

REVIEW

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The preparation of (4*H*)-imidazol-4-ones and their application in the total synthesis of natural products

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(4*H*)-Imidazol-4-ones are an important scaffold for a variety of applications, including natural products, medicine, agriculture, and other applications. Over the years, there have been a number of preparations published for the synthesis of imidazol-4-ones. This review discusses the progress made on the synthesis of imidazol-4-ones, and their application towards the total synthesis of a range of imidazol-4-one containing natural products. Emphasis is made on areas of the field that still need progress.

1. Introduction

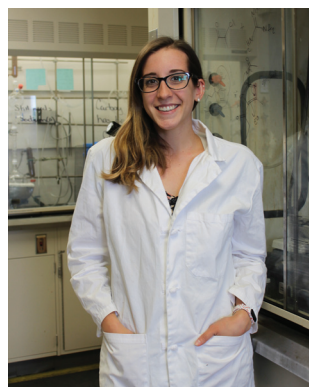
Heterocycles represent an important core in many isolated natural products. Imidazolones are five-membered heterocyclic rings containing two non-adjacent nitrogens and a carbonyl group. There are two isomers of imidazolones, depending on the placement of the carbonyl: imidazol-2-ones and imidazol-4-ones (Fig. 1A).

Imidazol-4-ones are an important heterocycle utilized for a large range of applications, including medicinal chemistry,^{1–5} fluorescent protein chromophores,^{6–8} agrochemicals,⁹ and natural products. This heterocyclic structural motif is also found naturally occurring in the body. Imidazol-4-ones are found as advanced glycation end products (AGE),^{10–12} post-translational modifications of several amino acids-aka 3,5-

dihydro-5-methylidene-4*H*-imidazol-4-one (MIO),¹³ and creatinine, a waste product used to indicate kidney health.¹⁴ Despite being found in a vast assortment of fields, there has never been a review on the preparative methods of imidazol-4-ones.

Preparation of (4*H*)-imidazol-4-ones goes back as far as 1907, when H. Finger first reported the synthesis of a (4*H*)-imidazol-4-one.¹⁵ Since then, a number of unique methodologies have been developed for the production of imidazol-4-ones. These methodologies can be used to produce three C5-substitution patterns, as shown in Fig. 1B. In an effort to centralize this information, section 2 of this review summarizes the methodologies developed for the synthesis of imidazol-4-ones. Details of each reaction are discussed, as well as any advantages or disadvantages to the method. Section 3 of this review will highlight the application of these preparative methods in the total synthesis of known imidazol-4-one containing natural products. Additionally, this section of the review presents several natural products that have yet to be synthesized.

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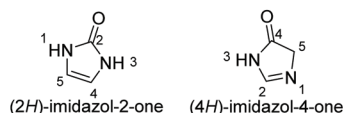
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Jetze Tepe

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A. Imidazolone isomers



B. C5-substitution patterns of imidazol-4-one

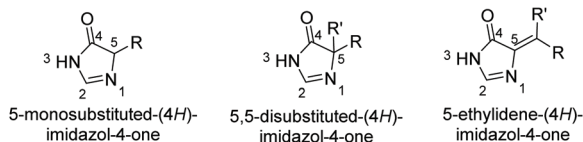


Fig. 1 Structures of imidazolones.

Overall, this review provides the first ever analysis of the known preparative methods of imidazol-4-ones, and the only review summarizing imidazol-4-one containing natural products.

2. Preparation of (4H)-imidazol-4-ones

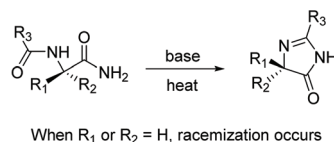
Since the first report of the synthesis of imidazol-4-ones, there have been numerous reported methods of preparation. In this section, many preparative methods of imidazol-4-ones will be discussed. For the purpose of this review, the methods have been categorized into three main transformations: condensation reactions, aza-Wittig reactions, and heterocyclic rearrangements.

2.1 Condensation reactions

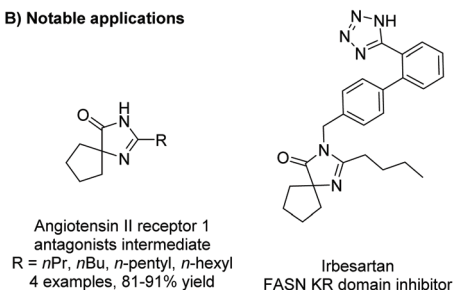
2.1.1 Cyclization of diamides. Under basic conditions, with or without heat, a diamide will cyclize to produce a range of substituted imidazol-4-ones. Some notable examples of this reaction being used within the last 5 years include the synthesis of derivatives of irbesartan for fatty acid synthase (FASN) KR domain inhibition^{5,16} and angiotensin II receptor 1 antagonists (Scheme 1).¹ This method has also been used to produce enantiopure 5,5-disubstituted-4-imidazolones from enantiopure diamides, but does not work well for the production of enantiopure 5-monosubstituted-4-imidazolones, as heat and base can cause the stereocenter to tautomerize.¹⁷ Additionally, this reaction has been used to produce a number of 5-ethylidene-4-imidazolones, with the alkene's conformation being driven by steric interactions with the imidazolone's carbonyl.

The diamide is a common intermediate in several preparative methods of imidazol-4-ones. One example is the condensation of an α -amino amide and acid derivative. Gillman *et al.* synthesized a number of imidazol-4-ones using an α -amino amide and carboxylic acid (see Scheme 2).¹⁸ Here, the amine and carboxylic acid were coupled together using a polymer-supported carbodiimide reagent, producing diamides in relatively low yields (10–50%), due to the steric bulk surrounding

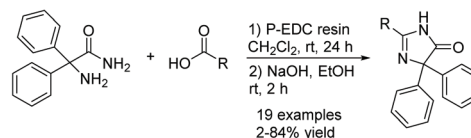
A) Transformation overview



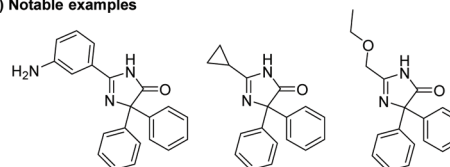
B) Notable applications



Scheme 1 General transformation from diamide to imidazol-4-one.

A) Gillman *et al.*'s method

B) Notable examples

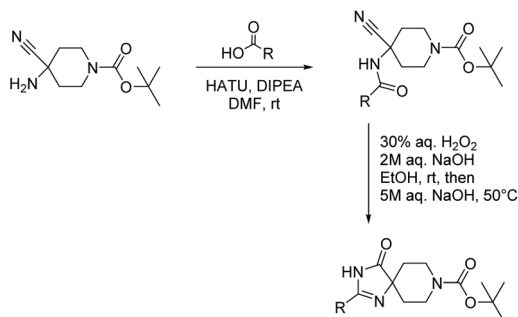
Scheme 2 Gillman *et al.*'s synthesis of imidazolones as neuropeptide Y5 receptor antagonists.

the amine. The diamide was then cyclized upon addition of sodium hydroxide in ethanol.

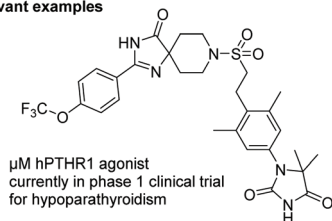
Diamides can also be produced through the oxidation of α -amino nitriles using hydrogen peroxide. α -Amino nitriles were first used to synthesize imidazol-4-ones in 1981 by Marinus Los.¹⁹ In the first step of this synthesis, an amine reacts with a carboxylic acid or acid chloride to produce an amide. The second step involves oxidation of the nitrile to an amide using hydrogen peroxide, which leads to the formation of an imidazol-4-one through cyclization of the diamide intermediate. Nishimura *et al.* used this methodology to produce a range of imidazol-4-ones as human parathyroid hormone receptor 1 (hPTHr1) agonists for treatment of hypoparathyroidism, shown in Scheme 3.^{20,21} One of their analogues, shown in Scheme 3B, is currently in a phase 1 clinical trial for the treatment of hypoparathyroidism.

2.1.2 Amino ester and cyanamide/guanidine. Amino esters are versatile building blocks used to synthesize a range of heterocycles, including imidazol-4-ones. The condensation of

A) Sato and co-workers' synthesis of hPTHR1 agonists



B) Relevant examples

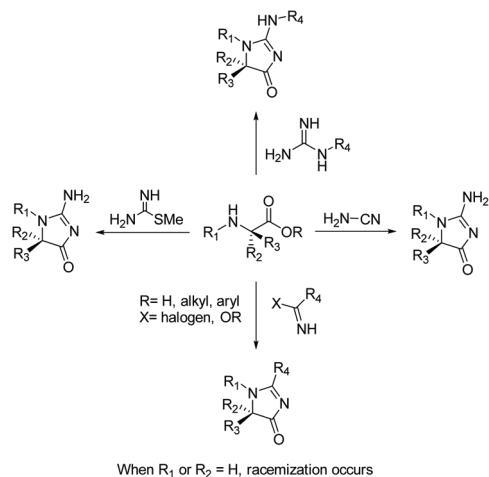


Scheme 3 The synthesis of piroimidazol-4-ones for treatment of hypoparathyroidism.

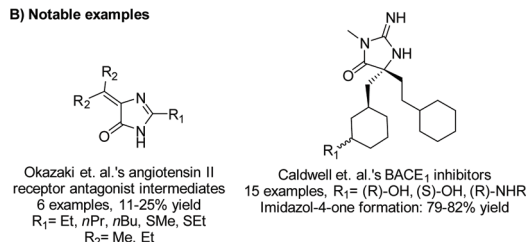
amino esters with cyanamides, guanidines, imino halides, imidates, or methyl carbamimidothioates has been used to produce a range of 5-monosubstituted, 5,5-disubstituted, and 5-ethylidene imidazol-4-ones for biological applications and natural product syntheses.^{22–25} Scheme 4 summarizes the different nucleophiles that react with amino esters to produce imidazol-4-ones. Also demonstrated in Scheme 4, this method can be used to produce enantiopure 5,5-disubstituted imidazol-4-ones, as this reaction is considered stereospecific when the 5-position is disubstituted, similar to the cyclization of diamides.²⁴

In 2020, Fathalla *et al.* utilized an intramolecular cyclization of amidine and amino ester to produce imidazoquinazolinones through a domino synthesis (Scheme 5).²⁶ Here, a range of benzimidoyl chlorides were reacted with glycine or L-alanine methyl ester hydrochloride to produce a few quinazolin-4(3*H*)-imines. The quinazolin-4(3*H*)-imine then undergoes a series of ring deconstructions and formations, ultimately producing some complex imidazoquinazolinones in 48–86% yield. This one-pot methodology was also used to construct pyrimidoquinazolinones by reacting benzimidoyl chloride with a β-alanine methyl ester.²⁶

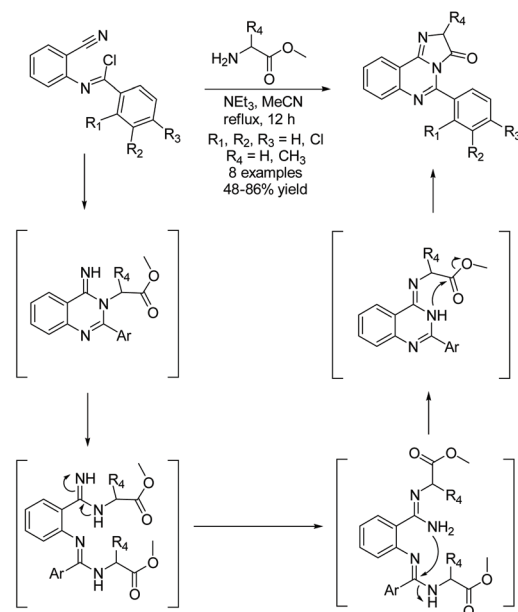
2.1.3 Imidate and α-imino ester. In section 2.1.2 imidates were used to produce a range of imidazol-4-ones upon reaction with α-amino esters. Moreover, imidates and thioimidates can be used to produce 5-ethylidene-4*H*-imidazol-4-ones when reacted with α-imino esters (Scheme 6).^{27,28} The first report of the cyclization of thioimide and α-imino ester was by Ikejiri *et al.* in 2012, where they synthesized five fused-ring 5-ethylidene-4*H*-imidazol-4-ones in 43–85% yield.²⁸ Scheme 7 displays the proposed mechanism for this reaction. The key step



B) Notable examples



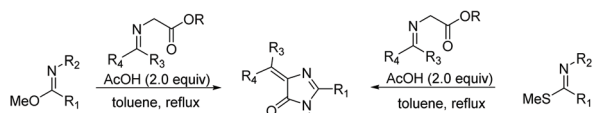
Scheme 4 Transformation of amino ester to imidazolone using a variety of nucleophiles.



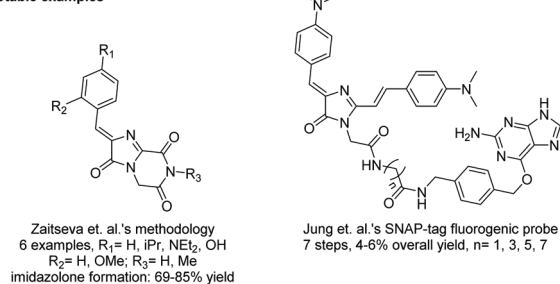
Scheme 5 Domino synthesis of imidazoquinazolinones.

to this mechanism is the formation of an aziridine, which then ring opens to the imidazol-4-one product. In the past two years alone, this reaction has been reported for the production of a number of fluorescent protein chromophores, which require the ethylidene moiety for their function.^{29–32} While

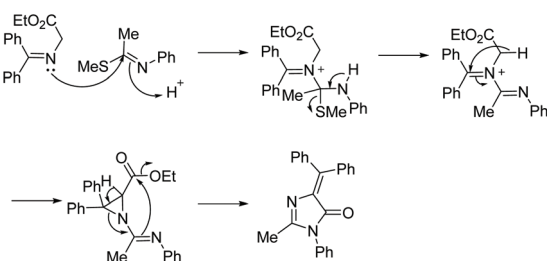
A) Transformation overview



B) Notable examples



Scheme 6 General condensation of iminoester and α -imino or α -amino ester.

