Review

A Review of the Synthetic Strategies toward Dihydropyrrolo[1,2-*a*]Pyrazinones

Pieterjan Winant [1,†], Tomas Horsten [1,†], Shaiani Maria Gil de Melo [2], Flavio Emery [2,*] and Wim Dehaen [1,*]

[1] Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium; pieterjan.winant@kuleuven.be (P.W.); tomas.horsten@kuleuven.be (T.H.)
[2] Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences at Ribeirao Preto of the University of Sao Paulo, Ribeirao Preto 14040903, SP, Brazil; shaianigil@usp.br
[*] Correspondence: flavioemery@usp.br (F.E.); wim.dehaen@kuleuven.be (W.D.)
[†] Both authors contributed equally to this work.

Abstract: Dihydropyrrolo[1,2-*a*]pyrazinone rings are a class of heterocycles present in a wide range of bioactive natural products and analogues thereof. As a direct result of their bioactivity, the synthesis of this privileged class of compounds has been extensively studied. This review provides an overview of these synthetic pathways. The literature is covered up until 2020 and is organized according to the specific strategies used to construct the scaffold: fusing a pyrazinone to an existing pyrrole, employing a pyrazinone-first strategy, an array of multicomponent reactions and some miscellaneous reactions.

Keywords: pyrrole; pyrazinone; heterocycle; natural product; cycloaddition; multicomponent reaction

1. Introduction

Nitrogen-containing heteroaromatic rings are valuable motifs in bioactive molecules and recurrent scaffolds present in drugs [1,2]. The application of nitrogen ring systems in drug development is related to their diverse properties, including relatively small conformational freedom, while retaining some polarity, compared to aromatic hydrocarbons. Additionally, commercial availability, synthetic tractability, chemical diversity and the tendency for functionalization should also be highlighted [3]. However, the wide chemical space of nitrogen heterocycles is not yet fully explored in the attempt to find new drug candidates.

Dihydropyrrolo[1,2-*a*]pyrazinone rings are found in the structure of a number of bioactive compounds, including synthetic and natural products isolated from various sources like fungi, plants or sponges. These natural products (some structures are shown in Figure 1) often contain one or two bromine substituents on the pyrrole ring. The simplest congeners are **longamide A** [4] and its nonbrominated analog **mukanadin C** [5] (not shown), **longamide B** [6], **hanishin** [7], **stylisine D** [8], **cyclooroidin** [9], and **agesamide** [10]. More complicated tetracyclic analogs include **dibromophakellstatin**, **dibromophakellin** [11] and the different **agelastatins A-F** [12,13]. One of the most complicated pyrrolopyrazinone natural products is **palau'amine** [14], and its structure has been seen as a challenge for total synthesis. Some related natural products are the higher oxidation state analogs **peramine** [15] and **nannozinone B** [16], containing the pseudoaromatic pyrazinone ring, the pyrrolodiketopiperazines **brevianamide T** [17] and **macrophominol** [18], and the oxopyrrole derivative **oxocyclostylidol** [19] (Figure 1).

Several bioactivities have been found for these pyrrolopyrazinone natural products. Hanishin shows cytotoxicity against non-small cell lung carcinoma [7], and agelastatin A and D display significant activity against different cell lines [20]. Longamide B was found to have antiprotozoal [21] and antibacterial [6] properties, with good potency against African

trypanosome. Palau'amine and the similar dibromophakellin and dibromophakellstatin inhibit the human 20S proteasome [22]. Peramine is an insect feeding deterrent [23].
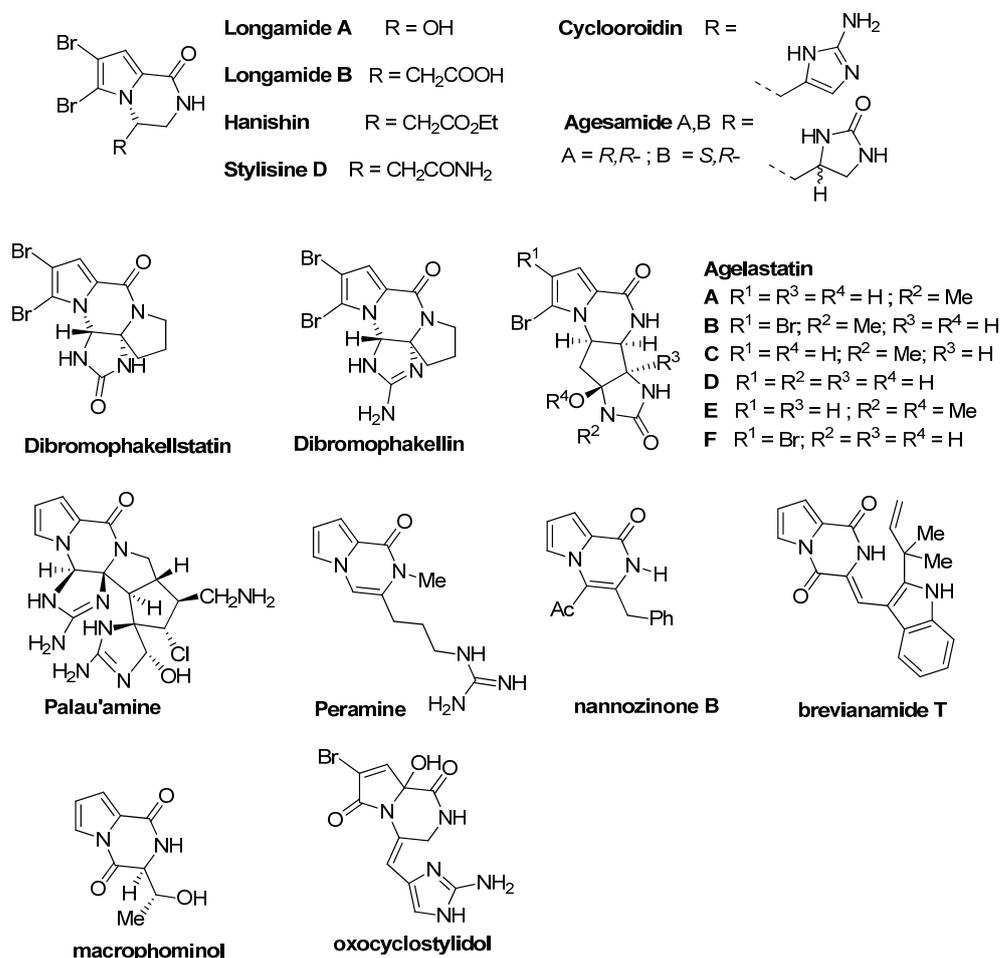

Figure 1. Pyrrolopyrazinone natural products.

In view of these bioactivities, there has been a keen interest in synthetic analogs, and pyrrolopyrazine is now recognized as a privileged scaffold. The best known example is **AS-3201** (**ranirestat**), a potent aldose reductase inhibitor [24] that has been granted orphan drug status for the treatment of diabetic neuropathy. Pyrrolopyrazines **1** have also been described as melanin-concentrating hormone (MCH-R1) antagonists of interest in antiobesity therapy [25]. Other notable bioactive derivatives are the HIV-1 integrase compounds **2** [26], the potent and noncompetitive mGluR1 antagonists **3** [27], the kinase inhibitors **4** [28] and **5** [29] and the immunosuppressive response indoleamine-2,3-dioxygenase 1 (IDO-1) inhibitors **6** [30] (Figure 2).

In this review, we will cover the different synthetic strategies leading to the dihydropyrrolopyrazinone scaffold. These include (1) the fusion of a pyrazinone to a pyrrole derivative, (2) the fusion of a pyrrole to a pyrazinone, (3) multicomponent reactions and (4) miscellaneous strategies. The literature will be covered until the end of 2020, and the focus is indeed on ring formation rather than an elaboration of substituents during the multistep total syntheses of complicated natural product analogs or the details of their biological properties. Also, we will not cover any examples that have indoles or other fused pyrrole rings in the structure, neither quinoxalines nor other fused pyrazines, since their chemistry is in most cases rather different. This review has a focus on the dihydropyrrolo[1,2-*a*]pyrazinones, in comparison to a recent general overview of the eight different pyrrololactam isomers [31].
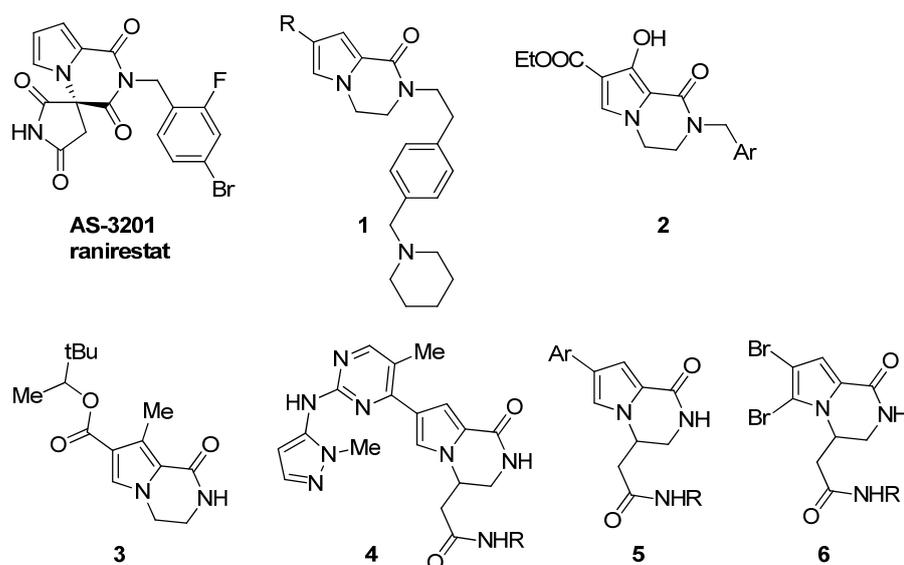
Figure 2. Synthetic bioactive dihydropyrrolopyrazinones.

