureas. It should be noted that the Mitsunobu reaction was performed in the presence of azide functional groups which could react in a Staudinger reaction, successful N-alkylation required careful ordering of reagent addition to mitigate the formation of the iminophosphorane (see Scheme 9). This tactic also avoids unmasking of the C2-amino group until very late in the synthesis which then avoids both potential chemoselectivity issues and significantly aids in compound processing as it mitigates the polarity of the molecule. Completion of the synthesis required removal of the DMAS-protecting groups by acid-catalyzed methanolysis and reduction of the C2 azides to the corresponding amines with Lindlar catalyst.

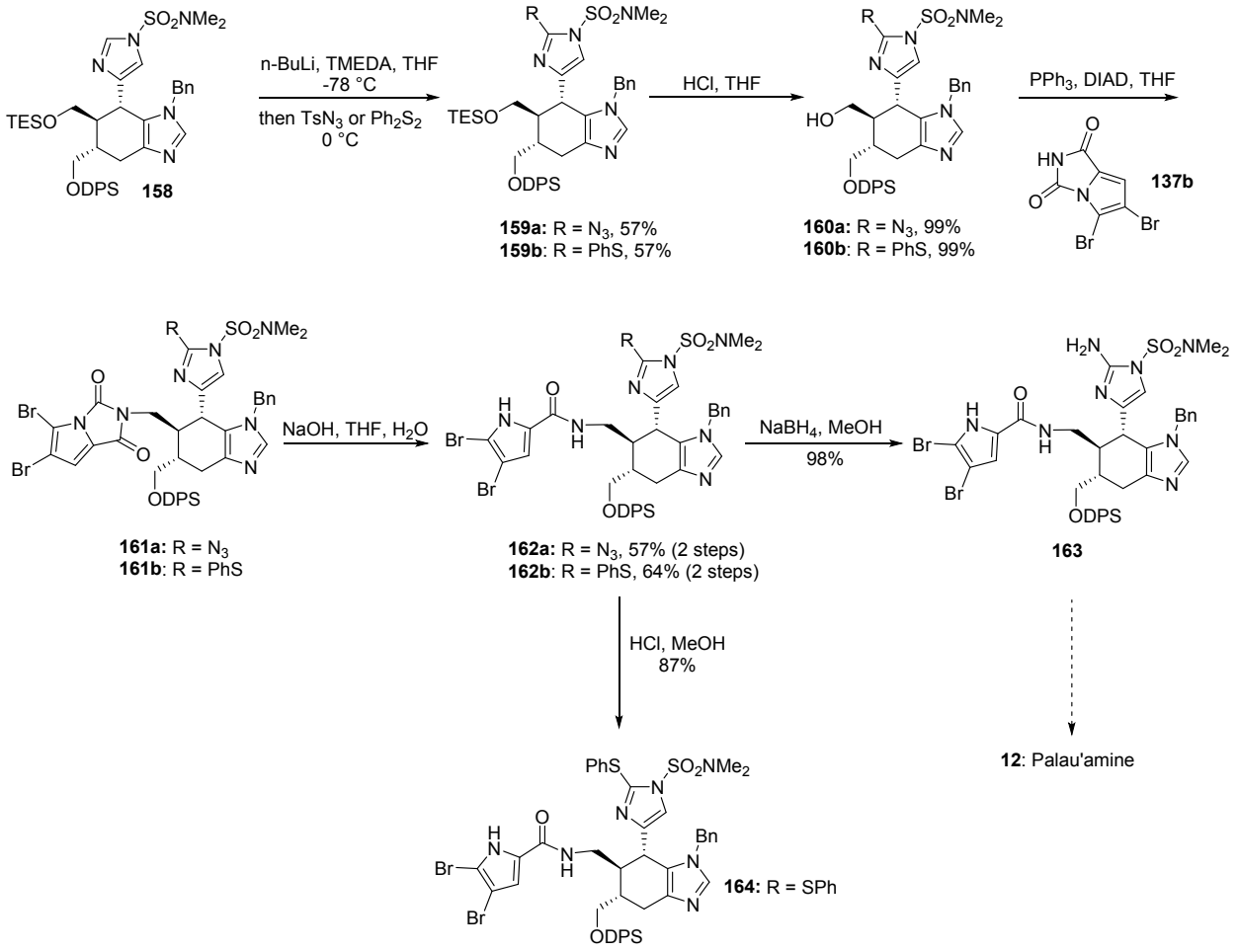


Scheme 26 - Jiang's approach to nagelamide K

Jiang's group also adopted a similar approach to install the dibromopyrrole-2-carboxamide in the synthesis dideamino version of nagelamide K **157** (Scheme 26).