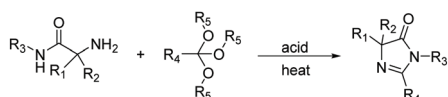


Scheme 7 Miyashita and co-worker's proposed mechanism for the formation of 5-ethylidene-4H-imidazol-4-ones.

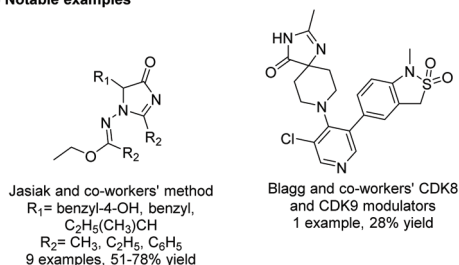
this method is used for the production of 5-ethylidene-4H-imidazol-4-ones, there are no reported cases of it being used to produce 5-monosubstituted or disubstituted imidazol-4-ones.

2.1.4 Orthoester and α -amino amide. Another way of synthesizing (4H)-imidazol-4-ones is through the condensation of orthoesters and amino amides (Scheme 8). One of the first

A) Transformation overview



B) Notable examples



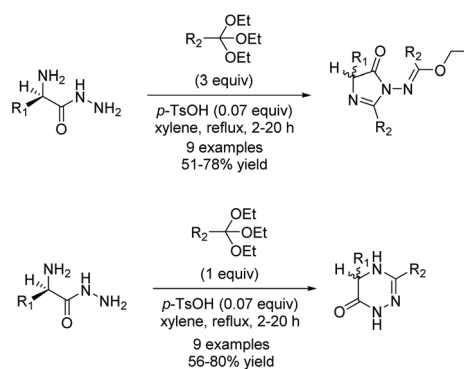
Scheme 8 General condensation of orthoester and α -amino amide.

reports of this reaction was in 1956 by Brunken and Bach.^{33,34} In this reaction, the amine from the amino amide reacts with an orthoester, creating an α -imino amide *in situ* which then cyclizes to form an imidazol-4-one. Typically, this reaction needs to be activated by acid and/or heat to get good conversion to cyclized product. Since the first report of this reaction, it has been used a number of times in the production of di- and tri-substituted imidazolones.^{35–37}

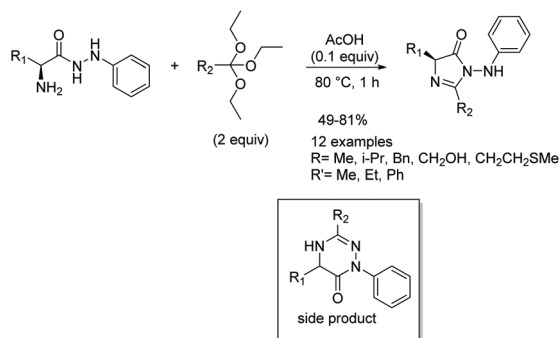
A study done by Jasiak and co-workers in 2013 demonstrates the synthesis of imidazol-4-ones from optically active α -amino carboxylic acid hydrazides (Scheme 9).³⁵ Nine examples were synthesized in good yields (51–78%). Additionally, several triazines were produced using almost the exact same conditions. It is known that excess orthoester is required to produce an imidazol-4-one as the major product. When equimolar amounts of orthoester and amino amide are used, the major product isolated is the triazine (Scheme 8). Interestingly, even though optically pure amino amides were used in this reaction, racemates were produced. While the chiral carbon is not directly affected by the transformation to imidazol-4-one, the carbon can tautomerize through hydrogen migration from the stereogenic carbon to the imino or carbonyl groups, causing a shift of the double bond, leading to loss of optical activity.

In 2014, Kacem and Hassine published an interesting modification to this reaction, leading to the synthesis of enantioselective, 5-monosubstituted imidazol-4-ones.⁹ This methodology involved a solvent-free condensation between chiral α -amino acid phenylhydrazides and triethyl orthoesters with catalytic dry acetic acid (Scheme 10). While solvent-free conditions produced the highest yields in the shortest amount of time, this reaction was also performed under a variety of solvents. Under solvent free conditions, all the compounds were prepared enantioselectively within an hour. While they do not mention why this reaction was enantioselective when previous reports were not, it may have to do with the milder conditions and shortened reaction time the solvent-free synthesis allowed for.

2.1.5 Diketone and amidine/guanidine. Condensation of a diketone and an amidine or guanidine is a common way to

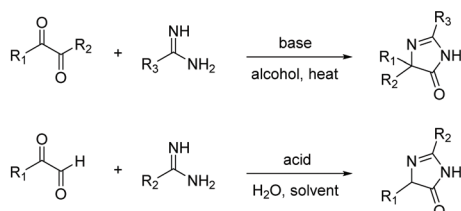


Scheme 9 Jasiak and co-workers' synthesis of imidazol-4-ones from optically active α -aminocarboxylic acid hydrazides.

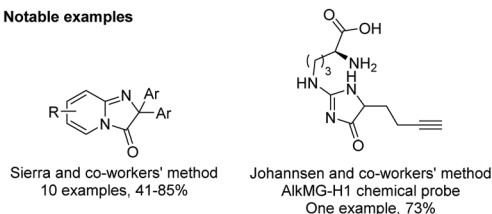


Scheme 10 Kacem and Hassine's solvent-free synthesis of imidazolones.

A) Transformation overview



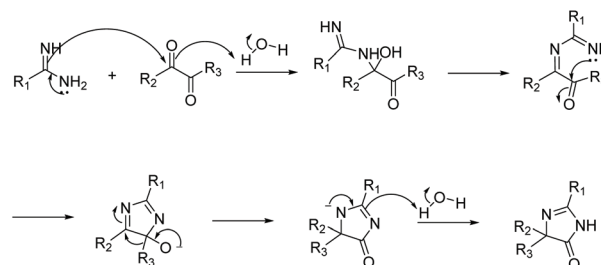
B) Notable examples



Scheme 11 General condensation of diketone and amidine to produce di- and tri-substituted imidazol-4-ones.

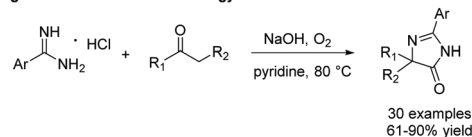
produce 5,5-disubstituted imidazol-4-ones (Scheme 11). One of the first reports of this reaction was in 1950.³⁸ In this reaction, the diketone and amidine react under basic conditions, creating a di-imine intermediate, which then cyclizes to a 5-hydroimidazole. The 5-hydroimidazole then undergoes a 1,5-dialkyl migration to produce the desired imidazol-4-one product. This mechanism is displayed in Scheme 12.³⁹ Furthermore, 5-monosubstituted imidazol-4-ones can be produced starting with an α -keto aldehyde under acidic conditions (Scheme 11). Over the past 10 years, this reaction has been used to produce imidazol-4-ones and 2-aminoimidazol-4-ones for an assortment of medicinal applications.⁴⁰⁻⁴² Additionally, this cyclization can be used to produce bicyclic imidazolones through the condensation of a diketone and 2-aminopyridine or 2-aminopyrimidine.^{43,44}

In 2015, Xie *et al.* reported a one-pot oxidative condensation of ketones and amidines (Scheme 13).³⁹ Here, molecular oxygen is used to oxidize the α -keto carbon to a diketone *in situ*, which then cyclizes under basic conditions to produce tri-substituted imidazol-4-ones, including spiroimidazol-4-

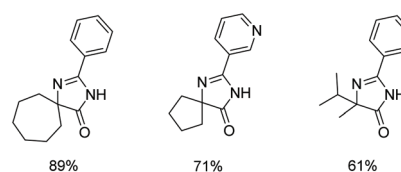


Scheme 12 Proposed mechanism for the cyclization of amidine and diketone to produce 5,5-disubstituted imidazol-4-ones.

A) Deng and co-workers' methodology



B) Relevant examples



Scheme 13 Deng and co-workers' synthesis of imidazol-4-ones from ketone and amidine containing starting materials.

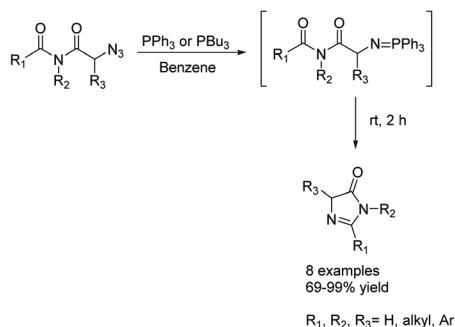
ones, in good yields (30 examples, 61–90% yield). This reaction has not been used to produce any enantioselective imidazolones thus far, mainly due to racemization which occurs during the 1,5-dialkyl migration.

2.2 Aza-Wittig reaction

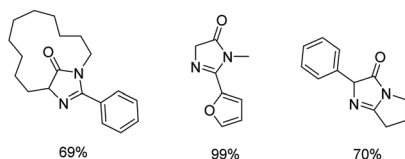
2.2.1 Intramolecular aza-Wittig reaction. The intramolecular aza-Wittig reaction is another common way to produce imidazol-4-ones. Takeuchi *et al.* was one of the first to report this reaction in 1989, using azido-substituted imides.⁴⁵ These imides reacted with triphenylphosphine to afford some 5-monosubstituted-4-imidazolones in good yields (69–99%) *via* a Staudinger reaction, followed by an intramolecular aza-Wittig reaction (Scheme 14).

Thus far, this reaction appears to be used mainly to produce a range of 5-ethylidene-4-imidazolones.⁴⁶⁻⁴⁹ There are two different pathways this reaction can be implemented to produce 5-ethylidene-4-imidazolones; both are shown in Scheme 15. In method A, the more popular method, the imidazol-4-one ring is formed from a terminal azidoimide.⁵⁰ Then, the 5-ethylidene substituent is added *via* a Knoevenagel condensation reaction. Method B first condenses the azidoamide and aldehyde to produce an internal azide.⁴⁹ This then reacts with triphenylphosphine, followed by an acid halide to produce an iminoyl halide, which will cyclize upon condensation with the present amide. Alkene conformation is driven

A) Takeuchi et. al.'s methodology

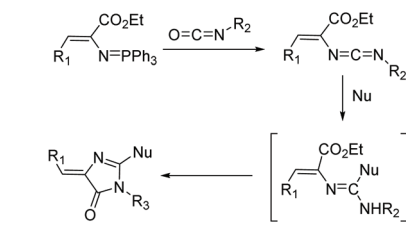


B) Relevant examples

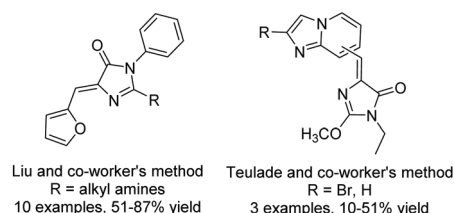


Scheme 14 Takeuchi et al.'s intramolecular aza-Wittig reaction to produce imidazolones.

A) Transformation overview

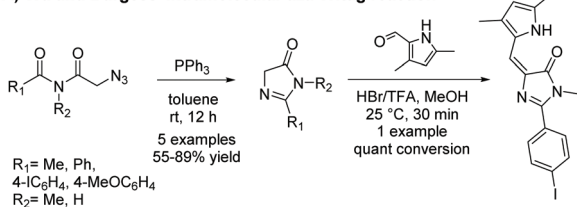


B) Notable examples

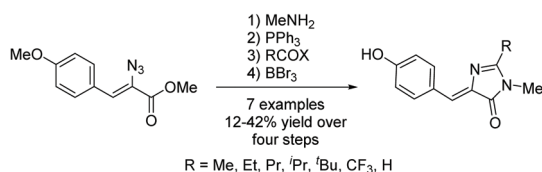


Scheme 16 General heterocumulene-mediated annulation initiated by an aza-Wittig reagent.

A) Wu and Burgess' intramolecular aza-Wittig reaction



B) Yampolsky and co-worker's intermolecular aza-Wittig reaction



Scheme 15 Aza-Wittig reaction to produce 5-ethylidene-4-imidazolones.

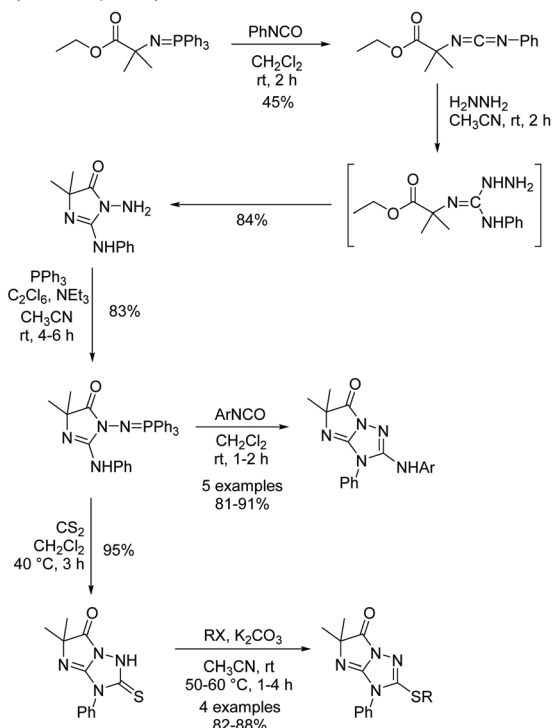
by steric interactions as well as the potential to hydrogen bond. Variations of this reaction have been used a couple times to produce 5,5-disubstituted-4-imidazolones.^{51,52}

2.2.2 Tandem aza-Wittig/heterocumulene-mediated annulation. The aza-Wittig reaction can also be used as part of a heterocumulene-mediated annulation reaction to produce imidazol-4-ones. The first report of this reaction was in 1992 by Molina *et al.* for the synthesis of aplisinopsin-like alkaloids.⁵³ In this reaction, an aza-Wittig reagent reacts with isocyanate to produce a heterocumulene intermediate. Upon addition of a nucleophile, the intermediate will cyclize to produce a variety of 5-ethylidene imidazol-4-ones. The mechanism and notable examples of this reaction are shown in Scheme 16. Some examples of nucleophiles (Nu) include alcohols, amines, thiols, and heterocycles.^{4,54-56}

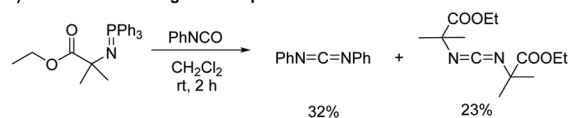
While more uncommon, the aza-Wittig/heterocumulene-mediated annulation can also be used to produce 5,5-disubstituted imidazol-4-ones. Yang and co-workers reported an interesting cascade of reactions to produce 3,5-dihydro-6*H*-imidazo[1,2-*b*]-1,2,4-triazol-6-ones (Scheme 17).⁵⁷ In this report they highlighted some abnormal aza-Wittig reactions, which led to unanticipated side products, reducing the yield of the isocyanate intermediate (Scheme 17B). It was noted that only the main aza-Wittig reaction product was produced when a similar but less sterically hindered iminophosphorane was used. Therefore, one limitation to this method is sterics, which can hinder formation of the isocyanate intermediate. This may explain why more 5,5-disubstituted imidazol-4-ones are not made *via* the aza-Wittig/heterocumulene mediated annulation methodology. There is also one report of this reaction being used to synthesize 5-monosubstituted imidazol-4-ones.⁵⁸ Interestingly, this reaction was performed stereospecifically, using enantiopure amino acids to produce enantiopure 5-monosubstituted imidazolones.