2. Fusion of a Pyrazinone to a Pyrrole Derivative

2.1. Starting from 2-Monosubstituted Pyrroles

The most common way toward pyrrolopyrazinones is fusing a pyrazinone to a pyrrole. One way to realize this is starting from *1H*-pyrrole-2-carboxamide bearing electrophilic groups on the amide that react in an intramolecular fashion with the nucleophilic pyrrole nitrogen. Several electrophilic groups are possible. Electron-poor alkenes can undergo aza-Michael addition, as in the base-catalyzed formation of *N*-benzyl longamide B derivative **8** from the corresponding open chain pyrrole-2-amide **7** after potassium carbonate (K$_2$CO$_3$)-catalyzed cyclization, bromination with *N*-bromosuccinimide (NBS) and saponification (Scheme 1) [32]. A similar aza-Michael cyclization was reported in the total synthesis of longamide B and cyclooroidin via the Wadsworth–Horner–Emmons olefination of longamide A [33,34] or in the 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU)-catalyzed cyclization of precursors to kinase inhibitors **5** [29]. An enantioselective aza-Michael cyclization (up to 56%ee) was realized with compounds analogous to **7** in the presence of a chiral *N*-benzylammonium phase transfer catalyst derived from quinine [35].
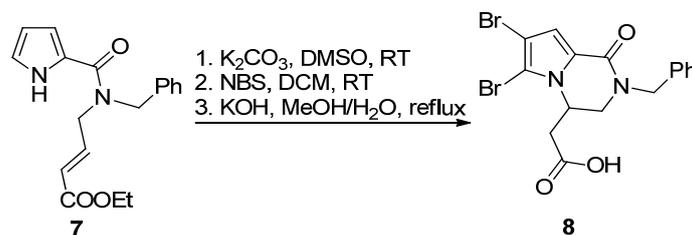
**Scheme 1.** Aza-Michael reaction leading to a longamide B derivative.

The total synthesis of (-)-agelastatin A involved a similar aza-Michael reaction to an enone intermediate **9**, which was generated by the oxidation of an allylic alcohol precursor [36] or by a metathesis reaction [37]. Different bases were tried for the cyclization of **9** to the intermediate **10** that then could be further elaborated to the natural product. It was found that diisopropylethylamine (DIPEA) in THF is a suitable base/solvent combination after the acidity of the pyrrole is increased by bromination, whereas nonbrominated pyrrole **9** resulted in the recovery of the starting material, rearrangement and/or decomposition [36,38,39]. Many variants of this cyclization have been described, with other base/solvent combinations like cesium carbonate in methanol [37] or THF [40] at room temperature, potassium carbonate in dimethyl sulfoxide (DMSO) at 100 °C [41],

trimethylamine in acetonitrile (ACN) at −20 °C [42] and triethylamine (Et$_3$N) in DMSO at room temperature with the in situ generation of enone **9** by the elimination of a sulfone group [43,44] (Scheme 2).
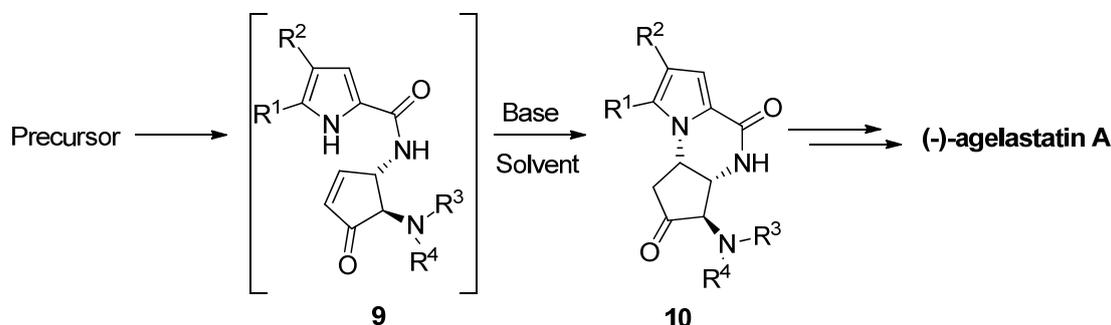

Scheme 2. Aza Michael reaction as part of (-)-agelastatin total synthesis.

Instead of changing the nucleophilicity of the pyrrole, the electrophilicity of the double bond may be increased by the addition of a Brønsted or Lewis acid. In fact, the biosynthesis of hanishin or longamide B has been described as involving the protonation of a precursor analogous to **7** by an appropriate enzyme [7]. In a bioinspired total synthesis of *rac*-agelastatin A, a cascade process occurs starting from a hemiaminal **11** that is converted with trifluoroacetic acid (TFA) into a reactive iminium salt **12** that cyclizes to intermediate **13** and then undergoes the addition of water to give the hydroxyl derivative **14**. The deprotection of **14** and cyclization by heating in the presence of silica (SiO$_2$) at 45 °C affords agelastatin A (68%) and a minor amount (13%) of its 4,5-epimer [45] (Scheme 3). We can also mention a similar report wherein trifluoroethanol functions as an acidic medium (40 °C) for the diastereoselective cyclization of **14** to agelastatin A [46]. *Rac*-cyclooroidin has been prepared in excellent yield (93%), by heating the formic acid salt of the acyclic precursor at 95 °C for 45 h in a sealed tube [47].
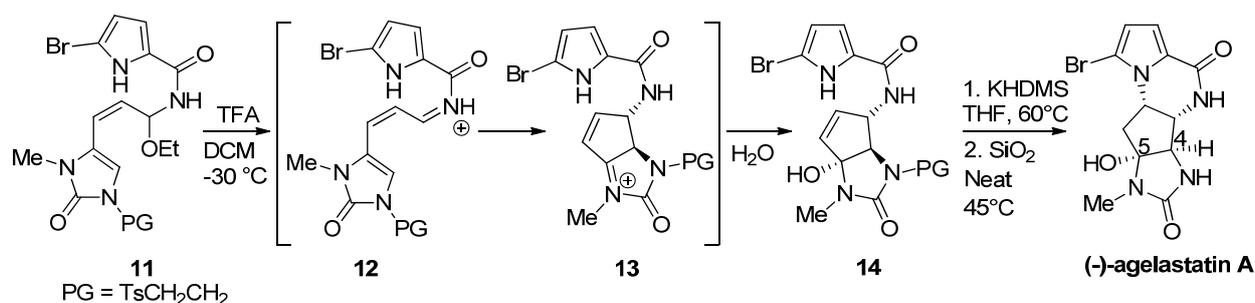
**Scheme 3.** Silica-promoted synthesis of (-)-agelastatin A.

The palladium-catalyzed cyclization of *N*-allyl pyrrole-2-carboxamide **15** (R^1 = H) leads to different products depending on the catalyst. In the presence of palladium acetate (0.1 eq), sodium acetate and tetrabutylammonium chloride (Bu$_4$NCl) in DMSO at 120 °C, the pyrrolo[1,2-*a*]pyrazine **16a** is formed. On the other hand, PdCl$_2$(CH$_3$CN)$_2$ catalyst (0.1 eq.) in a dimethylformamide (DMF)/tetrahydrofuran(THF) mixture at 100 °C, in the presence of a stoichiometric benzoquinone oxidant, gave a 1:1 mixture of the two isomeric [2,3-*c*] and [3,2-*c*] fused pyrrolopyridinone derivatives **17** and **18**, apparently as the result of cyclization involving the 2-position of the pyrrole followed by rearrangement [48]. Remarkably, when the Pd(OAc)$_2$ method was applied to the *N*-cinnamyl derivative **15** (R^1 = Ph), the dihydro derivative **19** was obtained in modest yield and different oxidants failed to afford the corresponding pyrrolo[1,2-*a*]pyrazine **16b** [49] (Scheme 4).
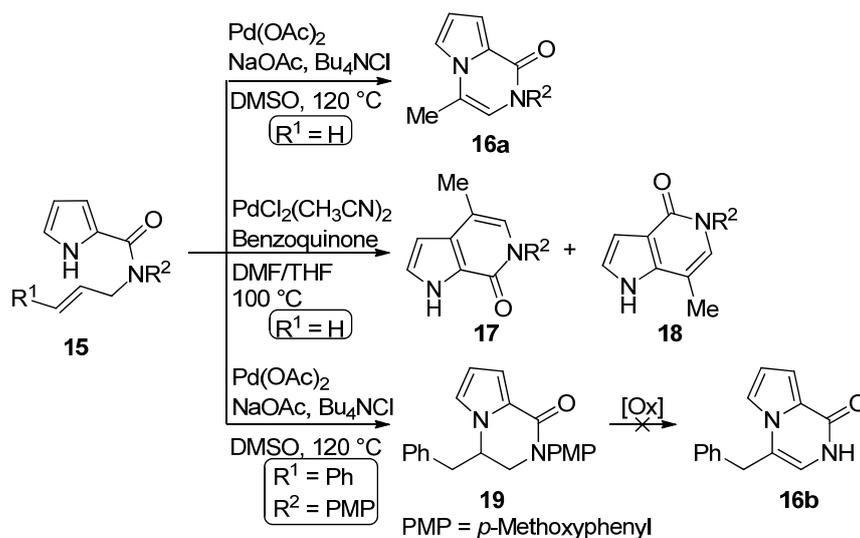
Scheme 4. Palladium-catalyzed cyclization of *N*-allyl pyrrole-2-carboxamide.