[42] Ni(0)-catalyzed dimerization of α-bromo urocanic acid was utilized to synthesize the scaffold **154** followed by ester **155** reduction to alcohol **156** and installed the dibromo hydantoin **137b** via a Mitsunobu reaction. Basic hydrolysis resulted in the formation of the desired pyrrole carboxamide derivatives from

hydantoins in **137b**, which upon treatment with acid removed the imidazolyl protecting group and completed the total synthesis of nagelamide K derivative **157**.

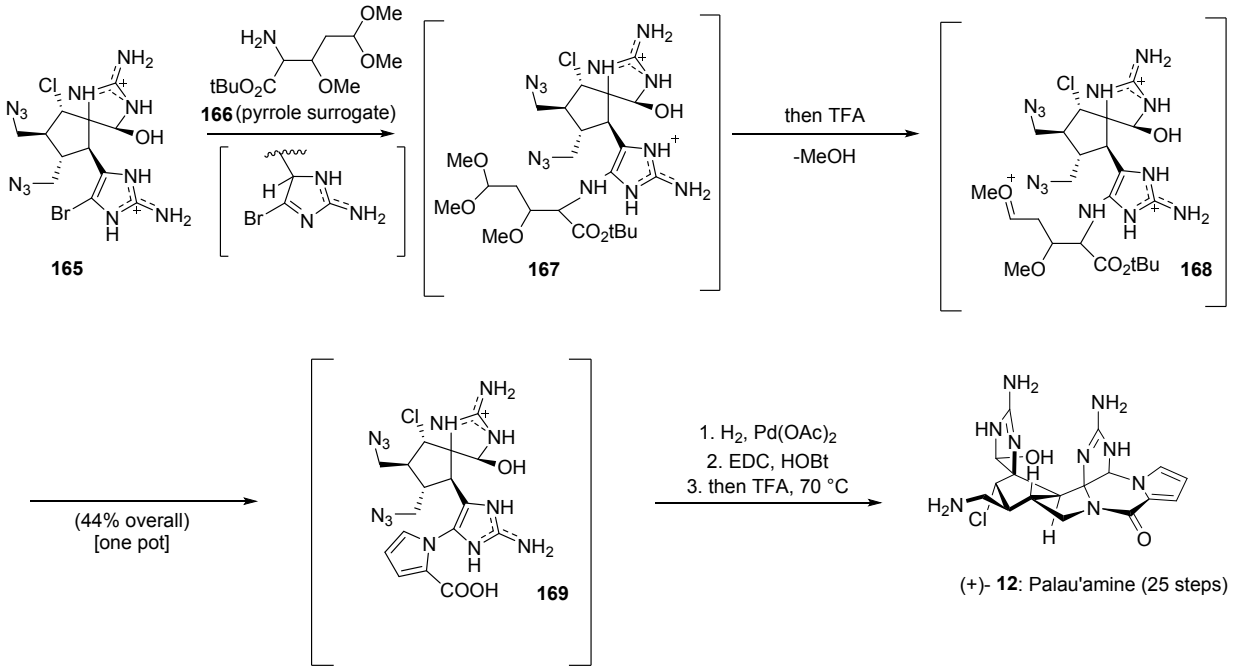
Our group recently described our progress towards the total synthesis of palau'amine (**12**) using dibromohydantoin **137b** via a Mitsunobu reaction (Scheme 27).[43] The azide group and phenyl thioether were employed as the C2-amino surrogates and introduced by metalation followed by treatment with TsN_3 or Ph_2S_2. Subsequent silyl ether deprotection resulted in the formation of the primary alcohol **160a-b** which was then reacted with dibromo hydantoin moiety **137b** via a Mitsunobu reaction. Base-mediated hydrolysis introduced the desired pyrrole carboxamide moiety in advanced intermediates **163** and **164** *en* route to palau'amine (**12**)