In 2019, a one-pot, three step reaction was reported by Ding and co-workers using an aza-Wittig/heterocumulene mediated annulation to produce a variety of bicycloimidazol-4-ones.⁵⁹ Scheme 18 describes their one-pot, three-step synthesis of a variety of bicycloimidazol-4-ones in good yields (68–85%). In this reaction, a (vinylimino)phosphorane is treated with a variety of aromatic isocyanates to produce a carbodiimide. 2-aminoethanol is then added to the reaction, which produces a guanidine intermediate that cyclizes upon the loss of ethanol. Then, upon addition of tosyl chloride (TsCl) and triethylamine (NEt_3), the primary alcohol is converted to a tosyl ether, which leaves upon the formation of the second ring. These three steps were performed in sequence, without isolation.⁵⁹

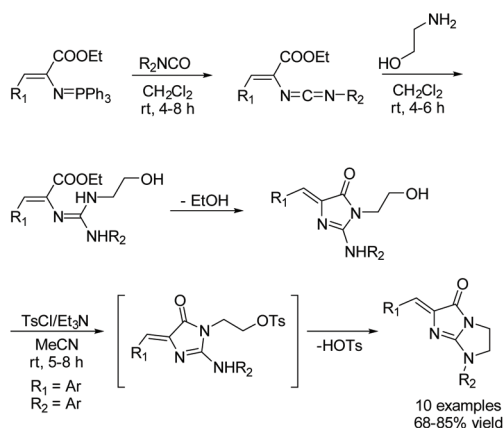
A) Reaction pathway



B) Abnormal aza-Wittig reaction products



Scheme 17 Yang and co-worker's synthesis of 3,5-dihydro-6H-imidazo[1,2-*b*]-1,2,4-triazol-6-ones.

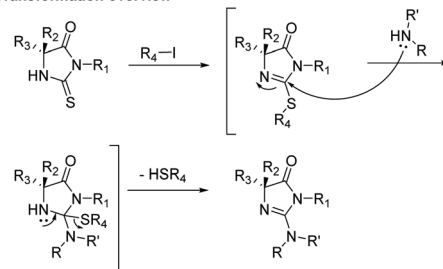


Scheme 18 One pot, multicomponent synthesis of bicycloimidazolones reported by Ding and co-workers.

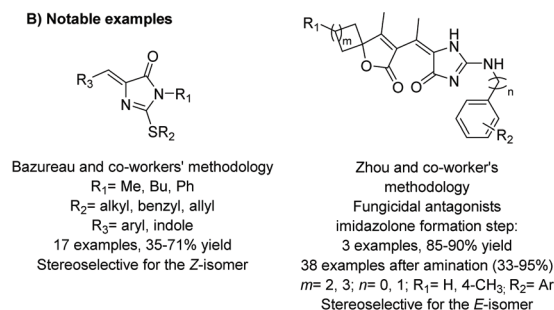
2.3 Heterocyclic conversion/rearrangements

2.3.1 Thiohydantoin conversion to imidazolone. One of the most commonly used methodologies for the production of imidazol-4-ones is the conversion of thiohydantoin using

A) Transformation overview



B) Notable examples

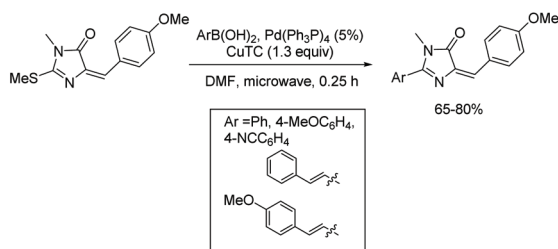


Scheme 19 Conversion of thiohydantoin into 2-aminoimidazolone.

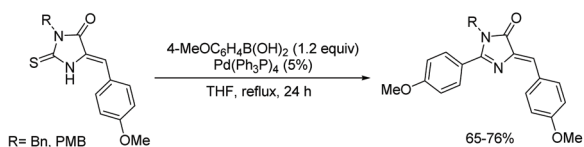
alkyl halides. This was first reported by Daboun and Ibrahim in 1981.⁶⁰ Since then, there have been numerous reports of this transformation being used to synthesize various imidazol-4-ones for medicinal applications^{61,62} and the total synthesis of natural products.⁶³⁻⁶⁷ Scheme 19 describes the basic transformation from thiohydantoin to 2-aminoimidazol-4-one. This reaction usually takes two steps. In the first step, the thiohydantoin is converted to 2-(alkylthio)imidazol-4-one by reacting the thiohydantoin with an alkyl halide and some base. The second step is then addition of a nucleophile (aniline, hydrazine, boronic acid, ether, *etc.*) with heat, which converts the 2-thioether to a variety of functional groups. Substitution at the 5 position of the ring is also versatile, withstanding mono- and di-substitution as well as an ethylidene functional group. Moreover, the 5-position substitution is not affected during transformation from thiohydantoin to imidazol-4-one, which allows this method to be used for the production of stereoselective compounds.⁶⁸ As with many of these methods, the stereochemistry of the 5-ethylidene group is driven by sterics, to avoid interactions with the imidazolone's carbonyl. This typically leads to the *Z*-isomer being favored.⁶² However, in some instances, the *E*-isomer may be favored, like in Zhou and coworker's work, mentioned in Scheme 19B.⁶¹ The *E*-isomer was identified from a X-ray crystal structure.

Ease of alteration of the 2-position of the thiohydantoin ring can lead to a multitude of unique imidazol-4-ones. Amination of the 2-position is performed with a desired amine and heat; this is the same procedure for substitution to a hydrazine. Etherification can be accomplished using an alcohol and some base, along with heat.⁶⁹ Arylation of the 2-position of the imidazol-4-one is also possible, following the Liebeskind-Srogl reaction. This method was first reported by Bourguignon and co-workers in 2004 (Scheme 20).⁷⁰ The

A) Bourguignon and co-workers' work:



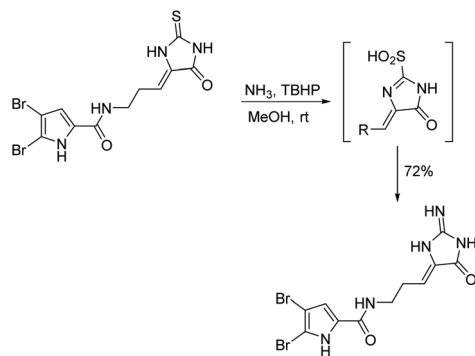
B) Tatibouët and co-workers' work:



Scheme 20 Conversion of thiohydantoin to 2-aryl-imidazol-4-one.

Liebeskind-Srogl reaction creates a C–C bond through the cross coupling of a boronic acid and thioether in the presence of copper(I) thiophene-2-carboxylate (CuTC) and tetrakis(triphenylphosphine)palladium ($\text{Pd}(\text{Ph}_3\text{P})_4$).⁷¹ Surprisingly, the authors report the *E*-isomer was isolated from the Knoevenagel condensation of 4-methoxy benzaldehyde and thiohydantoin. This led to isolation of *E*-imidazol-4-one. In another study, Tatibouët and co-workers reported the use of boronic acids and $\text{Pd}(\text{PPh}_3)_4$ to directly convert thiohydantoin into 2-aryl-imidazolones (see Scheme 20).⁷¹ In their work, the Knoevenagel condensation of 4-methoxy benzaldehyde and thiohydantoin led to the isolation of the *Z*-isomer of thiohydantoin and subsequently, *Z*-imidazol-4-one.

The conversion of thiohydantoin to 2-aminoimidazol-4-one can be performed using a one-pot, two step procedure with *tert*-butylhydroperoxide (TBHP) and aqueous ammonia in methanol at room temperature. This reaction was first mentioned in the total synthesis of dispacamide, reported by Lindel and Hoffmann in 1997 (Scheme 21).⁶³ In this reaction, TBHP is used to oxidize the sulfur to a sulfinic acid *in situ*, which is then easily removed by nucleophilic attack of

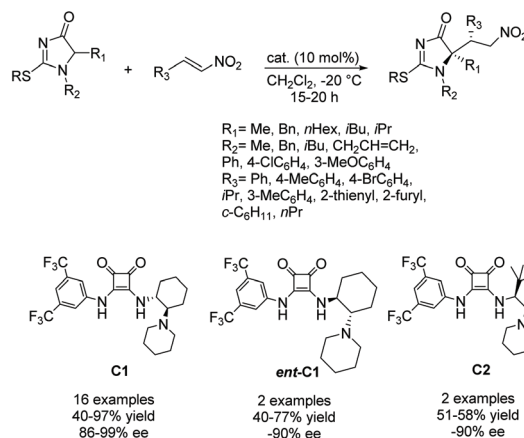


Scheme 21 First reported conversion of thiohydantoin to imidazolone using TBHP.

ammonia. Since this reaction was first reported, it has been used to synthesize a range of (4*H*)-imidazol-4-ones.^{67,72,73}

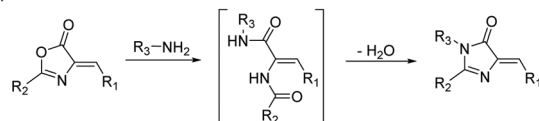
Palomo and co-workers have been working on a method to produce enantiopure 5,5-disubstituted imidazolones from 5-monosubstituted imidazolones.^{74–76} In their reaction, a 5-monosubstituted imidazolone reacts with an electrophile under the influence of a bifunctional Brønsted base/H-bond catalyst to create a stereoselective 5,5-disubstituted product (Scheme 22). Additionally, they used this method to produce some enantioselective bi- or tricyclic imidazol-4-ones. Since this first report, they have elaborated on the variety of groups used to enantioselectively alkylate the 5-position of the ring, including aldol products and enols. A variety of catalysts were also used, with varying success.^{74–76}

2.3.2 Oxazolone rearrangement. Rearrangement of an oxazolone ring upon addition of an amine can be used to produce di-substituted and tri-substituted imidazol-4-ones for a wide range of biological applications,^{2,77–80} total syntheses,⁸¹ and other applications.⁸² Scheme 23 displays the basic mechanism for this reaction. The reaction is initiated by nucleophilic attack of a primary amine, which opens the oxazolone ring into a diamide. The diamide will then cyclize to form an imidazol-4-one upon loss of water. Reagents used to promote this reaction can vary, and the reaction can be run under acidic, neutral, or basic conditions; however, most reactions require heat. Some popular conditions include refluxing the amine in pyridine or ethanol or refluxing with sodium acetate in acetic acid. A wide range of amines can be used as the nucleophile for the ring opening amination, including primary aryl, alkyl, benzyl, silyl and alkenyl amines, amino acids, ammonium acetate, and hydrazines.^{2,3,77} Additionally, the use of benzyl carbamimidothioate has been reported to produce 2-amino-4*H*-imidazol-4-ones.^{83,84} This reaction is mainly used to produce 5-ethylidene-4-imidazolones, but has been used several times to produce 5,5-disubstituted-4-imidazolones.^{85,86} There have been no reports of 5-monosubstituted imidazol-4-ones being produced *via* this method. A slight variation of the

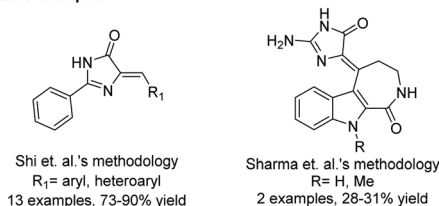


Scheme 22 Enantioselective reaction between imidazol-4-ones and nitroolefins.

A) Transformation overview



B) Notable examples



Scheme 23 General transformation of oxazolone to imidazolone.

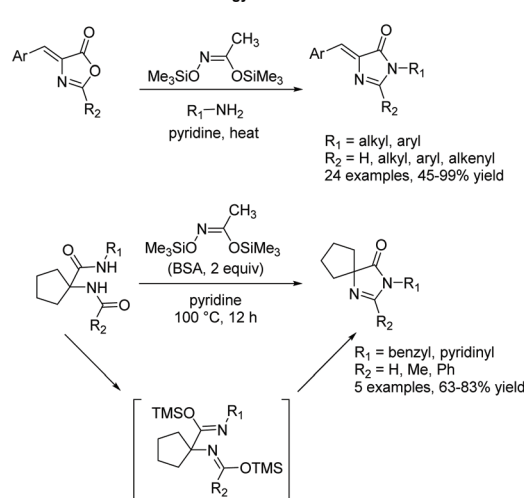
oxazolone rearrangement is the use of a thiazol-4(5*H*)-one, which ring opens upon addition of a secondary amine. The intermediate will then recyclize, releasing sulfur in the process. This reaction has been reported only a few times, beginning in 2007.^{87–89}

One of the downfalls of this reaction is the harsh conditions needed to convert from diamide to imidazol-4-ones, which limits this reaction, avoiding the use of sterically bulky amines. An interesting alteration to this reaction is described in an article by Bischoff and co-workers, where they used *N,O*-bistrimethylsilylacetamide (BSA) to promote the transformation of oxazolone to imidazol-4-one.⁹⁰ In this reaction, BSA is a dehydration reagent, used to speed up the dehydration of diamide under mild conditions. This reaction proved to be a mild, one-pot method to produce a range of imidazolones (Scheme 24). BSA provided them with a large tolerance towards a variety of functional groups, including 5,5-dialkyl and 5-benzylidene imidazolones as well as 2*H*- and 2-substituted imidazolones, in mild to good yields (45–99%).⁹⁰ Some of the highlights from this procedure include its compatibility with *tert*-butyl groups, formamides, activated double bonds, and *N*-arylamides, which are poorly reactive.