The cyclization reactions of pyrrole nitrogen onto alkyne substituents were studied in basic circumstances. Thus, *N*-imidazolylpropargyl-substituted pyrrole-2-carboxamide **20** was favorably converted to the pyrrolopyridazinone **21**, by an 6-*exo*-dig process, using cesium carbonate (Cs$_2$CO$_3$) in DMF at room temperature. Further deprotection and *exo*-double bond reduction yielded cyclooroidin analog **22** [50] (Scheme 5).
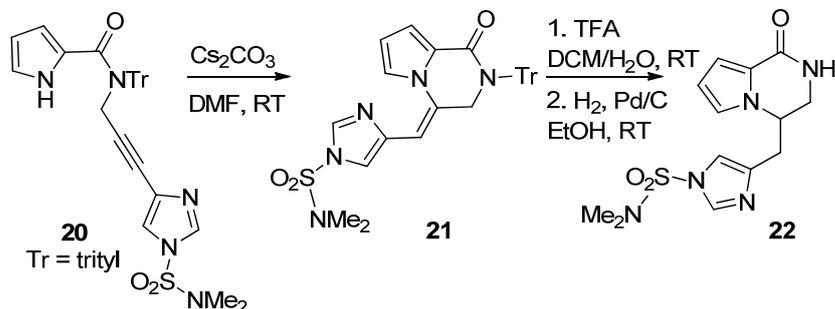
Scheme 5. Base-catalyzed ring closure of *N*-propargyl pyrrole-carboxamides.

Other examples of the base-catalyzed ring closure of *N*-propargyl derivatives were reported, with 30 mol% DBU in dichloromethane (DCM) at reflux temperature [51], which led to a mixture of pyrrolopyrazinone isomers **24** and **25** with an *exo* double bond and an *endo* double bond, respectively. The isomerization of the *exo*-isomers **24** to the thermodynamically preferred *endo*-product **25** and the deprotection mediated by triisopropylsilane (*i*Pr$_3$SiH) and TFA under microwave (MW) heating, only yielded **26** (Scheme 6).
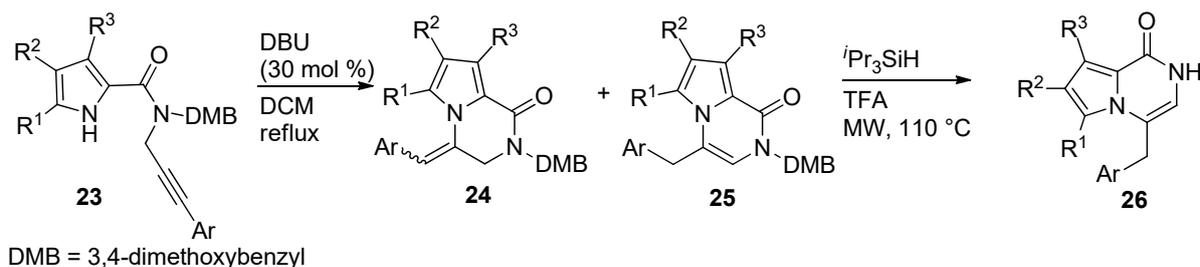
Scheme 6. Ring closure of *N*-(3-arylpropargyl) pyrrole-carboxamides.

An iridium (I) complex with chiral *N*-heterocyclic carbene ligand **29** was used as a catalyst for the intramolecular aminoallylation of acylpyrroles **27**, leading to (*R*)-vinyl-substituted pyrrolopyrazinones **28** [52] in e.e. of 92–95% (Scheme 7). In a subsequent report, an Ir/phosphoramidite catalytic system was explored to obtain the (*S*)-isomer, which is used as a starting material for the total synthesis of longamide B, hanishin or cyclooroidin analogs [53].
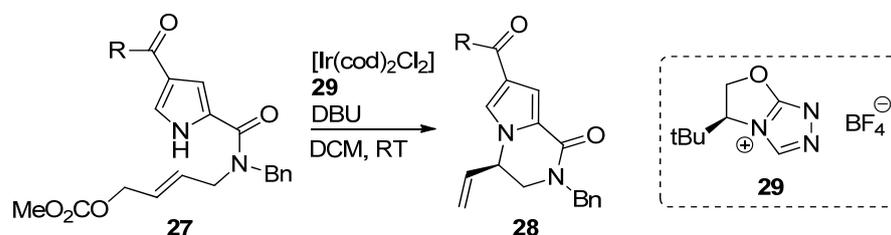
Scheme 7. Iridium-catalyzed intramolecular allylation strategy toward pyrrolopyrazinones.

Pyrrole-2-carboxamides **30** *N*-substituted with an acetal-protected aldehyde function cyclized upon acid-catalyzed deprotection. The outcome of the reaction is dependent on the reaction conditions. The treatment of **30** with 4-toluenesulfonic acid or HCl in acetone/water at room temperature gave longamide A, probably after the cyclization of the intermediate aldehyde **31**. Racemic longamide A can be separated into the two enantiomers through chiral chromatography, but these racemize at room temperature within minutes [54]. On the other hand, the isomeric pyrrolopyridine **32** was formed on the heating of **30** with methanesulfonic acid (MeSO$_3$H). **Longamide A** was formed on heating with methanesulfonic acid or on treatment with 4-toluenesulfonyl chloride, and trimethylamine gave the dehydrated pyrazinone **33** [55] (Scheme 8). Unprotected ketone analogs of **31** (with different degrees of bromination on the pyrrole ring) were shown to be in equilibrium with the hydroxypyrrolopyrazinones, but the oxidation of the pyrrole ring to a 2-hydroxypyrrolin-5-one with Selectfluor gave the ring-opened product [56].
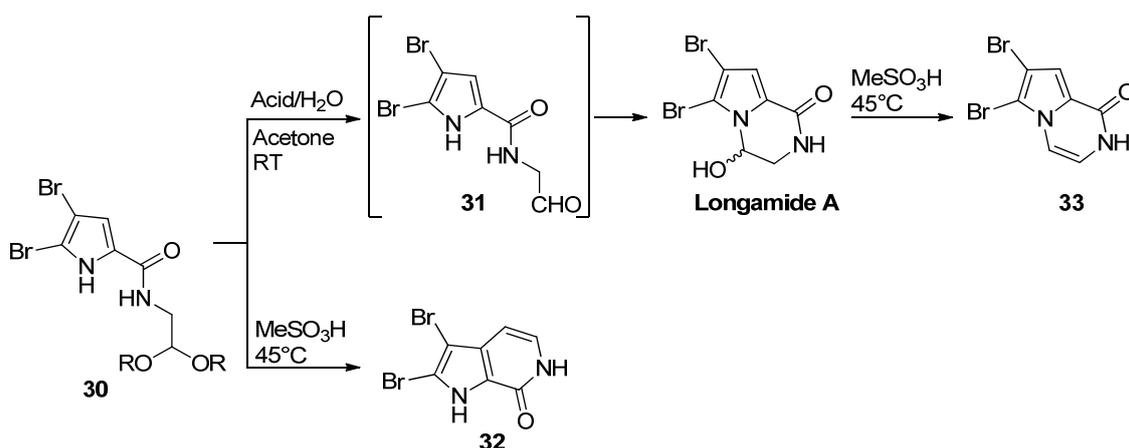
Scheme 8. Alternate intramolecular reactions of acetals and pyrrole.

The pyrrole-2-carbamide **34** (R = H) derived from prolinol on oxidation with 2-iodoxybenzoic acid (IBX) in DMSO at room temperature [57] or Dess–Martin (D-M) reagent in DCM at room temperature [58] gave the hydroxypyrrolopyrazinone **35**, which could be dehydrogenated with phosphoryl chloride (POCl$_3$) in pyridine at room temperature [57] or with mesyl chloride and DBU in DCM at room temperature [58] to afford the tricyclic compound **36** (Scheme 9). The compounds **35** and **36** (R = H, Br) were also obtained in a similar sequence from the reduction of the pyrrolecarboxamide connected to the Weinreb amide of proline with lithiumaluminium hydride [59] or with hydroxyprolinate

(diisobutylaluminum hydride reduction) [60], in the framework of total syntheses of dibromophakellstatin.
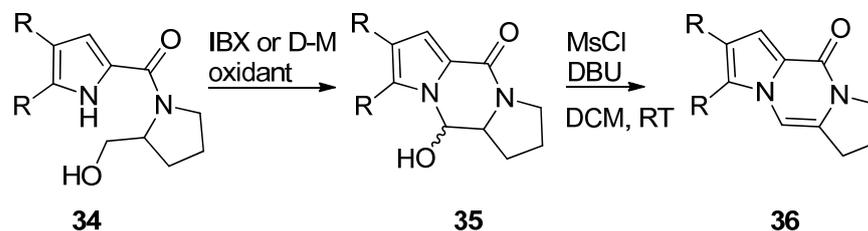
Scheme 9. Cyclization of prolinol derivatives.

Amides **37**, resulting from the condensation of 2-trichloroacetylpyrrole (or pyrrole-2-carboxylic acid and amidation reagents) and different amino esters derived from natural amino acids (shown here for proline), were cyclized with sodium hydride in THF to the diketopiperazine derivatives **38** in high yield. Several reports have appeared in the literature [59,61–64]. These compounds **38** could be oxygenated with molecular oxygen to a hydroperoxide and could be reduced in situ with dibutyl sulfide ((n-Bu)$_2$S) or triphenyl phosphine (PPh$_3$), affording the hydroxy product **39** in high yield [62] (Scheme 10). Recently, it was found that these diketopiperazines **38** could function as catalysts in oxygenation reactions [65], and the oxygenation of compound **38** in the presence of guanidine has also been mentioned as acting in the biogenesis of 2-aminoimidazolidinone metabolites from sponges [61].
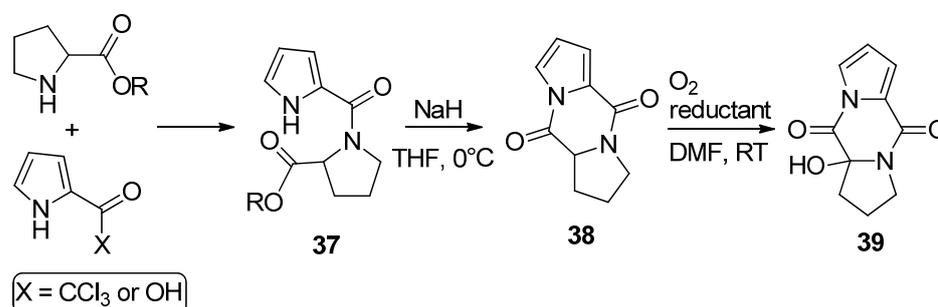
Scheme 10. Diketopiperazine derivatives from amino esters and pyrrole-2-carboxylic reagents.