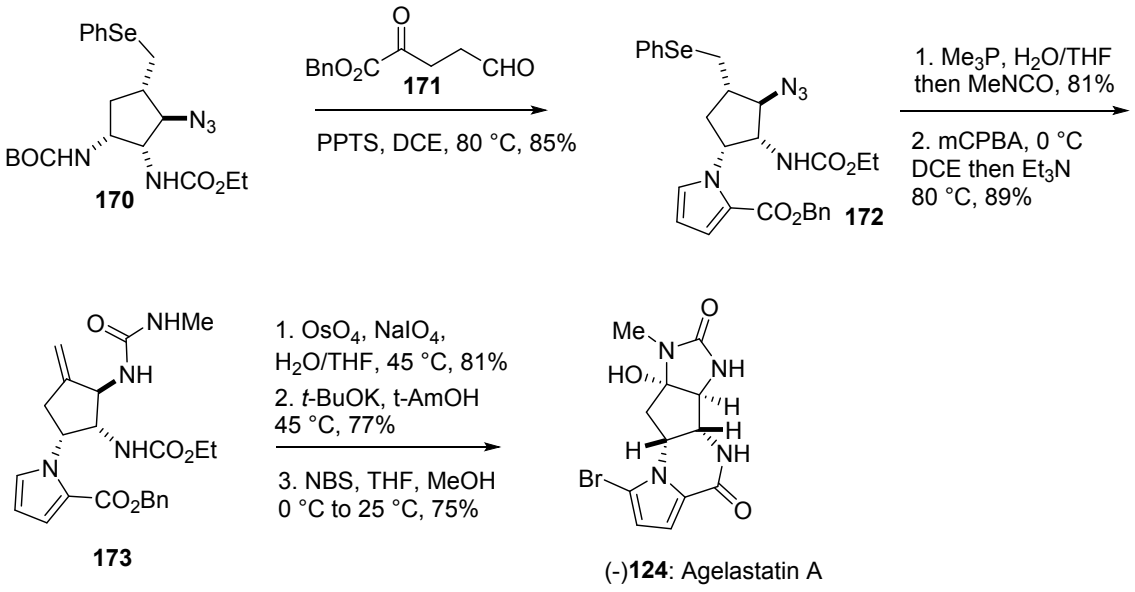
Scheme 27 – Studies towards total synthesis of palau'amine by Lovely

6. De novo pyrrole synthesis

In their total synthesis of palau'amine (**12**) Baran and co-workers used a nucleophilic pyrrole surrogate **166**, essentially a "pre-pyrrole" to install the pyrrole carboxamide group (Scheme 28).[44] The amino acid derivative **166** was reacted with 2-aminobromoimidazole in the presence of acetic acid to give corresponding amine **167** which upon treatment with trifluoracetic acid resulted in formation of the corresponding N-linked pyrrole acid **169** (through the oxonium cation **168**) in a moderate yield.