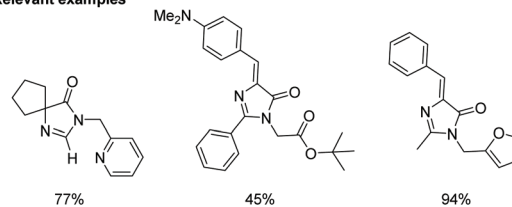
2.3.3 Oxidative pinacol-like rearrangement of imidazole.

The oxidative rearrangement of imidazoles is an alternative method of producing imidazol-4-ones. In this reaction, an oxidation source, like singlet oxygen or dimethyldioxirane (DMDO), is used to epoxidate the imidazole, which can subsequently undergo a pinacol-like rearrangement to form an imidazol-4-one (Scheme 25). One of the first reports of this reaction was by Guy Rio and Bernard Serkiz in 1975, where they used molecular oxygen as an oxygen radical source.⁹¹ Since then, this reaction has been performed using a variety of oxidants, such as DMDO,⁹² Davis reagent,^{93,94} *m*-chloroperoxybenzoic acid (mCPBA),⁹⁵ and other peroxides.⁹⁶ This reaction has been used to produce a wide range of imidazolones for natural product total synthesis, including calcaridine A, hymenialdisine, oxyseptrin and monobromodispacamide.^{97–101} Additionally, there is some evidence to support the formation of enantioselective products from the pinacol-like rearrange-

A) Bischoff and co-workers' methodology

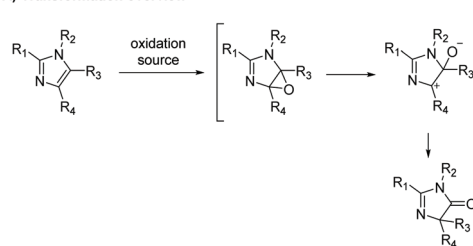


B) Relevant examples

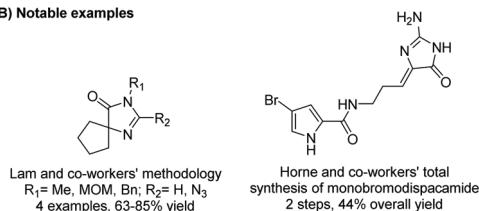


Scheme 24 Bischoff and co-workers' work on a BSA-mediated formation of imidazolones from oxazolones.

A) Transformation overview

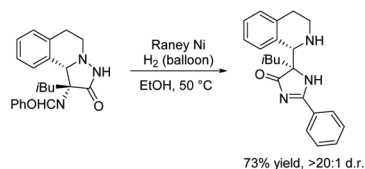


B) Notable examples



Scheme 25 General mechanism for the pinacol-like rearrangement of imidazole to imidazolone.

ment. Kimura and co-workers report a stereoselective 1,5-phenyl migration on several imidazolols upon addition of base in DMSO, producing 5,5-diarylated imidazol-4-ones (ee > 90%).¹⁰² In nature, the pinacol rearrangement is used to convert 2'-deoxyguanosine to a spiroimidazolone.¹⁰³ This reaction was found to occur naturally through single-electron oxidation under basic conditions (pH > 8) and can also take place



Scheme 26 Reductive rearrangement of pyrazolidine-3-one to imidazol-4-one.

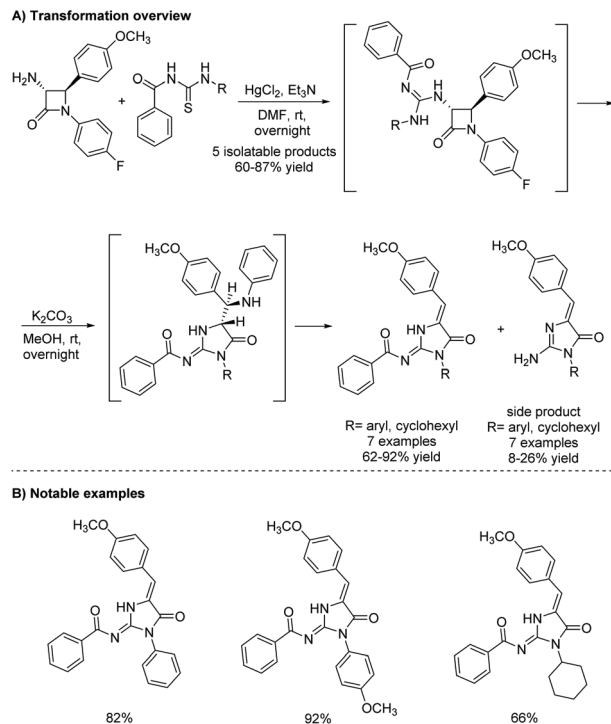
in acetic acid with *m*-chloroperbenzoic acid (mCPBA) or dimethyldioxirane (DMDO).¹⁰⁴

2.3.4 Rearrangement of pyrazolidin-3-one. In 2016, Su and co-workers reported the rearrangement of pyrazolidin-3-one using RANEY® nickel and hydrogen (Scheme 26).¹⁰⁵ RANEY® nickel and atmospheric hydrogen converts the pyrazolidine-3-one to imidazol-4-one through a reductive cyclization *via* cleavage of the nitrogen–nitrogen bond. Not much is reported on this reaction, as it has only been used once for the purpose of synthesizing an imidazolone, however, it has been used previously to produce an indolizidine from *N*-amino-3,4-dihydroisoquinoline.^{106,107}

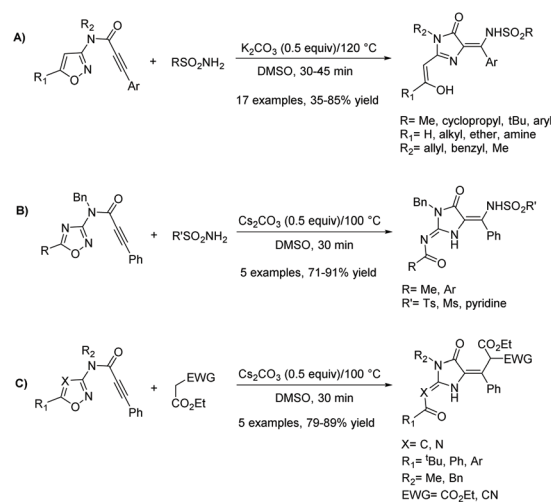
2.3.5 Ring expansion of amino-β-lactam. In 2015, Dražić *et al.* reported a base-promoted amino-β-lactam ring expansion that produced 2-amino-4-imidazolones (Scheme 27).¹⁰⁸ In this reaction, the amino-β-lactam reacts first with thiourea. Then, upon treatment with potassium carbonate, there is an amidolysis *via* the N1–C2 bond, which leads to rearrangement to a 5-membered imidazol-4-one ring. It was found that they could not isolate 2-guanidine β-lactams that contained an electron withdrawing group on the guanidine nitrogen. Instead, those compounds rearranged to a 5-membered ring without addition of potassium carbonate. Presumably, the electron withdrawing groups (*i.e.* NO₂, CN) allow for easier deprotonation, which makes triethylamine a strong enough base to deprotonate the guanidine, allowing it to react with the C2 carbon.

This rearrangement has been used previously to produce other heterocycles, like thiohydantoin, hydantoin, and imidazolines.^{109,110} In 2017, this methodology was used to produce leucettamine B and C.¹¹¹

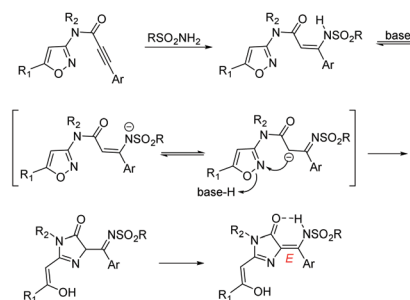
2.3.6 Boulton-Katritzky rearrangement of isoxazole. In 2019, Cai and co-workers reported a stereoselective synthesis of (*E*)-5-tetrasubstituted-ylidene-3,5-dihydro-4*H*-imidazol-4-ones starting from isoxazoles.¹¹² This reaction is a combination of a Michael addition reaction followed by a Boulton-Katritzky rearrangement, using a nucleophilic carbon during the rearrangement process. Several conditions were screened, including changes in the base, base equivalents, solvent, temperature, and time. Ultimately, the best conditions were reported as using potassium carbonate (0.5 equivalents) in DMSO at 120 °C for 45 minutes (81% yield). These conditions were used to produce a range of imidazol-4-ones, varying at three different positions (see Scheme 28A) in moderate to good yields (35–85%). Additionally, this reaction produced some 2-amino-4-imidazolones in good yields (71–91%) by altering the starting material (see Schemes 28B and C). The



Scheme 27 Habuš and co-workers' beta-lactam ring expansion to produce 2-amino-4-imidazolones.



D) Mechanism



Scheme 28 Cai and co-workers' synthesis of imidazol-4-ones *via* rearrangement of isoxazoles.

Table 1 Substitution patterns of imidazol-4-ones produced from referenced reactions, where green symbolizes produced scaffolds and red symbolizes scaffolds which have not been produced from that methodology

Reaction	5-Monosubstituted	5,5-Disubstituted	5-Ethylidene
Cyclization of diamides	Green	Green	Green
Amino ester and cyanamide/guanidine	Green	Green	Green
Imidate and α -imino ester	Red	Red	Red
Orthoester and α -amino amide	Green	Green	Red
Diketone and amidine/guanidine	Green	Green	Red
Intramolecular aza-Wittig reaction	Green	Green	Green
Tandem aza-Wittig/heterocumulene-mediated annulation	Green	Green	Green
Thiohydantoin conversion to imidazolone	Green	Green	Green
Oxazolone rearrangement	Green	Green	Green
Oxidative pinacol-like rearrangement of imidazole	Green	Green	Green
Rearrangement of pyrazolidin-3-one	Red	Green	Red
Ring expansion of amino- β -lactam	Red	Red	Green
Boulton-Katritzky rearrangement of isoxazole	Red	Red	Green

mechanism of this reaction is displayed in Scheme 28D. The *E* stereoselectivity is due to a hydrogen bond formation between the NH of the alkene and oxygen atom of the carbonyl group. Notably, this reaction has only been used to produce 5-ethylidene-4-imidazolones.

In summary, section 2 of this review aimed to highlight the known efforts towards the development of novel methodologies for the preparation of imidazol-4-ones. A number of methods were described, with examples of their usability for medicinal and other applications. Advantages and disadvantages of each method were highlighted, including the scope of the reaction, limitations to substitution patterns of the imidazol-4-ones, and abilities to produce enantioselective products.

Table 1 highlights the methods discussed in this section and summarizes the substitution patterns which can be produced from each method. There are six methods which can be used to produce all three substitution patterns: cyclization of diamides, cyclization of amino ester and cyanamide/guanidine, tandem aza-Wittig/heterocumulene-mediated annulation, thiohydantoin conversion to imidazolone, oxazolone rearrangement, and oxidative pinacol-like rearrangement of imidazole. Several of the other methods were specifically designed for the synthesis of 5-ethylidene-4-imidazolones, including the cyclization of imidates and α -imino esters, ring expansion of amino- β -lactam, and the Boulton-Katritzky rearrangement of isoxazole. There are plenty of methods for the production of 5-monosubstituted and 5,5-disubstituted imidazol-4-ones, however, there is a lack of methods that produce enantiopure 5-substituted imidazol-4-ones. In fact, there is only one reaction reported that produces enantiopure 5,5-disubstituted imidazol-4-ones stereoselectively from a starting material where the stereocenter was not already in place.^{74–76}

In the next section of this review, the preparation of imidazol-4-ones will be applied to a series of natural product total syntheses.

3. (4*H*)-Imidazol-4-one containing natural products and their total syntheses

There are many isolated (4*H*)-imidazol-4-one containing natural products known to date, however, they have never been summarized in one report. These natural products can be separated into three main categories: indole alkaloids, pyrrole alkaloids, and other 2-aminoimidazol-4-one alkaloids. Section 3 of this review covers all known (4*H*)-imidazol-4-one containing natural products, their biological activities, and efforts towards their total syntheses. Some of the methods highlighted in section 2 of this review will be used to produce these natural products.

3.1 Indole alkaloids

3.1.1 Aplysinopsin. The first aplysinopsin derivatives were isolated by Kazlauskas, Rymantas, and co-workers in 1977 from the dictyoceratid sponge *Aplysinopsis*.¹¹³ This family of natural products is derived from tryptophan and has been isolated from a number of different sources, including sponges and scleractinian corals.¹¹⁴ There are over 30 known variations of aplysinopsin, of which the imidazolone containing derivatives are displayed in Fig. 2.^{115–119} There are a number of hydantoin-containing aplysinopsin analogues as well, but for the purpose of this review we will only be discussing the (4*H*)-imidazol-4-one containing scaffolds. The natural derivatives of aplysinopsin differ by variations in the structure of the imidazolone ring (oxidation state, position and number of *N*-methylations), bromination pattern of the indole, presence and absence of a double bond on the 5 position of the imidazol-4-one ring, dimerization, and the stereochemistry.