Pyrrole-2-carboxylic acid, carbonyl compounds, isocyanides and amino esters undergo the four-component Ugi reaction to afford the adducts, which cyclized spontaneously at room temperature in methanol and triethylamine (Et$_3$N) to afford a library of polysubstituted pyrrole diketopyrazines **40** [66] (Scheme 11). An extensive discussion of pyrrolo-fused diketopiperazines is out of the scope of this review. Instead, we give a few additional key references [57,65,67–70].
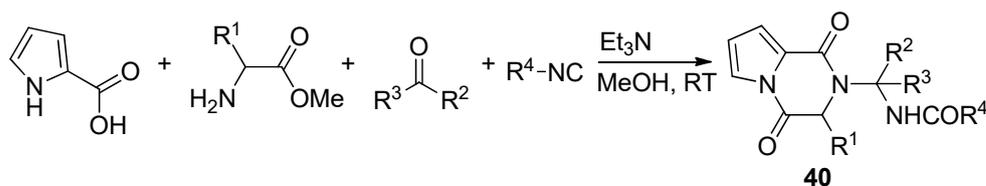

Scheme 11. Pyrrolopyrazinones by Ugi four component reaction.

2.2. Starting from 1-Monosubstituted Pyrroles

There are few examples in the literature of a 1-monosubstitued pyrrole that is converted to a pyrrolopyrazinone. Thus, the pyrrole **41** was prepared from aspartic acid

dimethyl ester and reacted with chlorosulfonyl isocyanate (CSI), affording the pyrrolopy-razinedione **42**. Reduction with sodium borohydride in methanol, and dehydration, gave the pyrazinone **43**, which was then reduced with Pt/C and H$_2$, simultaneously removing the bromine, to longamide B analogs **44** [71] (Scheme 12). Compounds analogous to **42** have also been prepared from the 2-trichloracetylation of **41** followed by substitution with primary amines [20,70].
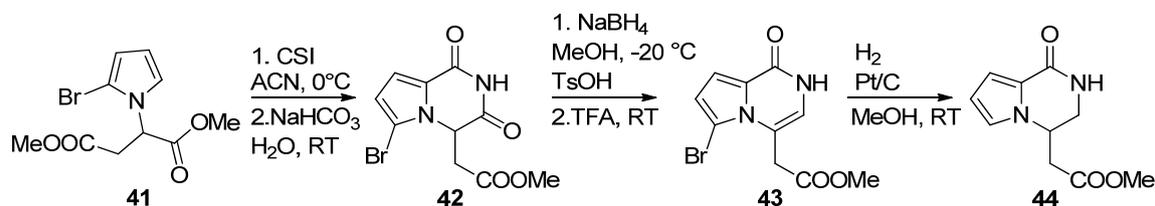
Scheme 12. Cyclization of 1-monosubstituted pyrrole with CSI.

### 2.3. Starting from 1,2-Disubstituted Pyrroles

There are a number of reports wherein a 1,2-disubstituted pyrrole was used as a starting material for the formation of a pyrrolopyrazinone. This may be done with (1) a single acyclic precursor containing an electrophilic carbonyl group at the 2-position and a nucleophilic substituent (mostly amine) at the 1-position, or (2) vice versa, or (3) the condensation of two components of which one contains the disubstituted pyrrole.

Thus, methyl 2-pyrrolecarboxylate **45** was combined with a nitroalkene **46** in the presence of potassium hydroxide to give a nitroalkyl-substituted pyrrole **47**, which was then reduced with sodium borohydride (NaBH$_4$)/cobalt(II)chloride (CoCl$_2$), and the amine **48** cyclized at reflux temperature in toluene after which ethanol was eliminated from **49** in basic medium, leading to the product **50** that was used as a starting material for the first total synthesis of peramide [23,72] (Scheme 13). As an alternative to a nitro compound, a N-CH$_2$CN functionality can be introduced, using iodoacetonitrile, which can be reduced to the amine, which then further cyclizes to a pyrrolopyrazinone [27].
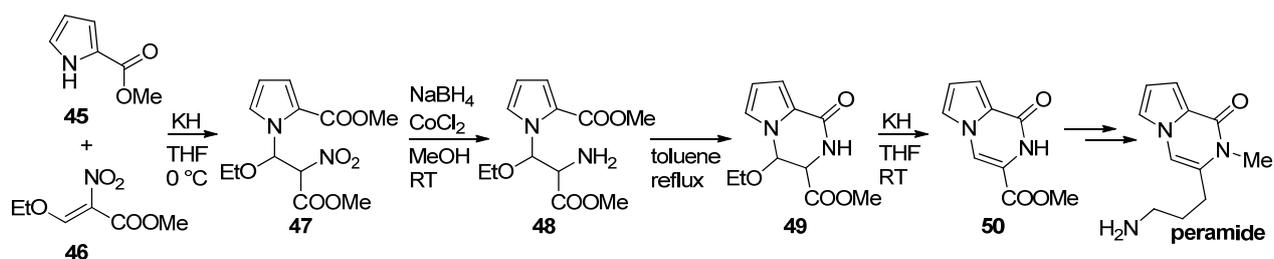
Scheme 13. First total synthesis of peramide.

The azide function is a common precursor for amine that can easily be generated in situ by catalytic reduction. Therefore, in the framework of a total synthesis of cyclooroidin, alcohol **51** was mesylated and converted into azide **52**, and catalytic hydrogenation followed by the addition of sodium hydride (NaH) resulted in the formation of the pyrrolopyrazinone **53**, which was then further elaborated to cyclooroidin [73] (Scheme 14). Similar strategies have been used in the total synthesis of (-)-hanishin [74] or in the synthesis of histone deacetylase inhibitors [75] and the inhibitors of the mycobacterium ATP synthase [76].
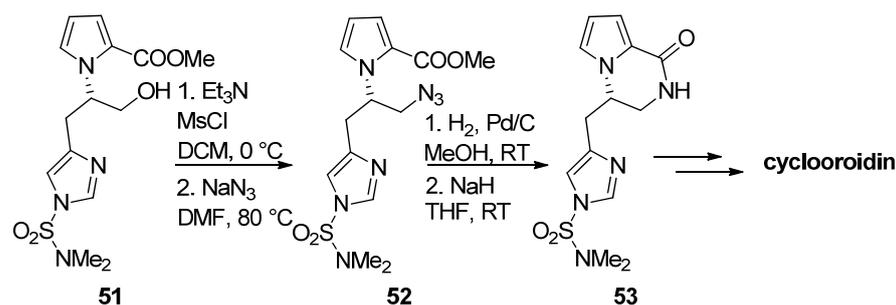
Scheme 14. Azides as intermediates in the total synthesis of cyclooroidin.

Typical amine-protecting groups like *tert*-butoxycarbonyl (Boc) and fluorenylmethoxy-carbonyl (Fmoc) can also be used in intermediates leading to pyrrolopyrazinones. Thus, the condensation of methyl 2-pyrrolocarboxylate **45** with cyclic sulfamidates **54** and the potassium *tert*-butoxide base gave the precursor **55**, which was deprotected with acid and then cyclized, mediated by triethylamine (Et$_3$N) [77]. The resulting pyrrolopyrazinone **56** can then be further elaborated to longamide B or hanishin [30,77,78] (Scheme 15). Further examples of this strategy have been reported toward longamide B derivative, kinase inhibitors [28] and mGluR1 antagonists [27], and we can also mention a Fmoc-based total synthesis of cyclooroidin [79].
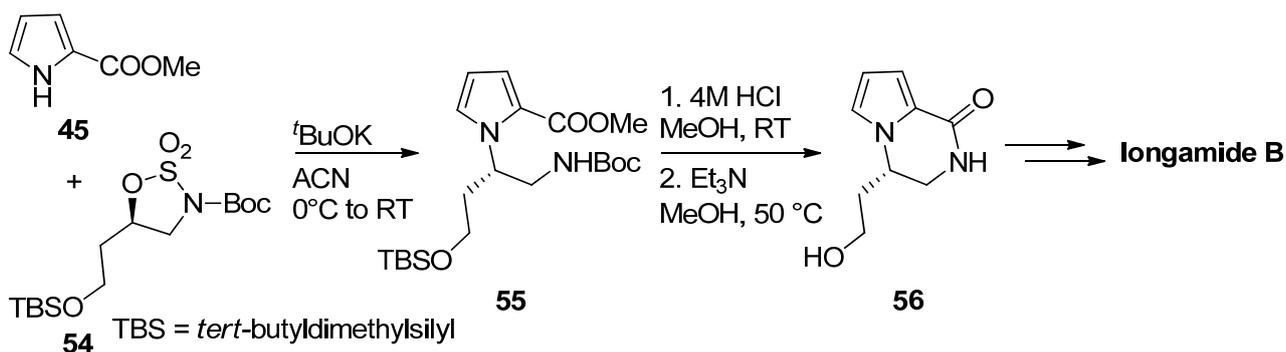
Scheme 15. Boc-strategy toward longamide B derivatives.