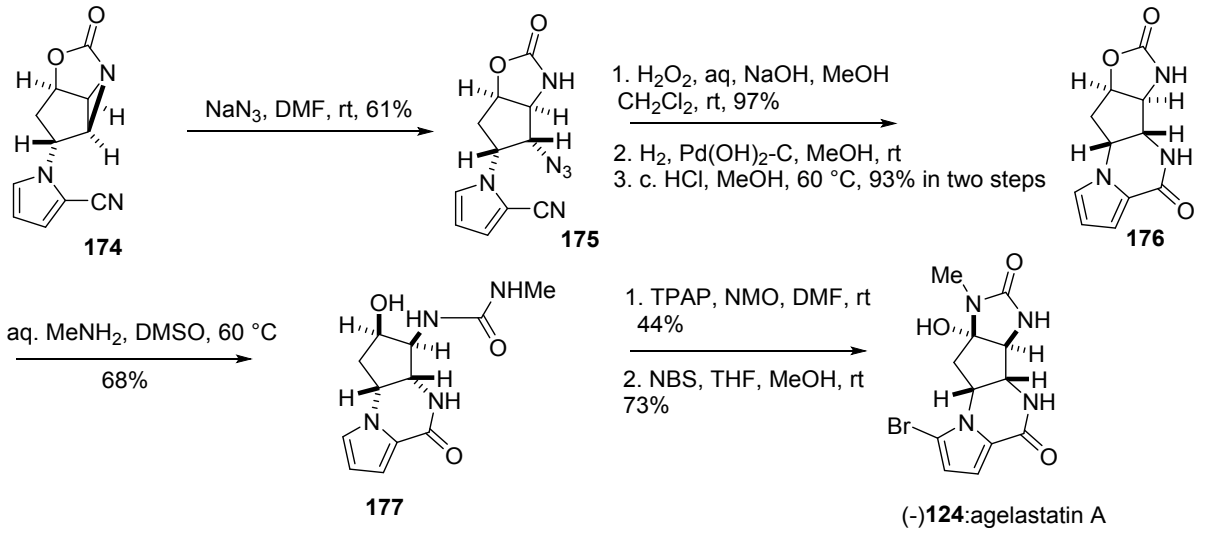


Scheme 28 - Total synthesis of palau'amine by Baran



Scheme 29 - Total synthesis of (-) agelastatin by Du Bois

Du Bois and When reported the enantioselective synthesis of (-)-agelastatin (**124**) as described in the Scheme 29.[45] A classical Paal-Knorr condensation of compound **170** and benzyl protected ketoaldehyde **171** resulted the formation of the pyrrole ring in compound **172**. Subsequent treatment with trimethyl phosphine and trapping of the iminophosphorane with methyl isocyanate installed the urea functionality in the compound **173**. The exocyclic alkene in **173** was introduced by oxidation of the selenide to the corresponding selenoxide followed by elimination. Then OsO_4/$NaIO_4$ mediated dihydroxylation-oxidative cleavage and spontaneous cyclization give rise to imidazolone ring and subsequent lactamization resulted in the formation the amide bond. Bromination of the pyrrole completed the synthesis.



Scheme 30 - Total synthesis of (-) agelastatin by Yoshimitsu

Yoshimitsu and coworkers reported the total synthesis of (-)-agelastatin A via oxazolidinone intermediate.[46] Hydrolysis of the nitrile group and azide reduction and resulted amide was treated with HCl to give the oxazolidinone ring in **176**. The urea motif in **177** was installed by heating with methylamine in DMSO. Then oxidation of alcohol followed by spontaneous cyclization resulted the methyl imidazolone and finally bromination of pyrrole furnished agelastatin A (**124**).

7. Amidation with Thio acids

In the context of several total synthesis projects in our lab, it became desirable to convert azides directly to amides. As we noted above, the double Mitsunobu reaction with a bromopyrrole hydantoin was used to install the pyrrole carboxamides units to complete the synthesis of nagelamide D (**51**), however, during the construction of the closely related nagelamide A (**8**) and nagelamide C (**197**), we observed an unexpected allylic transposition that we were unable to mitigate. Due to the failure of this approach, we considered using dibromopyrrole thio carboxylic acid as an alternative to install carboxamide moieties to complete the total synthesis of these alkaloids thereby avoiding the preparation of highly polar tetraamines and the trichloroketones.

A potential one-pot process to converting the azides to the corresponding amides can be achieved by reacting with thio acids. This conversion was reported initially by Just,[47] and explored further by Rosen.[48] According to Rosen's hypothesis, azides undergo in situ reduction to amines in the presence of a thio acid followed by sequential acylation resulting in the desired amide.

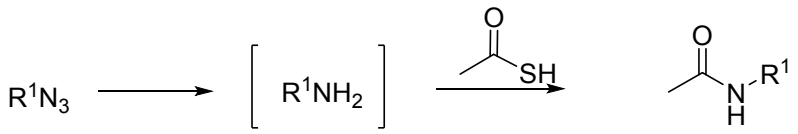


Figure 3 - Rosen's hypothesis for amidation via an amine intermediate

However, in 2003, Williams and co-workers conducted detailed mechanistic and theoretical studies on the thio acid-mediated amidation of azides.[49] According to their investigation, azides undergo amidation without forming the amine intermediate (Figure 3) rather they proposed that electron rich and poor azides undergo different reaction pathways towards amides but through a common intermediate called a thiatriazoline **182** (Figure 4). In electron poor systems, intermolecular attack of sulfur on the terminal azide nitrogen and subsequent nitrogen addition to the carbonyl resulted in the formation of the five-membered, thiatriazoline. Decomposition to desired amide occurs upon exclusion of S and N_2. In contrast, electron rich systems undergo [3+2] addition and form the thiatriazoline directly whereupon sulfur and nitrogen expulsion occur as before.