Aplysinopsins are known for their range of biological activities, including anticancer, antimicrobial, and antiplasmodial activities.¹¹⁵ However, the most significant biological activity is

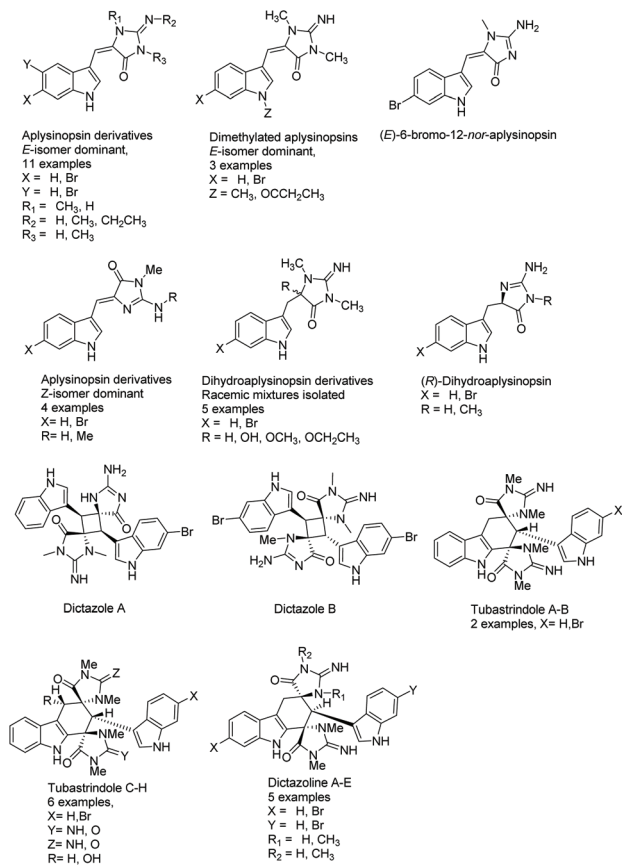
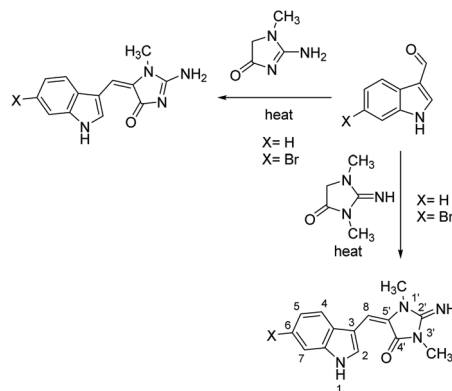


Fig. 2 (4*H*)-Imidazol-4-one containing derivatives of aplysinopsin.

modulation of neurotransmission through regulation of monoaminooxidase (MAO), serotonin receptors, and nitric oxide synthase (NOS) activities.¹²⁰ Methylaplysinopsin is a potent reversible MAO inhibitor, found to decrease MAO concentrations below 1 ng mL⁻¹ over 4–8 hours *in vivo*.¹²¹ 6-Bromoaplysinopsin was found to have an affinity for human serotonin 5-HT₂ receptors with a similar K_i as serotonin.¹¹⁵ 5,6-dibromo-2'-demethylaplysinopsin (*Z*) showed 100% inhibition of nNOS at 125 µg mL⁻¹ and 32% inhibition of iNOS.¹²⁰ Most recently, tubastrindole B was found to be a glycine-gated chloride channel receptor α1 selective GlyR antagonist (IC₅₀ = 25.9 µM with a IC₅₀ > 300 µM for α3).¹²² Aplysinopsin was not found to have any inhibitory activity in comparison. GlyRs play a pivotal role in running inhibitory neurotransmission in the spinal cord, brain stem and retina. This could be beneficial in the treatment of inflammatory pain, opioid-induced breathing disorders, epilepsy, and movement disorders.¹²²

Two of the original total syntheses for (*E*)-aplysinopsin and its 6-bromo derivative were reported by Guella *et al.* (1988) and Fattorusso *et al.* (1985).^{123,124} Their syntheses are summarized in Scheme 29 and include a method to produce *exo* and *endo* products. The key step is a Knoevenagel condensation of methyl creatinine with indol-3-carboxaldehyde and its 6-bromo derivative. Additionally, Guella *et al.* studied the photoisomerization of the (*E*) isomer and found they were able to increase

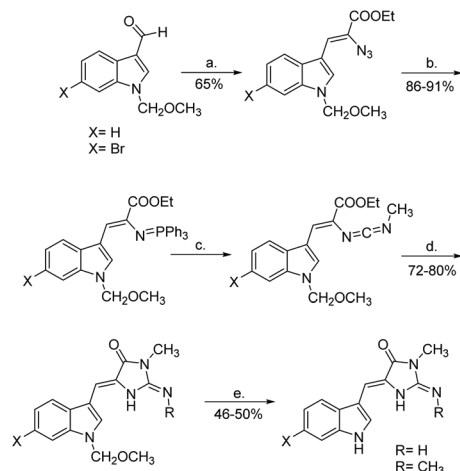


Scheme 29 First reported total synthesis of (*E*)-aplysinopsin derivatives.

the amount of (*Z*) isomer to establish H–C, C=O heteronuclear coupling constants for both.¹²⁴ Knowing that the (*E*) isomer has an appreciably larger coupling constant (10.5 Hz) than (*Z*) (5.1 Hz) has allowed researchers to quickly determine whether they synthesized the (*E*) or (*Z*) isomer in subsequent studies. This synthesis has since been used to make a variety of analogues,^{117,125} including 5,6-dibromo-2'-demethylaplysinopsin¹²⁶ and several series of N-alkylated aplysinopsin derivatives used for biological testing.^{127–129} The conditions for this reaction vary but typically require heat and addition of a base, such as piperidine. A microwave-assisted method has been reported as well, where the reaction was microwaved for 30–60 seconds with creatinine and NaOAc.¹²⁹

Since this first synthesis of aplysinopsin was published, many other groups have reported variations of the total synthesis of aplysinopsin and its derivatives.^{81,122,125,130} A particularly interesting synthesis was reported by Molina *et al.*^{53,131} The authors reported synthesizing several aplysinopsin derivatives through a tandem aza-Wittig/heterocumulene-mediated annulation (Scheme 30). Using this method, four different analogues of aplysinopsin were synthesized in moderate yields, all containing *Z*-isomerization. This paper was one of the first reports of synthesizing (*Z*)-aplysinopsin derivatives.¹³¹

There are other, unique derivatives within the aplysinopsin family that cannot be synthesized *via* the same means as reported above. Examples include dihydroaplysinopsin and 6-bromo-dihydroaplysinopsin, which were isolated and synthesized in 2015 by Shaker *et al.* (Scheme 31).¹¹⁹ The formation of (4*H*)-imidazol-4-one involved L-tryptophan being treated with N-hydroxysuccinimide and N,N-dicyclohexylcarbodiimide to form an activated NHS-ester. This was then introduced to aqueous sodium cyanamide, which produced the protected imidazolone in good yields. Because they started with optically pure amino acids (L-tryptophan), Shaker used the configuration of the final synthesized products, which were determined as (*S*) even after partial racemization occurred, to determine the configuration of the natural products as (*R*) based on measured optical rotation.¹¹⁹



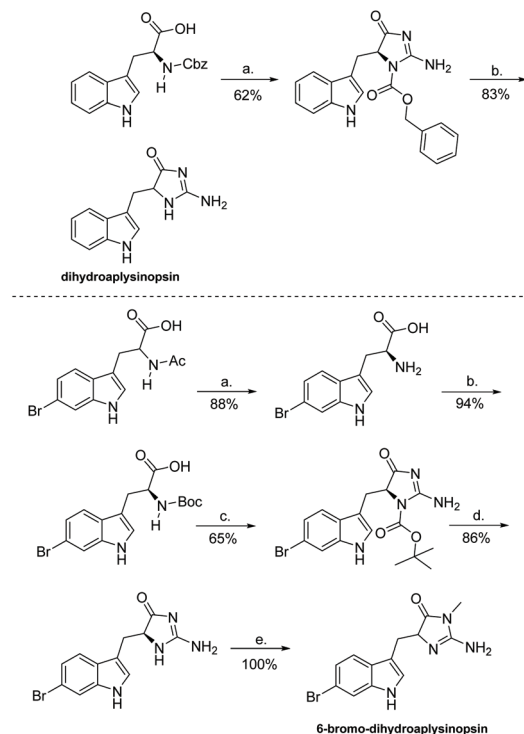
Scheme 30 Iminophosphorane-mediated ring formation to produce (Z)-aplysinsin derivatives. Reagents: (a) $\text{N}_3\text{CH}_2\text{COOC}_2\text{H}_5$, NaOEt, EtOH, -15°C , (b) PPh_3 , CH_2Cl_2 , rt, (c) $\text{CH}_3\text{-NCO}$, toluene, rt, (d) NH_2R , toluene, 45°C , (e) HCOOH , reflux.

Another unique scaffold from the aplysinsin family is dictazole. Dictazole A and B are distinctive aplysinsins, formed through the dimerization of two aplysinsin monomers. Several papers report on the synthesis of dictazole A and B through a [2 + 2] cycloaddition of aplysinsin monomers. The first report of the formation of dictazole B was in 2014 by Skiredj *et al.*¹¹⁶ The authors were able to isolate 14% of dictazole B through a heterodimerization of an *endo* and *exo* monomer of 6-bromoaplysinsin (Scheme 32). Additionally, they isolated 19% yield of the anti, head-to-tail homodimer of the *exo* starting material. The same group has published several other variations to this synthesis in similar yields.^{132,133}

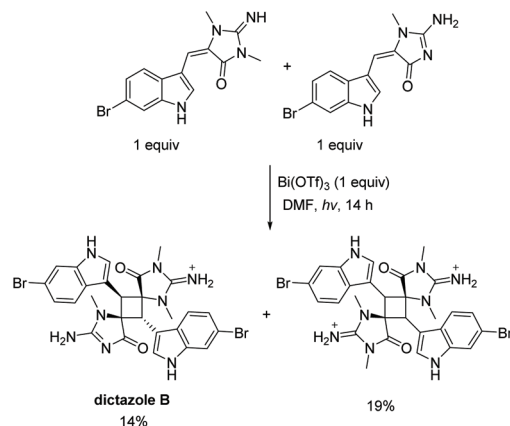
Skiredj *et al.* also worked on the total synthesis of tubastrindole B, the ring expanded product of dictazole B.¹³⁴ Scheme 33 illustrates their reported aplysinsin cascade, where ring expansion of dictazole B occurred upon addition of heat and trifluoroacetic acid. This mimics the proposed biomimetic formation of tubastrindole A–H and dictazoline A–E.¹³⁴

3.1.2 Rhopaladins A–D. Rhopaladins A–D were first isolated by Sato *et al.* in 1998 from the marine tunicate *Rhopalaea sp.*¹³⁵ Their structures are shown in Fig. 3. Their geometry was determined as (Z) by running a NOESY experiment on rhopaladin C. Sato *et al.* reported that rhopaladin C showed some antibacterial activity and rhopaladin B exhibited inhibitory activity against *c-erb-2* kinase and cyclin dependent kinase 4 ($\text{IC}_{50} = 7.4$ and $12.5 \mu\text{g mL}^{-1}$, respectively).¹³⁵

The first total synthesis of rhopaladin D was reported by Fresneda *et al.* in 2000 (Scheme 34).¹³⁶ The key step to imidazol-4-one formation was an intermolecular aza-Wittig reaction, where the intermediate reacted with indolyl-3-glyoxylyl chloride to produce an imidoyl chloride, which cyclized to form the central imidazolone ring. This total synthesis was completed in 6 steps, with an overall yield of 19%. However, after step (e), the product was isolated as a 6 : 4 mixture of *E/Z*



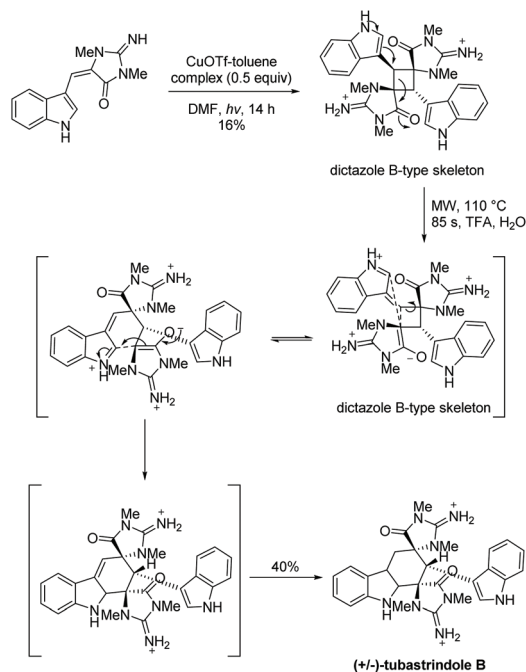
Scheme 31 Total synthesis of dihydroaplysinsin and its 6-bromo derivative. Reagents: (a) 1. THF, DCC, NHS, 0°C , 3 h, 2. NaNHCN , H_2O , rt, 16 h, (b) MeOH, Pd/C, H_2 , rt, 1 h. Reagents: (a) Borate buffer, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, pH = 8.5, L-aminoacyclase, 38°C , 48 h, (b) 1,4-dioxane, H_2O , KOH, Boc_2O , rt, 16 h, (c) 1. THF, DCC, NHS, 2 h 2. NaNHCN , H_2O , rt, 16 h, (d) MeCN, SnCl_4 , 0°C , under Ar, 45 min, (e) MeCN, EtOH, MeI, rt, 24 h.



Scheme 32 The first total synthesis of dictazole B.

isomers and, even after chromatographic separation, the *Z* isomer underwent isomerisation to *E* isomer upon sunlight irradiation. Thus, the rhopaladin D they synthesized was a mixture of *E/Z* isomers as well. The other three rhopaladin analogues have yet to succumb to a total synthesis.

3.1.3 Nortopsentine D. Nortopsentine D was isolated in 1996 from the axinellid sponge *Dracmacidon sp.*¹³⁷ It is part of



Scheme 33 The first total synthesis of tubastrindole B.