An effective example of a two-component reaction leading to the pyrrolopyrazinone scaffold is the reaction of *N*-(2-bromoethyl)pyrrole-2-carboxylates **57** with amines, leading to the *N*-substituted bicyclic derivatives **58** (Scheme 16). Probably the reaction starts with the substitution of the bromine by the amine, followed by lactamization. Several examples were reported [25,27,80]. In the framework of agelastatin total synthesis, some examples were reported where, in the presence of sodium hydride, an amide substituted a bromine at the side chain connected to nitrogen, proving that the opposite order of reactions is also possible [81,82].
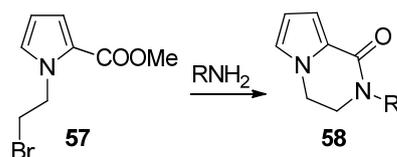
Scheme 16. Bromine substitution and lactamization with primary amines.

The condensation of hydrazine in ethanol with the triester **59** led to the *N*-aminopyrrolo pyrazinone **60**, which, upon treatment with sodium nitrite and acid, gave the deaminated derivative **61**, and the condensation of **60** with dimethyl acetylenedicarboxylate (DMAD) catalyzed by BF$_3$/acetic acid (BF$_3$·AcOH) complex in acetonitrile afforded the interesting

pyrazolo-fused analog **62** [83]. A related cyclization of 1-alkynylpyrrole-2-carboxylate **63** and hydrazine hydrate occurred with remarkable selectivity. Electron-rich aryl groups or alkyl groups R give the pyrrolopyrazinone **64a,b**, whereas for R = 4-nitrophenyl, only the 1,2,4-triazine **65c** is obtained. The phenyl substituted analogs **63d** gave a mixture of the two products **64d** and **65d** [84] (Scheme 17).
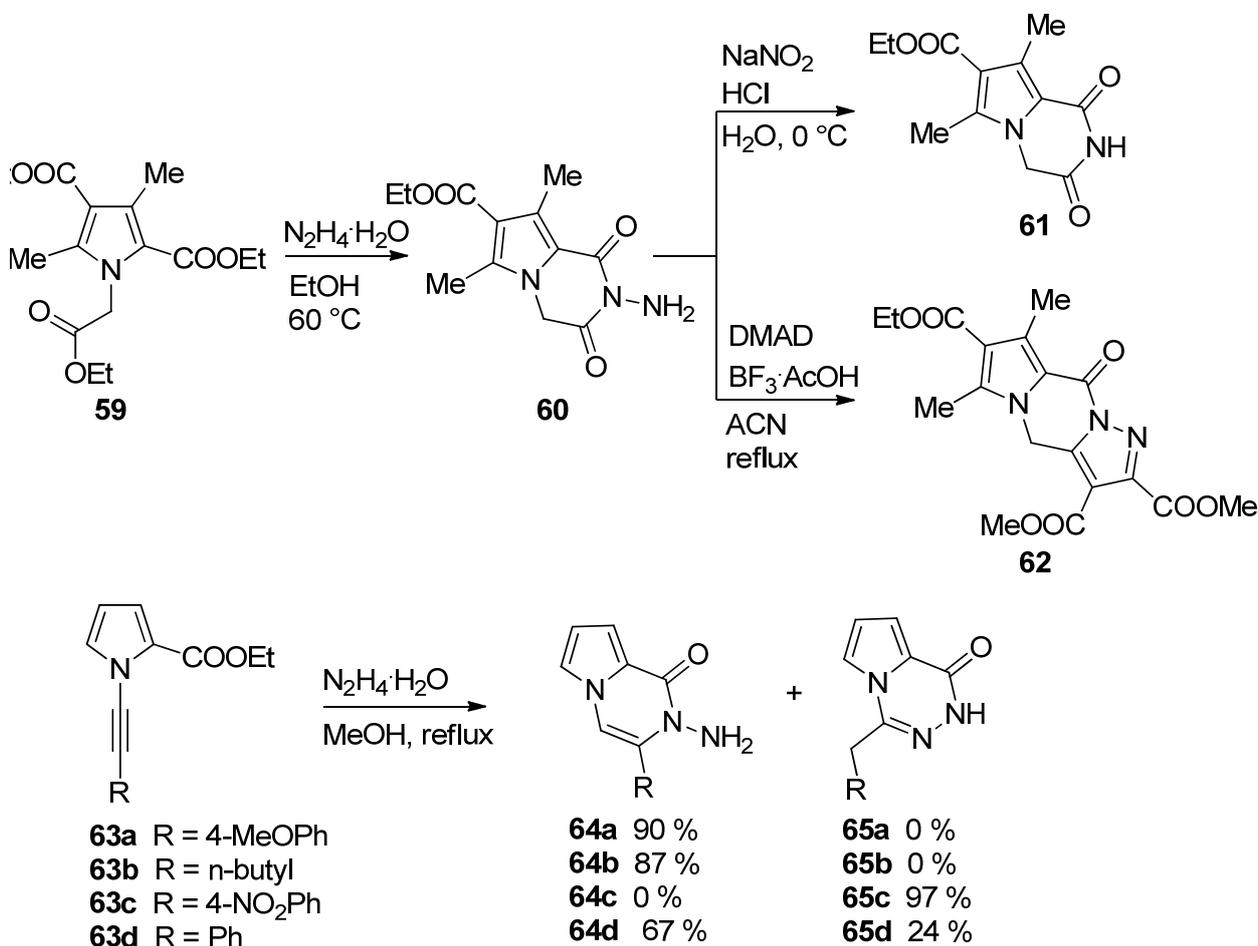
Scheme 17. Reactions of biselectrophilic pyrroles with hydrazine.

N-Propargylpyrrole-2-carboxamides **66** prepared in situ were cyclized to pyrrolopyrazinones **67** using NaH in DMF at room temperature [85], which was applied to a total synthesis of peramide [86] (Scheme 18).
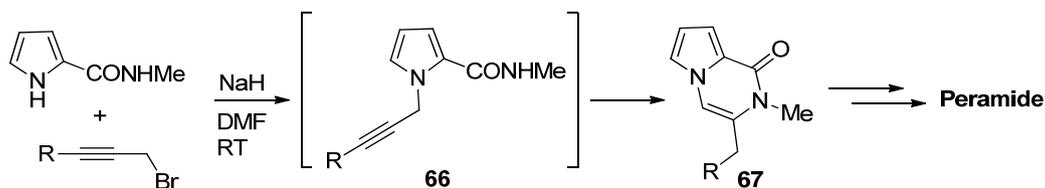
Scheme 18. *N*-propargylpyrrole-2-carboxamide synthesis and cyclization.

N-(phenacyl)substituted pyrrole-2-carboxylates **68** (R = H) reacted with methylamine (MeNH$_2$) in methanol at reflux to give direct access to pyrrolopyrazinones **69**. The diaryl-substituted analogs **68** (R = Ar), on the other hand, gave the amidation product **70**, which could be converted to the diaryl analog of **69** (R = Ar) by heating **70** at reflux in a 85% phosphoric acid/ethanol mixture [87] (Scheme 19). An early study of the synthesis of

analogs of **69** involved the condensation of amines with intermediate pyrrolo-1,4-oxazines (derived from the *N*-alkylation of 2-(trichloroacetyl)pyrrole with chloroacetone) [88]. When acetal-protected 1-acetaldehyde 2-carboxamidepyrrole is deprotected in reflux acetic acid, the unsubstituted derivative of pyrrolopyrazinone analog of **69** was obtained [89].
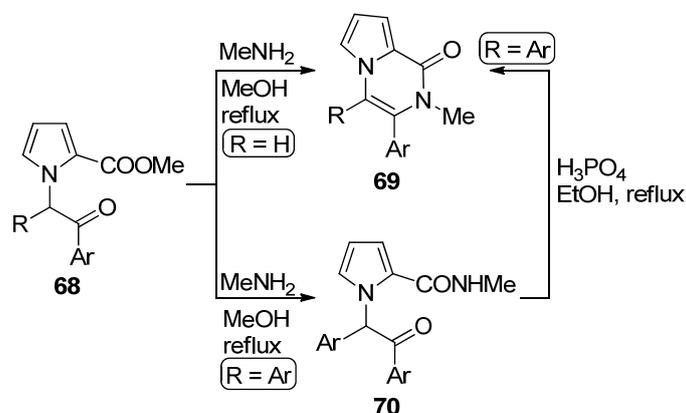
Scheme 19. Cyclization of *N*-phenacylpyrroles and methylamine.

The carboamination of *N*-allyl pyrrole carboxamide **71** (R = Ts) with allyl chloride in the presence of 10 mol% Pd(II) hexafluoroacetoacetate (Pd(hfacac)$_2$) and potassium dihydrogenphosphate in toluene/water at 50–80 °C leads to dihydropyrrolopyrazinone **72** [90]. A similar reaction carried out with the same catalyst in the presence of benzoquinone in DMF/water gave the oxygenated analog **73** [91]. Similarly, the carboamination of **71** (R = *p*-methoxyphenyl, PMP) with aryl bromides in the presence of Pd(OAc)$_2$/*S*-Phos catalyst at 100 °C afforded the dihydropyrrolopyrazinone **74** [92] (Scheme 20).
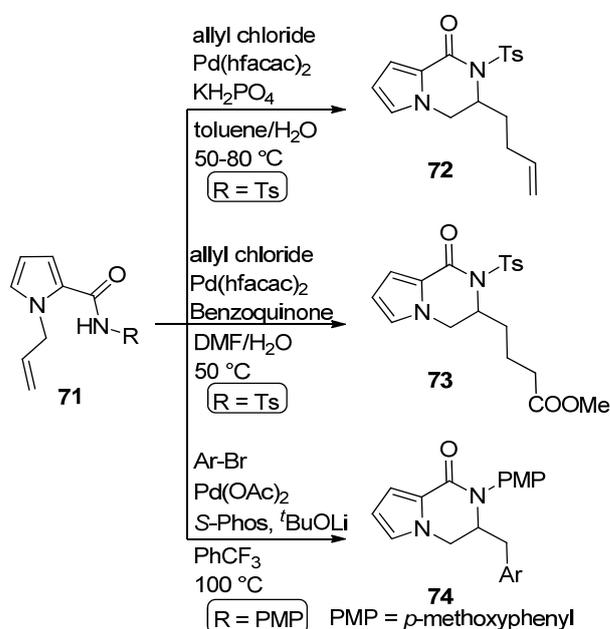
Scheme 20. Pd(II)-catalyzed carboamination reactions.