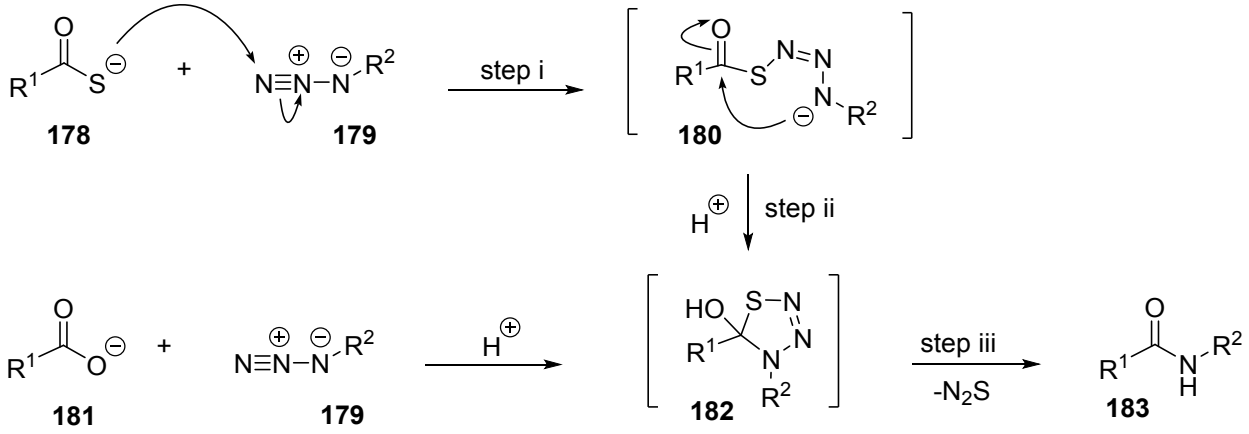
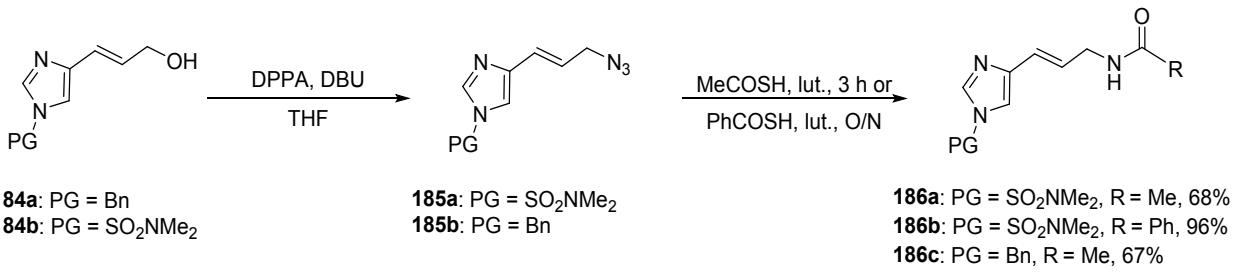


Figure 4 - Modified mechanism

In 2017, our group reported the first thio acid mediated amidations in imidazole derivatives. Several model systems were investigated permitting the installation of the acetamide and benzamide moieties with good yields (Scheme 31).[3, 50]