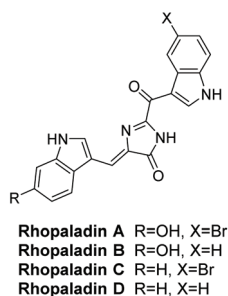
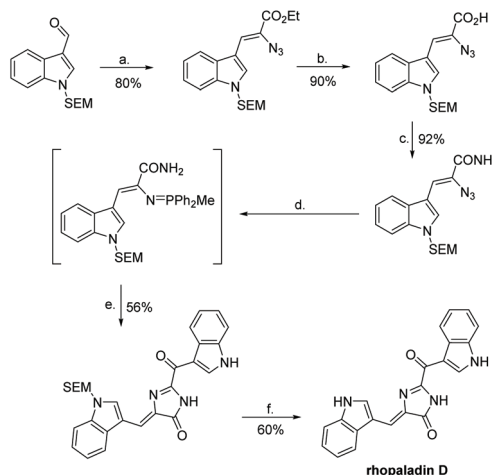


Fig. 3 Rhopaladin A–D.

a family of imidazole-diylbis(indole) alkaloids. While most of this family is comprised of imidazole linkers, nortopsentine D contains a (4*H*)-imidazol-4-one as its core scaffold (Fig. 4). This natural product was tested for its cytotoxicity against KB tumor cells, antibacterial activity (*S. Aureus*), and antifungal activity (*Candida albicans*), but it proved inactive for all three. However, when methylated (Fig. 4), nortopsentine D proved to be highly cytotoxic, with an $EC_{50} = 0.014 \mu\text{g mL}^{-1}$, or 18 nM.¹³⁷ The total synthesis of nortopsentine D has yet to be reported.

3.1.4 Kottamides A–D. Kottamides A–D are 2,2,5-trisubstituted (4*H*)-imidazol-4-one alkaloids isolated in 2002 from the New Zealand ascidian *Pycnoclavella kottae* (Fig. 5).¹³⁸ The stereochemistry of C5 was never deduced for kottamides A–D, however they were able to confirm the *Z*-configuration of the enamide using J_{HH} measurements. Kottamides A–D were found to have a range of biological activities, including anti-inflammatory and anti-metabolic, as well as cytotoxicity towards several tumor cell lines. Kottamide D was found to



Scheme 34 First total synthesis of rhopaladin D. Reagents (a) $\text{N}_3\text{CH}_2\text{COOEt}$, NaEtO , EtOH , -15°C ; (b) LiOH , THF , H_2O ; (c) carbonyldiimidazole (CDI), NH_3 , DMF ; (d) PPh_2Me , THF ; (e) indolyl-3-glyoxytyl chloride, polymer-bound BEMP, THF ; (f) TBAF, THF , reflux.

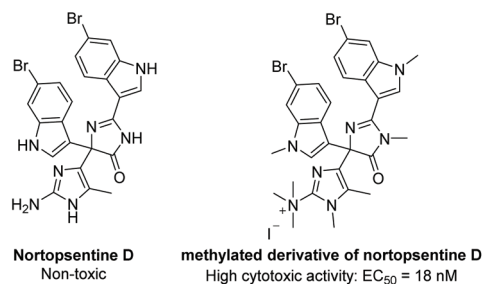


Fig. 4 Structures of nortopsentine D and its methylated derivative.

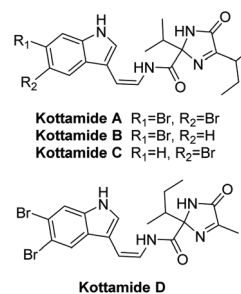


Fig. 5 Kottamides A–D.

have potent anti-metabolic activity in cells using MTT assays ($IC_{50} = 6\text{--}10 \mu\text{M}$).¹³⁸ Kottamides A–D were also assayed for cytotoxic and antimicrobial properties. All four were found to have moderate activity against P388 cells. Kottamide A was tested for cytotoxicity/antiviral activity against the African Green Monkey kidney cell line (BSC-1) infected with the RNA virus PV110. It was found to have some antiviral activity (zone size 1–2 mm) and moderate cytotoxicity (zone size $> 4.5 \text{ mm}$),

240 μg loading).¹³⁸ The total synthesis of kottamide A–D has yet to be elucidated.

3.1.5 Other indole alkaloids. An unnamed (4*H*)-imidazol-4-one containing indole alkaloid natural product was isolated from the marine tunicate *Dendrodoa grossularia* in 1998 by Riche and coworkers (Fig. 6).¹³⁹ They were able to identify the relative stereochemistry of compound 1 by measuring the optical rotation and isolating a single-crystal X-ray structure of the compound.

The first total synthesis of compound 1 was completed by Hupp and Tepe in 2008 (Scheme 35).^{140,141} In this synthesis, the quaternary carbon was formed *via* a oxazole rearrangement reaction, which produced an hydantoin product. The hydantoin was then converted into a thiohydantoin, which was reacted to form a 2-aminoimidazolone through standard conditions. In total, this total synthesis took 14 steps and had an overall yield of 12%. One thing to note with this total synthesis is the product was a racemate of compound 1.

3.2 Pyrrole alkaloids

3.2.1 Dispacamide. Dispacamide and its mono-brominated derivative were first isolated by Cafieri *et al.* in 1996 from four Caribbean *Agelas* sponges.¹⁴² Cafieri *et al.* later isolated displacamides C and D, which are racemic mixtures of the 9-hydroxyl derivatives of displacamides A and B, in 1997 from the same sponges.¹⁴³ In 2014, displacamide E was isolated by Ebada *et al.* from two Indonesian *Stylissa* sponges.¹⁴⁴ These natural products are known precursors to the oroidin family and their cyclized derivatives, like hymenialdisine.¹⁴⁵ Their structures are displayed in Fig. 7. Dispacamides have proven to have a range of useful biological activities, including antihistamine and antimalarial activity. Dispacamides C and D have been found to have impressive antihistamine activity when tested on isolated Guinea pig ileum; with just 1 μM , the response to histamine was almost completely abolished.¹⁴³ Moreover, displacamide B was found to have potent antiplasmodial activity ($\text{IC}_{50} = 1.34 \mu\text{g mL}^{-1}$) against the multiple-drug resistant strain of *P. falciparum*, while being devoid of any cytotoxicity towards rat myoblast cells at 90 $\mu\text{g mL}^{-1}$.¹⁴⁶

The first total synthesis of displacamide A was reported in 1997 by Lindel *et al.*⁶³ In this synthesis, the authors coupled an aliphatic aldehyde with thiohydantoin using piperidine to provide stereochemically pure (*Z*)-alkylidene thiohydantoin. This was then *S*-methylated and converted to a 2-amino-4-imidazolone upon treatment with heat and $\text{NH}_3/\text{NH}_4\text{Cl}$ in methanol. They also reported an attempt to directly coupling creati-

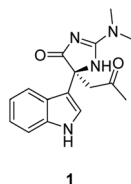
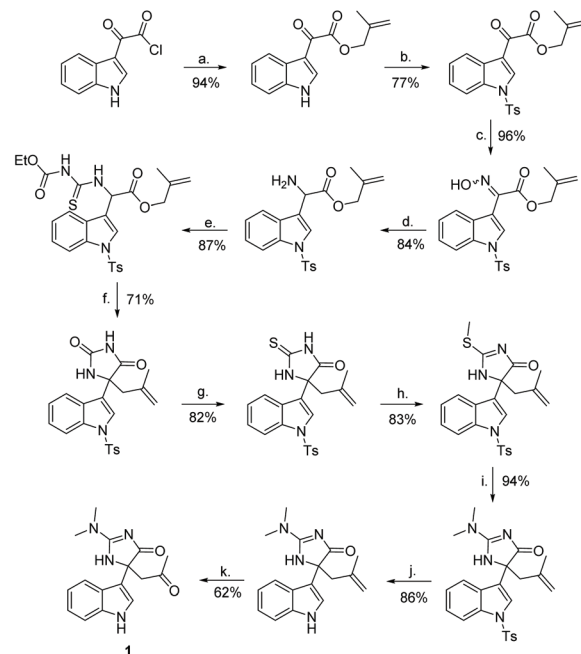


Fig. 6 Indole alkaloid isolated from *D. grossularia*.



Scheme 35 The total synthesis of indole alkaloid 1. Reagents (a) 2-methylprop-2-en-1-ol, ethyl acetate, rt, 16 h; (b) TsCl, DMAP, DIPEA, CH_2Cl_2 , rt, 16 h; (c) $\text{NH}_2\text{OH}\cdot\text{HCl}$, dioxane/ H_2O , pyridine, reflux, 16 h; (d) Zn, AOH, 0 $^\circ\text{C}$, 2 h; (e) *O*-ethyl carbonisothiocyanatide, CH_2Cl_2 , rt, 16 h; (f) 1. EDCl, Et_3N , CH_2Cl_2 , 0 $^\circ\text{C}$ to reflux, 9 h, 2. NaOMe, MeOH, rt, 4 h, 3. HCl (aq.), 5 min; (g) Lawesson's reagent, toluene, reflux, 24 h; (h) MeI, DMAP, DIPEA, CH_2Cl_2 , rt, 2 h; (i) dimethylamine in THF, sealed tube, 75 $^\circ\text{C}$, 4 h; (j) KOEt, EtOH, reflux, 24 h; (k) 1. OsO_4 , NMO, rt, 4 h then 2. NaIO_4 , 0 $^\circ\text{C}$, 2 h.

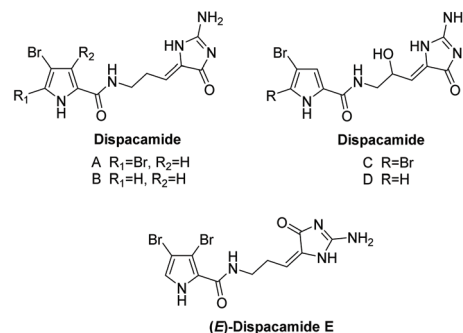
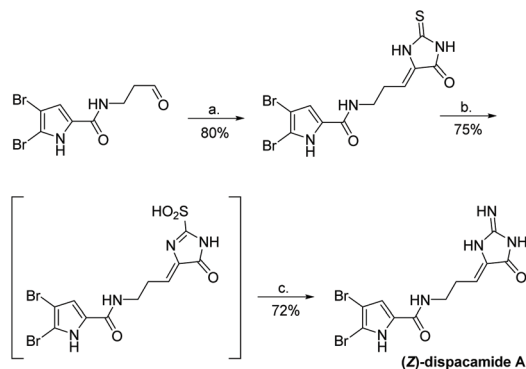


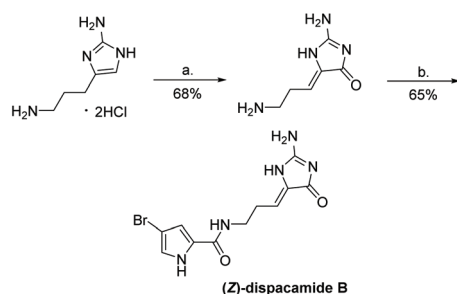
Fig. 7 Dispacamide derivatives.

nine with an aliphatic aldehyde, which was unsuccessful. The full synthesis is shown in Scheme 36.

Dispacamide B was first synthesized a year later, in 1998, by Olofson *et al.* (Scheme 37).⁹⁹ In this synthesis, the key step is the oxidation of imidazole to imidazol-4-one using bromine and DMSO. The full synthesis, shown in Scheme 37, was performed in two steps and had an overall yield of 44%. Ando *et al.* has reported similar syntheses, using tetra-*n*-butylammonium tribromide-DMSO to convert the 2-aminoimidazole to 2-amino-4-imidazolone.^{147,148}



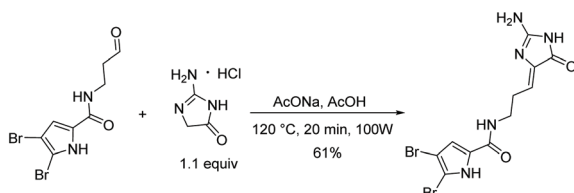
Scheme 36 The first total synthesis of dispacamide A. Reagents (a) piperidine, EtOH/H₂O (8:2), rt, 4 h, (b) aq. 25% NH₃, aq. 70% TBHP, MeOH, rt, 12 h.



Scheme 37 The first total synthesis of monobromo-dispacamide. Reagents: (a) Br₂, DMSO, rt, (b) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt.

The most recently reported total synthesis of dispacamide A was in 2012, where the authors directly condensed creatinine with an alkyl aldehyde under acidic conditions with heat to complete their total synthesis in 61% yield.¹⁴⁹ This reaction accomplished what Lindel *et al.* unsuccessfully attempted in 1997 by using a different set of conditions.⁶³ This one step, microwave-assisted procedure is shown in Scheme 38.

3.2.2 Hymenialdisine. Hymenialdisine was first isolated in 1981 by C. A. Mattia *et al.* from the sponge *Acanthella aurantiaca*.¹⁵⁰ Since then, a few other derivatives of hymenialdisine have been isolated from various marine sponges (see Fig. 8).^{151–153} Hymenialdisine has been found to have a number of different biological activities, most notable as a nM kinase inhibitor (by competing with ATP for binding the kinases), resulting in inhibition of the pro-inflammatory tran-



Scheme 38 Microwave-assisted total synthesis of dispacamide A.

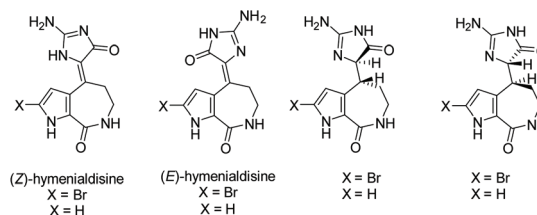
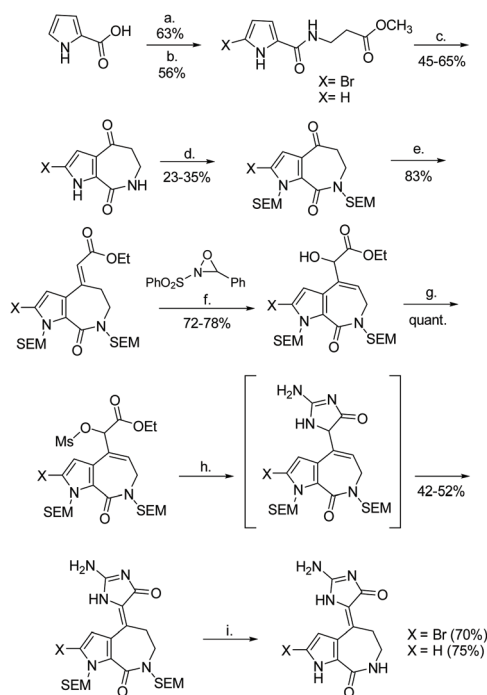


Fig. 8 Isolated derivatives of hymenialdisine.