Allylpalladium species can function as electrophiles in cyclization reactions leading to pyrrolopyrazinones, and this has mainly been used in the context of the total synthesis of natural products. Thus, an enantioselective synthesis of agelastatin A reported by Trost et al. involved firstly the palladium-catalyzed allylation starting from the prochiral bisprotected cyclopentenediol **75** with 5-bromopyrrolecarboxylate **76** in the presence of a

chelating chiral bisphosphine catalyst, affording the precursor that then, after conversion to the *N*-methoxyamide **77**, underwent a second intramolecular allylation to afford pyrrolopyrazinone **78**, which could then be further elaborated to agelastatin A [93] (Scheme 21). Many variants on this allylation strategy, mostly as a part of agelastatin natural product total syntheses, were reported [94–99].
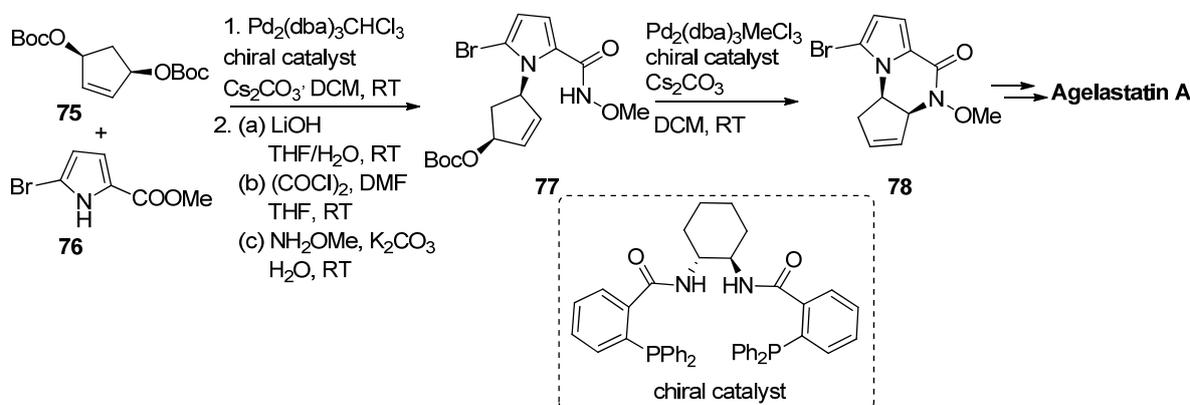
Scheme 21. Palladium-catalyzed intramolecular allylation strategy toward pyrrolopyrazinone.

A remarkable domino reaction of pyrrole-2-carboxamides **79** and vinyl selenones **80** (R^2 = H, alkyl) in basic medium occurs via an initial Michael addition, followed by the intramolecular substitution of intermediate **81**, leading to pyrrolopyrazinone **82**. In the case of styryl selenone **80** (R^2 = Ph), the *N*-(1-phenylethenyl)pyrrole **83** is formed instead [100] (Scheme 22).
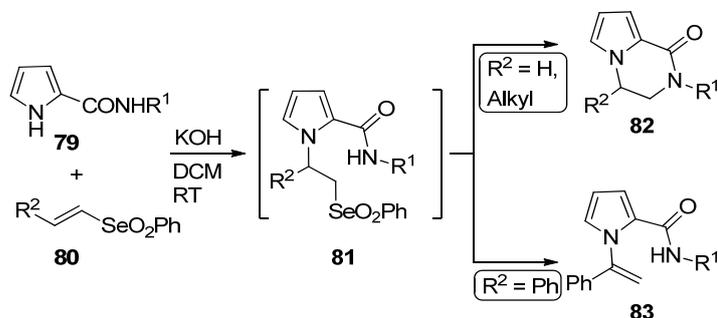
Scheme 22. Domino reaction of pyrrole-2-carboxamides and vinyl selenones.

The Castagnoli–Cushman reaction (CCR) is a ring opening/ring closure reaction of cyclic anhydrides with imines. When applied to anhydride **84**, prepared from the diacid with trifluoroacetic anhydride, condensation with different imines **85** in 1,2-dichloroethane (DCE) at room temperature led to a large variety of trisubstituted pyrrolopyrazinones **86** [101] (Scheme 23). The reaction has also been applied to substituted pyrrole anhydrides **84** [102].
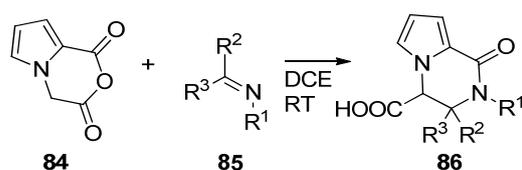
Scheme 23. Castagnoli–Cushman reaction of pyrrole cyclic anhydrides.

The multicomponent Ugi reaction has been applied to *N*-(2-oxopropyl)pyrrole-2-carboxylic acids **87**. In this case, two of the four components (the acid and the ketone) of

the Ugi reaction are present on the pyrrole moiety, and two more are added under the form of an isonitrile and an amine. This leads to a library of polysubstituted pyrrolopyrazinones **88** [103] (Scheme 24). Compounds of this type have been described as dengue inhibitors [104].
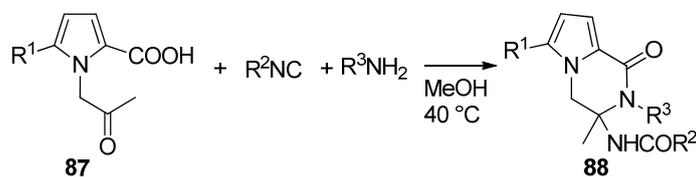
Scheme 24. Ugi reaction toward pyrrolopyrazinones.

Different approaches to *rac*-dibromophakellin or other tetracyclic marine natural products rely on the intramolecular cycloaddition of a reactive intermediate **90** generated after the oxidation of aminoimidazole **89**. This chemistry has been reviewed before [105]. Recently, an intermolecular variant has been described starting from tricyclic **91**, which was reacted with guanidine derivative **92** after oxidation with (diacetoxyiodo)benzene (PIDA) and sodium tetrafluoropropoxide (NaTFP) base. Fair amounts of cycloadduct **93** were obtained together with a minor amount of open chain compound **94**. The reduction of **93** with an excess of SmI$_2$ then gave the *rac*-phakellin [106] (Scheme 25). Other approaches involving regio- and stereoselective additions of nitrogen species to analogs of **91** have been mentioned in the framework of dibromophakellstatin total syntheses [58,105,107–109].
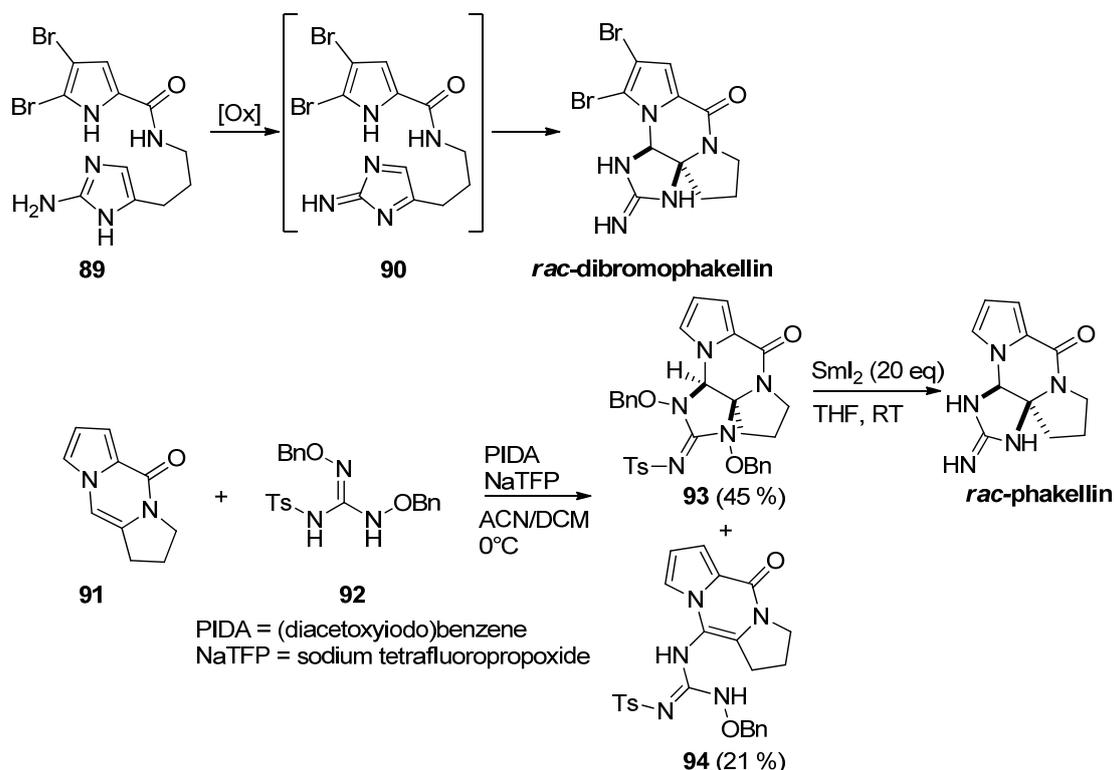
Scheme 25. Oxidative additions of aminoimidazoles and guanidine derivatives toward phakellin natural products.