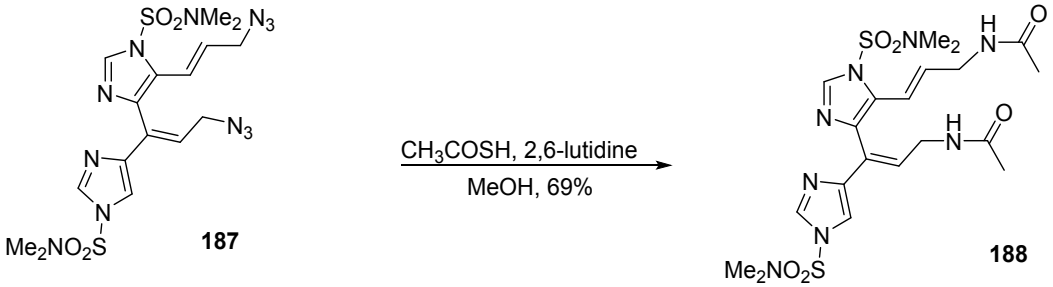
184a: PG = Bn
184b: PG = SO_2NMe_2

185a: PG = SO_2NMe_2
185b: PG = Bn

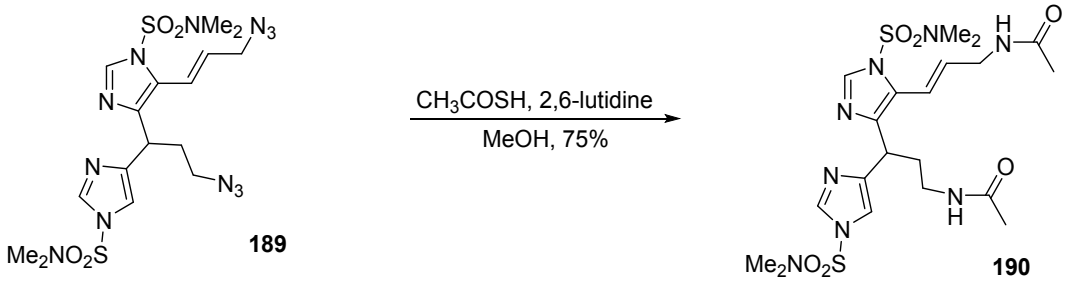
186a: PG = SO_2NMe_2, R = Me, 68%
186b: PG = SO_2NMe_2, R = Ph, 96%
186c: PG = Bn, R = Me, 67%

Scheme 31 - Acetamides and benzamides on oroidin model systems

Extension of this chemistry to advanced nagelamide intermediates was also successful resulting in formation of diacetamides in good yield (Scheme 32).



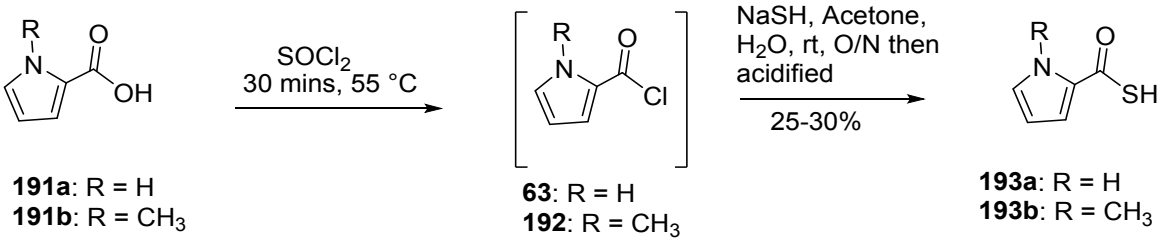
Nagelamide C (**197**) model system



Nagelamide A (**8**) model system

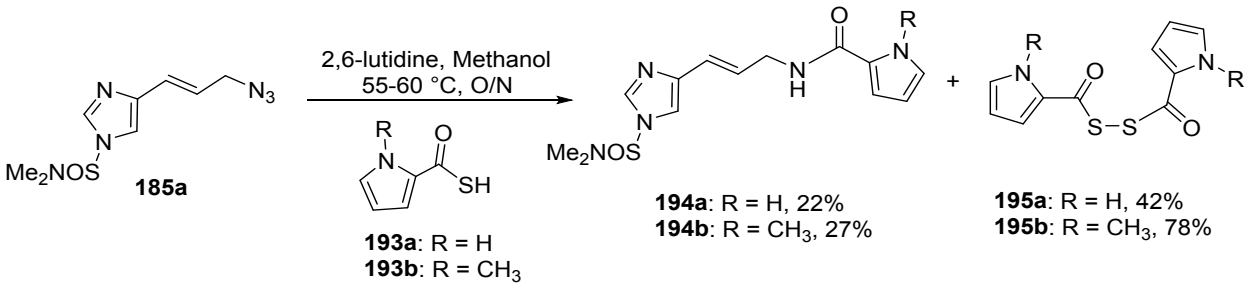
Scheme 32 - Diacetamide formation in nagelamide C and A systems

In light of these encouraging results, extension to the thio pyrrole acid was investigated. It is noteworthy that at the outset of our study there were few reports in the literature of this subfamily of thio acids. We were able to synthesize thio pyrrole carboxylic acid (**193a**) and methyl pyrrole thioacid (**193b**) through the corresponding pyrrole acid chlorides **63** and **192** (Scheme 33) and the reaction with NaSH, in modest yields.[3]