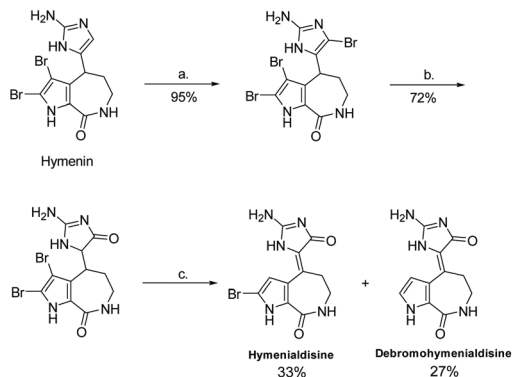
scription factor, NF-κB.^{84,154–156} Additionally, derivatives of hymenialdisine were found to be highly potent inhibitors of checkpoint kinase II (IC₅₀ = 8 nM).^{83,157–159} Moreover, it has been found to have some antitumor and anti-inflammatory activity.¹⁶⁰

The first total synthesis of (Z)-hymenialdisine and (Z)-debro-hymenialdisine was reported in 1995 by Annoura and Tatsuoka.²³ This synthesis required 9 steps, starting from a 2-carboxyl-pyrrole, and had an overall yield of 1.5%. The imidazolone formation step took a α -ether-ester and cyclized it with guanidine to produce an imidazol-4-one (Scheme 39).

In 1997, Horne and co-workers reported a different synthesis of (Z)-hymenialdisine and (Z)-debro-hymenialdisine, where the formation of the imidazolone ring came from the



Scheme 39 The first total synthesis of hymenialdisine and debromohymenialdisine by Annoura and Tatsuoka. Reagents (a) SOCl₂, cat. DMF, toluene, 60 °C, 1 h, then H₂NCH₂CH₂COOMe, Et₃N, CH₂Cl₂, rt, 3 h; (b) NBS, THF, rt, 2 h; (c) 10% aq. NaOH-MeOH (2:1), rt, 5 h, then PPA-P₂O₅, 100 °C, 1 h; (d) NaH (2 eq.), SEMCl (2 eq.), DMF, rt, 2 h; (e) (EtO)₂POCH₂COOEt, NaH, DME, 50 °C, 24 h; (f) KHMDS, THF, -78 °C, 2 h; (g) MsCl, Et₃N, CH₂Cl₂, 0 °C; (h) guanidine, DMF, 50 °C, 5 h; (i) 5% aq. HCl-MeOH (1:1), 80 °C, 2 h.

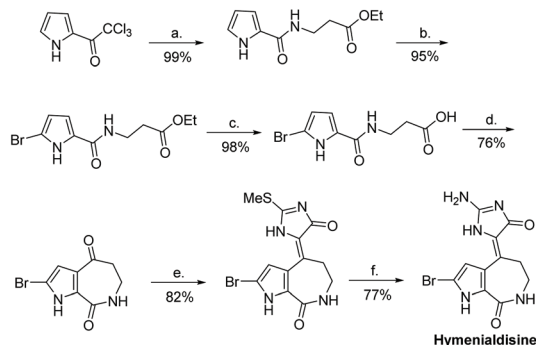


Scheme 40 Synthesis of hymenialdisine and debromohymenialdisine through the oxidation of 2-amino-4-bromoimidazole. Reagents (a) Br_2 , TFA, rt; (b) $\text{AcOH}/\text{H}_2\text{O}$, reflux (c) $\text{CH}_3\text{SO}_3\text{H}$, HBr (cat.), 90°C , sealed tube, 12 h.

oxidation of 2-amino-4-bromoimidazole under acidic conditions with heat (Scheme 40).¹⁰⁰ This reaction took only three steps and had an overall yield of 23% and 18%, respectively.

In recent years, Saleem and Tepe reported a new total synthesis for hymenialdisine and its de-brominated derivative, illustrated in Scheme 41.¹⁶¹ In this synthesis, 2-(methylthio)-1,5-dihydro-4*H*-imidazol-4-one was condensed with 2-bromoaldisine. The methylthio group was converted to an amino substituent *via* reaction with ammonium hydroxide. This total synthesis took 6 steps and had an overall yield of 44%. Another paper used a very similar condensation reaction between 2-methylthiol-imidazol-4-one and 2-bromoaldisine, at somewhat lower yields.¹⁶² The (*E*)-hymenialdisine and dihydrohymenialdisine derivatives have yet to be synthesized.

3.2.3 Spongiacidins A and B. Spongiacidins A and B were isolated by Inaba *et al.* in 1998 from the sponge *Hymeniacidon*.¹⁶³ Their structures are shown in Fig. 9. This class of natural products is part of the hymenialdisine family, differing by their bromo substitution pattern and alkene stereochemistry. Spongiacidin A was identified as being cyto-



Scheme 41 An efficient total synthesis of hymenialdisine. (a) $\text{H}_2\text{NCH}_2\text{CH}_2\text{COOEt}\cdot\text{HCl}$, Et_3N , DCM, rt; (b) DBDMH, MeOH/THF , -78°C -rt; (c) LiOH or KOH , EtOH , H_2O , rt, 18 h; (d) P_2O_5 , MeSO_3H , 110°C , 2 h; (e) 2-(methylthio)-1,5-dihydro-4*H*-imidazol-4-one, TiCl_4 , THF , -10°C -rt; (f) NH_4OH , THF , sealed tube, 110°C .

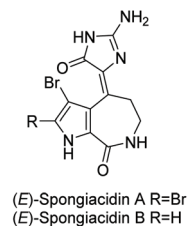
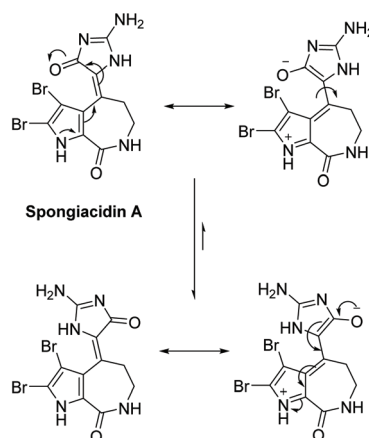


Fig. 9 Spongiacidin A and B.

toxic to L5178Y and HCT116 cancer cell lines. It was also found to be a protein kinase inhibitor.¹⁶⁴ Unlike hymenialdisine, there have been no reports of the total synthesis of spongiacidins A or B. This may be in part due to the spontaneous conversion of spongiacidin's (*E*)-isomer to the (*Z*)-isomer, driven by the reduction of steric strain upon conversion.¹⁶⁵ The proposed isomerization is shown in Scheme 42. The steric strain exerted between the C-3 bromine and oxygen on C-15 prevents a straightforward synthesis of the (*E*)-isomer required to produce spongiacidin.

3.2.4 Agesamines A–C. Agesamine A and B were isolated by Katsuki *et al.* in 2019 from the sponge *Agelas sp.*¹⁶⁶ Agesamine C was isolated by Kovalerchik *et al.* in 2020 from the sponge *Agelas oriodes*.¹⁶⁷ Their structures are illustrated in Fig. 10. Agesamine A and B were found to have some cytotoxicity towards HeLa cells, and although the synthesis of the related hydantoin analogue has been reported,^{168,169} the total syntheses of agesamines A–C have yet to be completed.

3.2.5 Donnazoles A and B. Donnazoles A and B were isolated by Al-Mourabit and co-workers in 2012 from the marine sponge *Axinella donnani* (Fig. 11).¹⁷⁰ These natural products are dimeric members of the same class of pyrrole-aminoimidazole (PAI) alkaloids as oroidin, sceptrin, massadine, and palau'amine. The structure's absolute configuration was determined by comparison of their circular dichroism (CD) with sceptrin. To date, there has been no biological activity reported for donnazoles A and B. While some efforts have been made



Scheme 42 Isomerization of (*E*)-spongiacidin A to the (*Z*)-isomer.

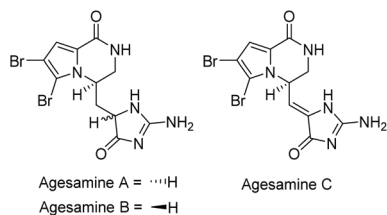


Fig. 10 Agesame derivatives.

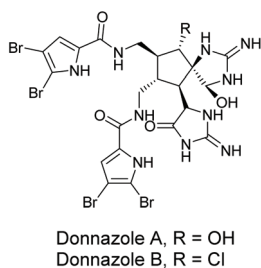


Fig. 11 Donnazoles A and B.

towards developing the methodology needed to produce donnazoles A and B,¹⁷¹ they have yet to be synthesized.

3.2.6 Oxsceptrin. Oxsceptrin was first reported by Rinehart and coworkers, isolated from the Caribbean sponge *Agelas conifera* in 1991.¹⁷² Ohizumi and coworkers later isolated this natural product from the marine sponge *Agelas nemoechinata*.¹⁷³ It is believed to be the product of the oxidation of sceptrin. The structures of oxsceptrin as well as the unoxidized sceptrin are displayed in Fig. 12. Oxsceptrin exhibits some antiviral and antibacterial activity.^{172,173}

The total synthesis of oxsceptrin was completed by Baran and coworkers in 2007, when they performed an oxidation of sceptrin to give oxsceptrin as a 1 : 1 mixture of diastereomers (Scheme 43).¹⁰¹ In this synthesis, sceptrin was reacted with aqueous peracetic acid to give 50% yield of diol product, along with a recovered 35% of sceptrin. The diol was then converted to a ketone using acetic acid and heat. This synthesis was completed in two steps from sceptrin, with an overall yield of 32%.

3.3 Other 2-amino-(4H)-imidazol-4-one alkaloids

3.3.1 Phorbatopsins A–C. Phorbatopsins A–C were isolated by Nguyen *et al.* in 2012 from the Mediterranean sponge

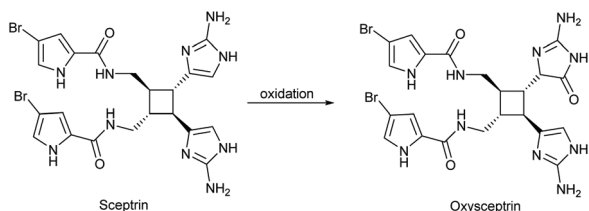
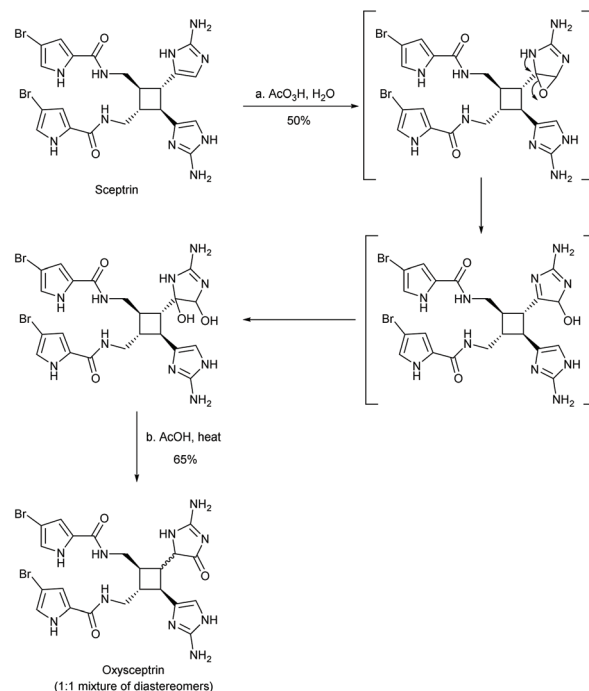


Fig. 12 Structures of oxsceptrin and sceptrin.



Scheme 43 The first total synthesis of oxsceptrin.

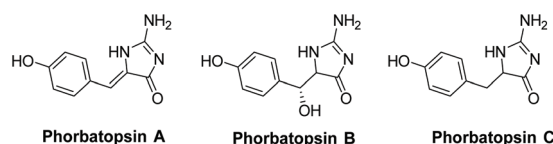
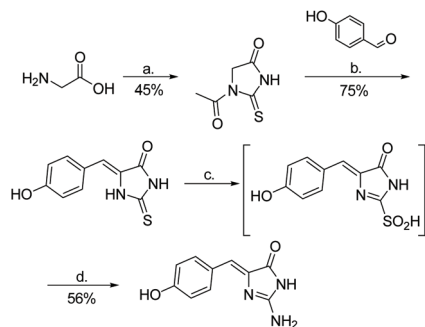


Fig. 13 Isolated phorbatopsin analogues.

Phorbas topsenti (Fig. 13).¹⁷⁴ One biological application for these compounds is their antioxidant activity, which was tested using the Oxygen Radical Absorbance Capacity (ORAC) assay. All were shown to have some activity, with phorbatopsin A being most active, having an ORAC value of 0.88 (which is comparable to the positive control Trolox's ORAC value of 1). Derivatives of phorbatopsin A were also tested for antitumor activity, with several derivatives having over 90% inhibition at a concentration of 50 μM .⁷²

The first total synthesis of phorbatopsin A was reported in 2013 (Scheme 44).⁷² In this synthesis, glycine was treated with NH_4SCN under acidic conditions. The formed thiohydantoin was then condensed with 4-hydroxybenzaldehyde and converted to a 2-aminoimidazolone using TBHP and ammonia. Phorbatopsin A was produced in four steps with an overall yield of 19%. Phorbatopsins B and C have yet to be synthesized.

3.3.2 Polyandrocarpamines A and B. Polyandrocarpamines A and B were isolated by Davis *et al.* in 2002 from the Fijian ascidian *Polyandrocampa sp.*¹⁷⁵ Their structures are shown in Fig. 14. Polyandrocarpamine A was found to have selective cytotoxicity against the CNS cell line SF 268 with a GI value of



Scheme 44 The first total synthesis of phorbatopsin A. Reagents (a) NH_4SCN , Ac_2O , AcOH , reflux, 2 h; (b) NaOAc , AcOH , reflux, 5 h; (c) TBHP , MeOH , rt, 2 h; (d) NH_3 , MeOH , rt, 10 h.