Different strategies for the total synthesis of palau'amine have been reported, and an exhaustive discussion is beyond the scope of this text, so the reader is referred to some dedicated reviews [110]. One of methods that stand out is the ring contraction of the macrocycle **95** reported by Baran as the final step toward palau'amine [111]. One other remarkable process is a cascade reaction of precursor **96** with the initial deprotonation and

ring opening of the tetrahydropyrazole toward intermediate **97a** followed by formation or the pyrrolidine ring of intermediate **97b** and subsequent formation of the diketopiperazine **98**, which then was further elaborated to palau'amine [112] (Scheme 26).
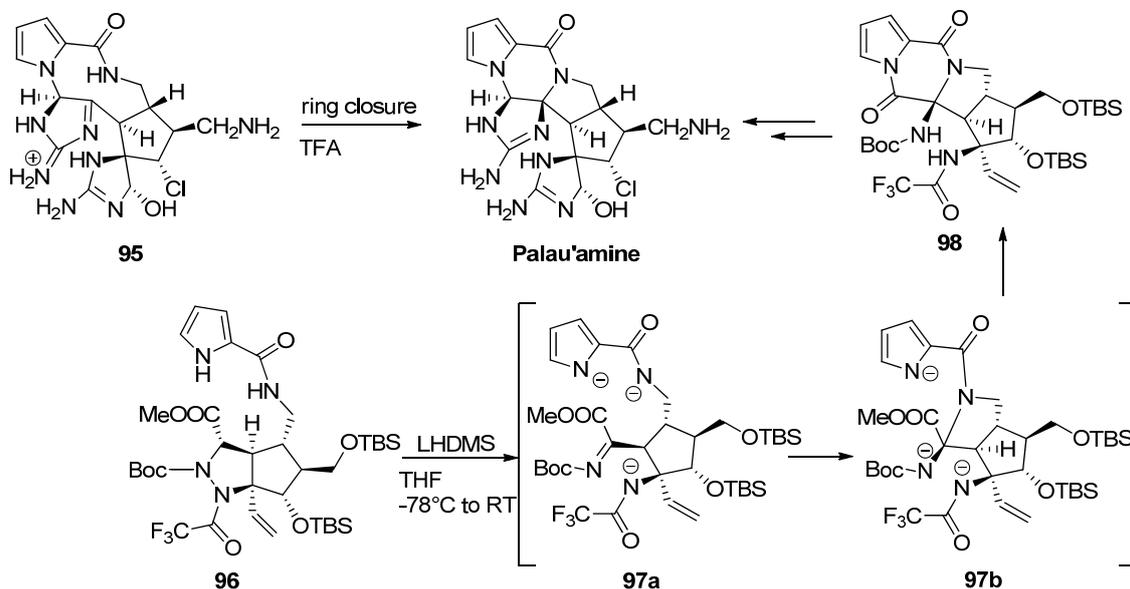
Scheme 26. Different cyclization strategies to palau'amine.

A final strategy toward pyrrolopyrazinones starting from pyrrole building blocks is through the ring expansion of pyrrolizidine derivatives, using the Beckmann rearrangement of the phenyl derivative **99**, and, after condensation with hydroxylamine and heating in polyphosphoric acid (PPA), the pyrrolopyrazine **100** is obtained [113] (Scheme 27).
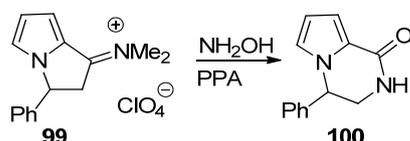
Scheme 27. Ring expansion of pyrrolizidine to pyrrolopyrazinone.

2.4. Fusion of a Pyrrole to a Pyrazinone Derivative

This approach has been much less studied than the pyrrole-first method, with only a few reports so far. Thus, the integrase inhibitors **2** were obtained, starting from pyrazinone **101** and diethyl ethoxymethylene malonate **102**, by heating at 100 °C in toluene. The resulting enamine **103** was then cyclized with lithium bis(trimethylsilyl)amide LHMDS at 80 °C in THF, affording compound **2** [26] (Scheme 28).
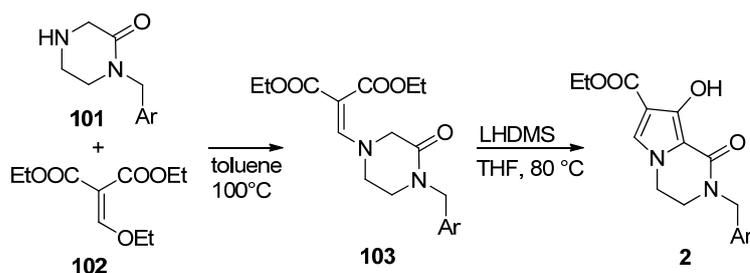
Scheme 28. Synthesis of hydroxy-substituted pyrrolopyrazinones.

An efficient two step synthesis of polysubstituted pyrrolopyrazinones started with the Vilsmeier–Haack chloroformylation of readily available ketones **104** to afford biselectrophilic 2-chloroacrolein intermediate **105**, which was then condensed with pyrazinones **106** in the presence of *N*-methylmorpholine (NMM) base in DMF at 115 °C, affording compounds **107** in fair yields, in some case accompanied with the isomer **108** [114] (Scheme 29).
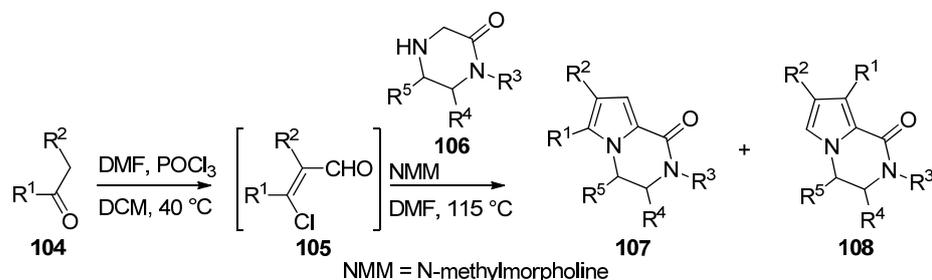
Scheme 29. Two-step synthesis of pyrrolopyrazinones from 2-chloroacroleins.

Isoxazolino-fused piperazinones **111** were prepared via the 1,3-dipolar cycloaddition of nitrones **110**, which was in equilibrium with the open chain oximes **109**, to dimethyl acetylene dicarboxylate (DMAD). Remarkably, upon heating a rearrangement occurs to pyrrolopyrazinones **112**, presumably via a multistep ring contraction/ring expansion mechanism [115] (Scheme 30).
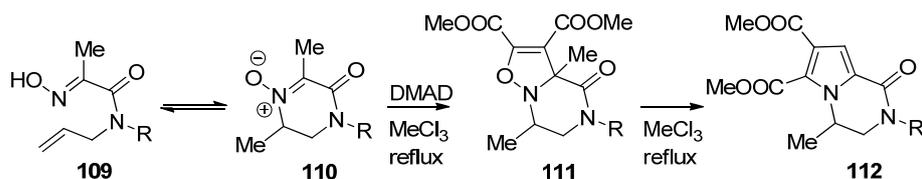
Scheme 30. Synthesis and rearrangement of isoxazolinopyrazinones.

Diketopiperazines **113** underwent base-catalyzed aldol condensations with different aldehydes, affording adducts that, in the case of acetal substituents, as for **114**, underwent camphorsulfonic acid (CSA)-mediated cyclization on heating in toluene to pyrrolodike-topiperazines **116**. The aldol condensation products **115** resulting from alkynyl aldehydes underwent gold-catalyzed cyclization under similar conditions, giving an alternative preparation for compounds **116** with a larger scope of R^1-substituents [116] (Scheme 31).
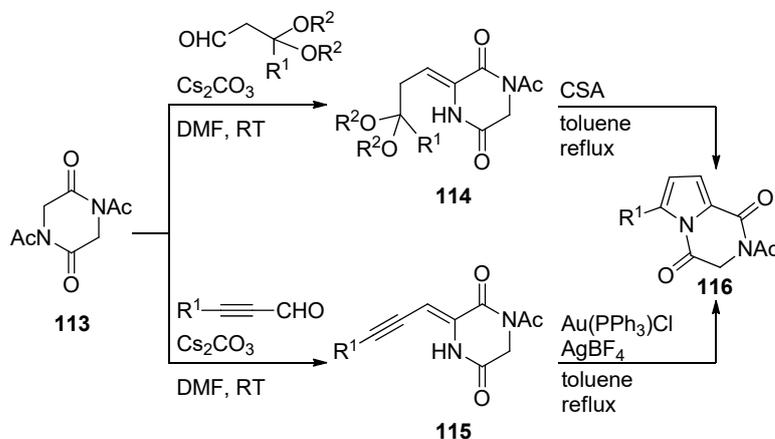
Scheme 31. Brønsted and Lewis acid-catalyzed cyclization reactions of diketopiperazines.