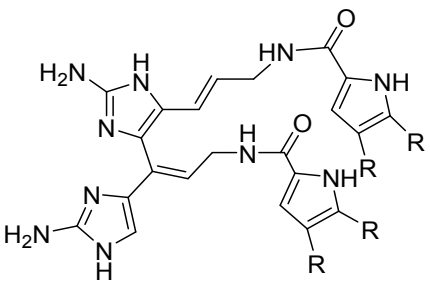


Scheme 33 - Pyrrole thio acid synthesis

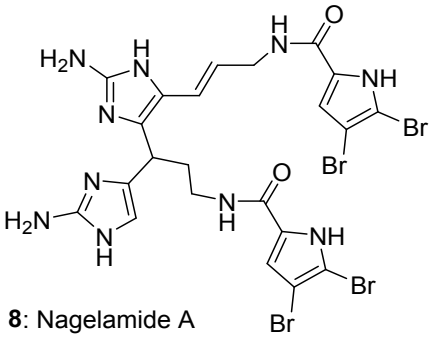
These thio acids were reacted with oroidin models to obtain the corresponding carboxamides **194a** and **194b** in addition to the oxidation products **195a-b** (Scheme 34). While the yields are moderate at the present time, in principle the chemistry can be used to complete the total synthesis of nagelamide A (**8**), C (**197**) and S (**196**) (Figure 5).



Scheme 34 - Use of pyrrole thio acid in imidazolyl systems



196: R = H: Nagelamide S
197: R = Br: Nagelamide C



8: Nagelamide A

Figure 5 - Nagelamide A, C and S

Summary

In the course of this review, we have highlighted the various and most recent methods of amide bond construction used in the synthesis of PIAs systems. Pyrrole trichloroketones were used most frequently with relevant amines to install pyrrole carboxamide moiety in natural products. Even though this method is very common and direct, it has some limitations such as the precursor amines are highly polar and thus hard to purify and handle. In addition, in some cases the yields with these derivatives have been low. Masked pyrrole carboxamides like (bromo)hydantoins are good substitutes to circumvent some of the experimental handling problems. However, (bromo)hydantoins caused problems during the installation with the allylic alcohols due to allylic transposition that is a function of the Mitsunobu chemistry used for their installation.[30] Recent studies with pyrrole thio acids show promise for improving the installation of the pyrrole carboxamide group to PIAs, however additional optimization of the reaction conditions both for their preparation and their reaction are still required.

Abbreviations

AcCl – Acyl Chloride

n-BuLi - n-Butyllithium

$(BOC)_2O$ - Di-tert-butyl dicarbonate

BOP - Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE - 1,2-Dichloroethane

DEAD - Diethyl azodicarboxylate

Dess Martin Periodinane - 3-Oxo-1,3-dihydro-1λ^5,2-benziodoxole-1,1,1-triyl triacetate

DIAD - Diisopropyl azodicarboxylate

DIBAL - Diisobutylaluminium hydride

DMAP - 4-Dimethylaminopyridine

DMF - Dimethylformamide

DMSO - Dimethyl sulfoxide

DPPA - Diphenylphosphoryl azide

EDC - 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

HOBt - 1-Hydroxybenzotriazole

LDA - Lithium diisopropylamide

2,6-Lutidine - 2,6-Dimethylpyridine

MsCl - Methanesulfonyl chloride

NCS - *N*-Chlorosuccinimide

NBS - N-Bromosuccinimide

NMO - N-Methylmorpholine N-oxide

$Pd_2(dba)_3$ - Tris(dibenzylideneacetone)dipalladium(0)

PPTS - Pyridinium p-toluenesulfonate

TBAF - Tetra-n-butylammonium fluoride

TBTU - O-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate

TMEDA - Tetramethylethylenediamine

TPAP - Tetrapropylammonium perruthenate

TBSCl - *tert*-Butyldimethylsilyl chloride

TFA - Trifluoroacetic acid

TrCl - Triphenylmethyl chloride

THF - Tetrahydrofuran

TsN_3 – Tosyl azide

p-TsOH - *p*-Toluenesulfonic acid

Conflicts of interest

There are no conflicts to declare.

Acknowledgement

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