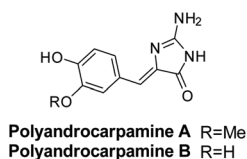
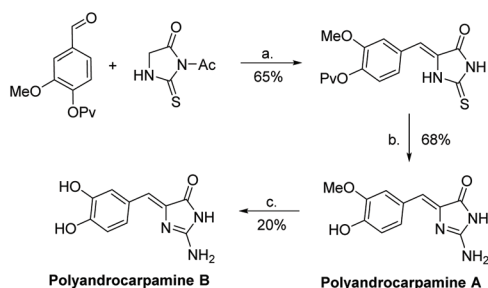


Fig. 14 Polyandrocarpamine A and B.

65 μM .¹⁷⁶ Then, in 2017, both derivatives were found to inhibit mammalian and protozoan DYRK and CLK kinases.¹⁷⁷

The first total synthesis of polyandrocarpamine A and B was reported by Davis *et al.* after their isolation in 2002.¹⁷⁵ This synthesis contains only three steps: condensation of an aryl aldehyde and thiohydantoin, then conversion to 2-aminoimidazolone using tetrabutyl hydrogen peroxide (TBHP) and ammonia. Polyandrocarpamine A was converted to polyandrocarpamine B through a demethylation using a boron tribromide dimethyl sulfide complex. The full synthesis of polyandrocarpamines A and B were completed in 44% and 9% overall yield, respectively (Scheme 45). In 2009, Davis *et al.* reported a microwave assisted synthesis, producing polyandrocarpamine A and B in one step with yields of 56% and 80%, respectively.¹⁷⁸

3.3.3 Leucettamine B and C. Leucettamine B was first isolated by Chan *et al.* in 1993 from the marine sponge *Leucetta*



Scheme 45 The first total synthesis of polyandrocarpamine A and B. Reagents (a) NaOAc , AcOH , reflux, 2 h; (b) TBHP (15 equiv.), aq. NH_4OH , MeOH , rt, 72 h; (c) $\text{BBr}_3\text{-SMe}_2$, DCE , reflux, 15 min.

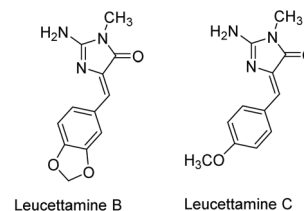


Fig. 15 Imidazolone-containing leucettamine natural products.

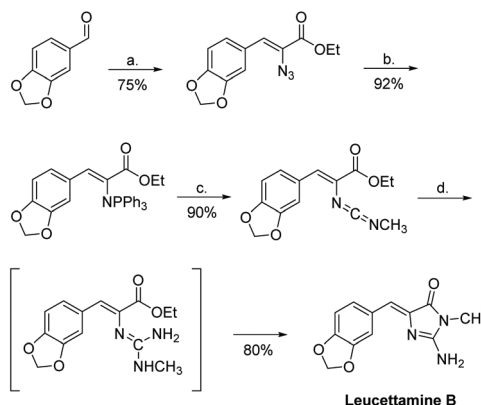
microraphis,¹⁷⁹ and leucettamine C was isolated from *Leucetta* sponges in 2003.¹⁸⁰ These compounds have since been isolated from several other natural sources.^{181,182} Their structures are shown in Fig. 15. While leucettamine B and C have limited biological activity, derivatives of leucettamine B have been found to inhibit protein kinase activity.^{66,177,183}

Leucettamine B was first synthesized in 1994 by Molina *et al.*¹⁸⁴ The synthesis was completed in four steps, with an overall yield of 50% (Scheme 46). In this synthesis, the key transformation is an aza-Wittig/heterocumulene-mediated annulation to build the 2-aminoimidazolone ring.

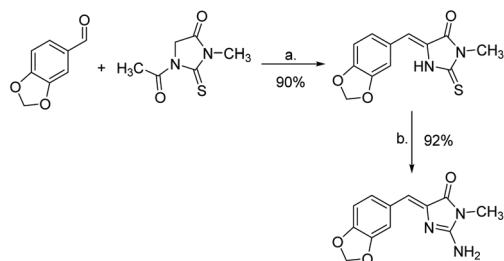
Another popular method of synthesizing leucettamine B is through the condensation of thiohydantoin and an aryl aldehyde or imine. This is then converted to a 2-aminoimidazole through varying conditions. The first report of this synthesis was in 1999 by Roué and Bergman, which produced leucettamine B in 83% yield.¹⁸⁵ Their synthesis is shown in Scheme 47. Since then, several other similar methods have been reported.^{64,186,187}

The most recently reported total synthesis of both leucettamines B and C was in 2017 by Dražić *et al.*¹¹¹ Their synthesis is shown in Scheme 48 and starts with a β -lactam, which first reacts with *N*-(methylcarbamothioyl)benzamide and then undergoes a ring expansion under basic conditions to produce the desired imidazol-4-one. This was the first report of the total synthesis of leucettamine C.

3.3.4 Calcaridines A and B. (+)-Calcaridine A was first isolated by Edrada *et al.* in 2003 from the sponge *Leucetta*.¹⁸⁸



Scheme 46 The first total synthesis of leucettamine B. Reagents (a) $\text{N}_3\text{CH}_2\text{COOEt}$, NaOEt , -15°C ; (b) Ph_3P , CH_2Cl_2 , rt; (c) CH_3NCO , toluene, rt; (d) NH_3 , sealed tube, 45°C .



Scheme 47 Synthesis of leucettamine B via a thiohydantoin intermediate. Reagents (a) $\text{CH}_3\text{CO}_2\text{H}$, CH_3COONa , heat; (b) NH_3 , TBHP.

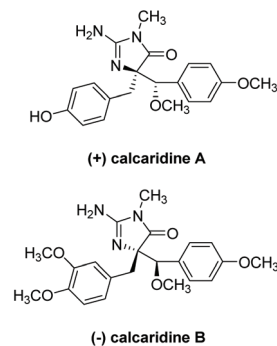
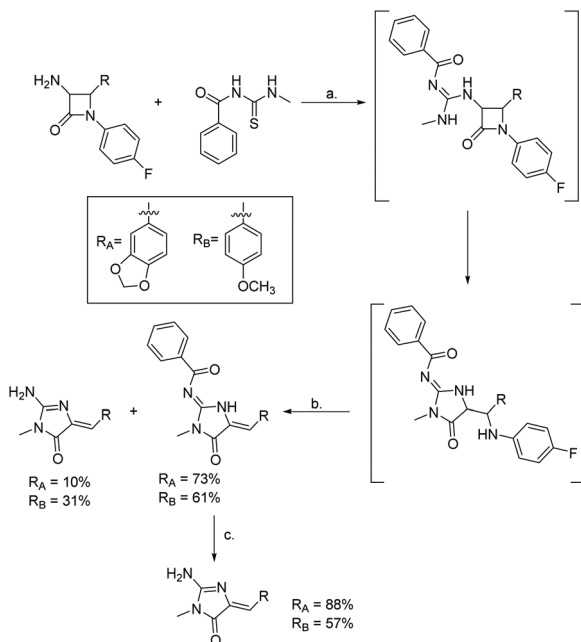
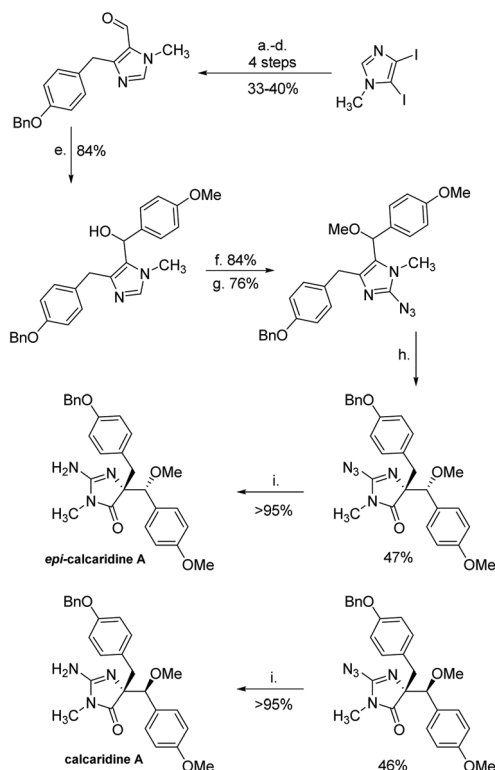


Fig. 16 Calcaridine A and B.



Scheme 48 Total synthesis of leucettamines B and C via β -lactam ring expansion. Reagents (a) HgCl_2 , Et_3N , DMF, rt, overnight; (b) K_2CO_3 , MeOH, rt, overnight; (c) K_2CO_3 , MeOH, 50°C , overnight.

(-)-Calcaridine B was isolated by Tang *et al.* in 2019 from the marine sponge *Leucetta chagosensis*.¹⁸⁹ Their structures are shown in Fig. 16. (-)-Calcaridine B was found to exhibit mild cytotoxicity toward the MCF-7 cancer cell line with an IC_{50} value of $25.3\ \mu\text{M}$, whereas (+)-calcaridine A has no known biological activity to date. The first total synthesis of calcaridine A was reported by Koswatta *et al.*^{97,190} In this synthesis (Scheme 49), a 2-azidoimidazole is converted to a 2-amino-4-imidazolone through sequential oxidation and reduction after a number of alkylation steps. This total synthesis was inspired by the proposed biomimetic synthesis. In this proposed pathway, calcaridine A is said to be derived from the rearrangement and/or oxidation of naamine A, an imidazole-containing natural product, also isolated from *Leucetta* sponges. The downside to this synthesis is the isolation of both (+)-calcaridine A and its epimer. They attempted to convert the individual diastereomers into each other upon reaction with catalytic



Scheme 49 The first total synthesis of calcaridine A. Reagents (a) EtMgBr , CH_2Cl_2 , rt, then *N*-methyl-formanilide; (b) ethylene glycol, *p*-TsOH, PhH, reflux; (c) EtMgBr , THF, rt, then aryl aldehyde; (d) HCl (aq.), THF, reflux, then Et_3SiH , TFA, CH_2Cl_2 , rt; (e) $4\text{-MeOC}_6\text{H}_4\text{MgBr}$, THF, reflux; (f) NaH, THF, 0°C -rt to 0°C , then MeI; (g) BuLi, THF, -78°C , then TsN_3 ; (h) *N*-sulfonylaziridine, CHCl_3 , rt; (i) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , EtOH.

HCl in methanol, but found no discernable epimerization, even at a range of different temperatures. (-)-Calcaridine B has yet to be synthesized.

4. Conclusions

In section three of this review, the known imidazol-4-one containing natural products and their total syntheses were dis-

Table 2 Summary of common transformations used in the synthesis of (4*H*)-imidazol-4-one containing natural products

Thiohydantoin conversion	Knoevenagel condensation	Aza-Wittig/Heterocumulene mediated annulation	Oxidative pinacol-like rearrangement of imidazole	Condensation of ester and guanidine/cyanamide
Dispacamide Hymenialdisine Polyandrocarpamine A Polyandrocarpamine B Leucettamine B Indole alkaloid 1 Phorbatopsin A	Dispacamide Hymenialdisine Polyandrocarpamine A Polyandrocarpamine B Leucettamine B Aplysinopsin	Aplysinopsin Leucettamine B	Hymenialdisine Monobromodispacamide Calcaridine A Oxysceptrin	Hymenialdisine Dihydroaplysinopsin

cussed in detail. Table 2 summarizes the main imidazolone formation steps found in the mentioned total syntheses. Interestingly, most of the total syntheses followed one of a few common methods for imidazol-4-one formation. Seven of the natural products were formed *via* a conversion of thiohydantoin to imidazol-4-one, and the majority of these total syntheses also employed a Knoevenagel condensation to substitute the 5-position of the ring. All the natural products synthesized by this combination of reactions were 5-ethylidene-4-imidazolones. The aza-Wittig/heterocumulene-mediated annulation was also used to produce a couple 5-ethylidene-4-imidazolone containing natural products, namely aplysinopsin and leucettamine B. Two other approaches to synthesizing 5-ethylidene-4-imidazolones utilized in the total synthesis of natural products were an intermolecular aza-Wittig reaction, which was used to synthesize rhopaladin D, and a β -lactam ring expansion, used to synthesize leucettamines B and C.

Moreover, a number of imidazol-4-one containing natural products have yet to be synthesized, namely rhopaladins A–C, nortopsentine D, kottamides A–D, dispacamides C–E, dihydrohymenialdisine derivatives, spongiacidins A–B, agesamines A–C, donnazoles A–B, phorbatopsin B and C, and (–)-calcaridine B. Analyzing the natural products that have yet to be synthesized, most of them are 5-monosubstituted or 5,5-disubstituted imidazol-4-ones. While there are many preparative methods highlighted in section 2 to produce these imidazolones, the majority of them have not been utilized in any total syntheses. Two reactions used to produce 5-mono or 5-disubstituted-4-imidazolone containing natural products highlighted in section 3 are the oxidative pinacol-like rearrangement of imidazole to produce oxysceptrin and calcaridine A and the condensation of ester and guanidine or cyanamide, used to produce dihydroaplysinopsin.

In summary, this review has covered a large range of preparative methods of imidazol-4-ones. Within section 2 of the review, advantages and disadvantages of each method were discussed, as well as their versatility upon substituting the 2 and 5 positions of the ring. Section 3 applied those preparative methods to a range of total syntheses of natural products. This section also highlighted several natural products that have yet to succumb to total synthesis. Here, the disparity between total syntheses of 5-ethylidene-4-imidazolones and other imidazol-4-ones became apparent. Looking towards the future, it is evident more effort is needed in the realm of 5-monosubsti-

tuted and 5,5-disubstituted imidazol-4-ones, specifically highlighting enantioselective methods which can be used for the total synthesis of natural products. Overall, this review highlighted the importance of imidazol-4-ones in a variety of applications, and the preparative methods explored to date.

Conflicts of interest

There are no conflicts to declare.

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