2.5. Multicomponent Reactions

A three-component reaction of 1,2-diaminoethane, dialkyl acetylene dicarboxylate and different biselectrophiles present a very straightforward way to pyrrolopyrazinones. Probably the diamine first reacts with the electrophilic acetylene, and the intermediate pyrazinone derivative **117** then cyclizes with the biselectrophile. Thus, reaction with bromopyruvate in acetonitrile or water at reflux resulted in diester **118** [117,118]. On the other hand, reactions with nitrostyrene, catalyzed by sulfamic acid (SA) in acetonitrile [119] or Fe_3O_4@SiO_2-OSO_3H magnetic nanoparticles in water [40] afforded aryl derivatives **119**, and condensation with methyl- or arylglyoxal in ethanol at reflux with *p*-toluenesulfonic acid (TsOH) catalysis gave hydroxyl derivatives **120** [120] (Scheme 32).
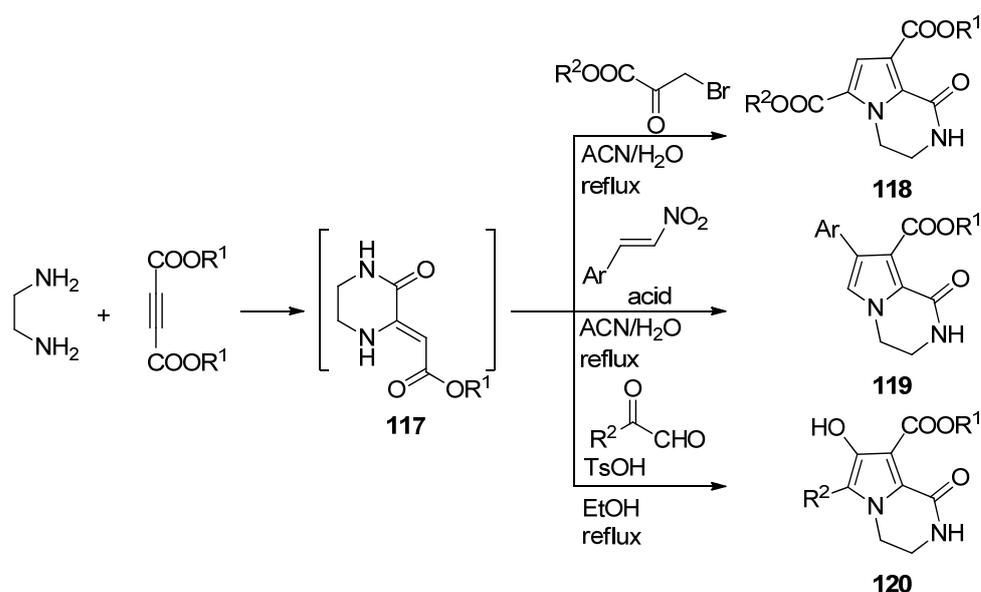
Scheme 32. Three-component reactions leading to dihydropyrrolopyrazinones.

In a variant of this three component reaction, 1,2-diaminoethane and ethyl pyruvate are combined at room temperature in acetonitrile, and then α-bromo ketones are added and the mixture heated in the presence of iron (III) chloride to afford **122** via the reaction of intermediate pyrazine **121** with the bromoketone [121] (Scheme 33).
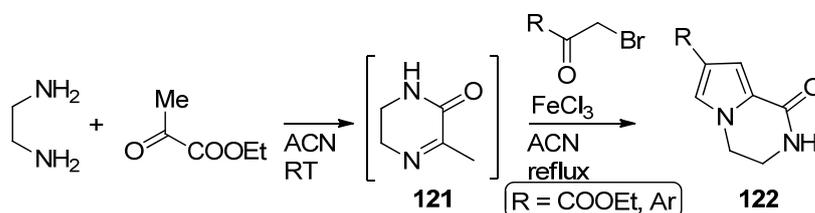
Scheme 33. Three-component reaction with ethyl pyruvate.

2.6. Miscellaneous

The ABDE core of palau'amine was constructed from the dibromide salt of diamine **123** and triscarbonyl compound **124** by a cascade reaction involving a Paal–Knorr pyrrole synthesis, leading to intermediate pyrrole **125**, which, after neutralization, undergoes subsequent lactamization to afford tetracyclic **126** [122] (Scheme 34).
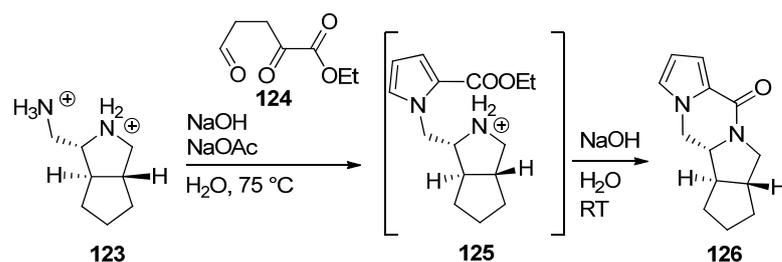
Scheme 34. Cascade process to the ABDE core of palau'amine.

Pyrrolidino-fused diketopiperazines **127** could be oxidized to the pyrrolodiketopiperazines **128** after sequential deprotonation, phenylselenation, oxidation with dimethyldioxirane (DMDO)/elimination and aromatization of the intermediate pyrroline by heating with selenium dioxide in dioxane. Earlier attempts to aromatize **127** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave a lower yield (20–30%) and was accompanied by difficult purification [107]. Recently, the proline-derived compound **129** was oxidized to the pyrrole **130** with MnO_2 in THF at 85 °C without effecting the vinyl or dihydropyrazinone parts [123] (Scheme 35).
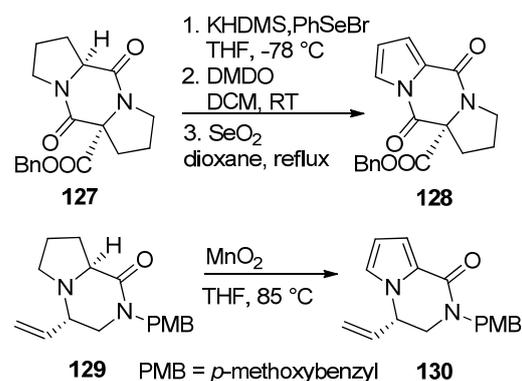
Scheme 35. Aromatization of pyrrolidino-fused diketopiperazines and pyrazinones.

The condensation of *N*-(2-aminoethyl)aziridine with two equivalents of diethyl acetylenedicarboxylate gave the triester **131**, the same compound that could be obtained through the ring transformation of the furan tetraester **132** and 1,2-diaminoethane [124] (Scheme 36).
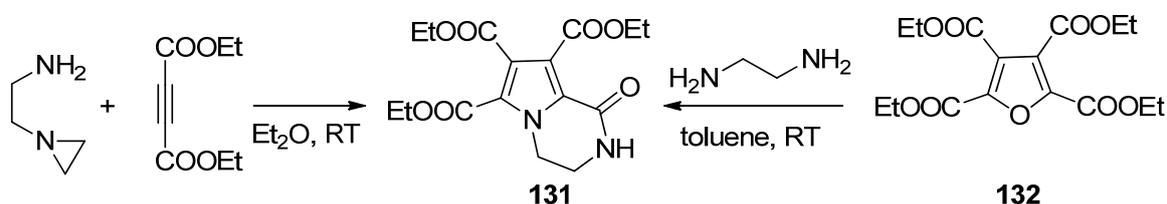
Scheme 36. Formation of pyrrolopyrazinone triesters.

3. Conclusions

The abundance of dihydropyrrolo[1,2-*a*]pyrazinones in natural products, as well as molecules exhibiting biological activity, has instigated a decade-long exploration of synthetic strategies towards these privileged structures. In this review, we classified these strategies in four main categories: (1) the fusion of a pyrazinone to a pyrrole derivative, (2) the fusion of a pyrrole to a pyrazinone, (3) multicomponent reactions and (4) miscellaneous strategies. In the pyrrole-first technique, the pyrazinone core is most often formed via intramolecular reaction, starting from either 2-monosubstituted, 1-monosubstituted or 1,2-disubstituted pyrroles. Due to the accessibility of these functionalized pyrroles and the

often straightforward nature of the ring closing reactions, a wide array of functional groups or substitution patterns can be easily introduced, explaining this being the predominant strategy for the synthesis of pyrrolopyrazinones.

Compared to the pyrrole-first strategy, fusing a pyrazinone to a pyrrole is much less studied, and only a few reports have been published. The two-step synthesis of starting from 2-chloroacroleins presented in the review proves very effective compared to the pyrrole-first strategy, which is often composed of a multistep procedure. This strategy therefore has the potential of becoming the standard for the synthesis of 3,4-dihydropyrrolopyrazinones with a pyrrole core substitution pattern that is unable or difficult to attain with the pyrrole-first strategy.

The bisnucleophilic character of pyrazinone derivatives was also cleverly employed in several multicomponent reactions starting from diaminoethane and either dialkyl acetylene dicarboxylate or ethyl pyruvate. The pyrazinone-based intermediate formed in the reaction is able to react with a range of biselectrophiles forming pyrrolopyrazinones with a range of substitution patterns.

Miscellanious reactions including a cascade reaction, a pyrrolidine oxidation toward the pyrrole and an unusual condensation reaction were also described.

The different strategies discussed in this review have already been applied in the total synthesis of various naturally occurring and synthetically challenging products. The biological activity of these core structures is certainly going to remain a motivation for chemists in the analysis of these privileged structures. By designing new synthesis pathways or improving upon the existing ones, the overall process will be made even more efficient, and possible substitution patterns will be broadened, inevitably leading to novel drug candidates.

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Abbreviations

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
Ar	Aryl
Bn	Benzyl
Boc	Tert-butoxycarbonyl
CCR	Castagnoli–Cushman reaction
CSA	Camphorsulfonic acid
CSI	Chlorosulfonyl isocyanate
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAH	Diisopropylaluminium hydride

DIPEA	Diisopropylethylamine
D-M	Dess–Martin
DMAD	Dimethyl acetylenedicarboxylate
DMB	3,4-Dimethoxybenzyl
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Et	Ethyl
Fmoc	Fluorenylmethoxycarbonyl
hfacac	Hexafluoroacetylacetone
IBX	2-iodobenzoic acid
LHDMS	Lithium bis(trimethylsilyl)amide
Me	Methyl
MeOH	Methanol
NMM	*N*-methylmorpholine
Ox	Oxidation
PG	Protecting group
Ph	Phenyl
PIDA	Diacetoxyiodobenzene
PMP	4-methoxyphenyl
PPA	Polyphosphoric acid
RT	Room Temperature
S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBS	Tertbutyl silyl
tBu	Tert butyl
TFA	Trifluoroacetic acid
TFP	Tetrafluoropropoxide
THF	Tetrahydrofuran
Tr	Trityl
Ts	Tosyl

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