Synthesis of the Pyrrole-Imidazole Alkaloids

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Abstract: This review article gives a detailed account on the chemistry of the pyrrole-imidazole alkaloids from marine sponges. The pyrrole-imidazole alkaloids share a key building block, oroidin being the underlying structural motif of a diverse range of exclusively marine alkaloids. After outlining the reactivity of 2-amino-4(5)-vinylimidazoles, biomimetic and non-biomimetic total syntheses of the non-cyclized, cyclized, and ‘dimerized’ pyrrole-imidazole alkaloids developed over the past 30 years are discussed in a comprehensive manner. Beyond the identified pyrrole-imidazole alkaloids the theoretical cyclization map based on oroidin contains many white spots and thereby opportunities to assemble novel pyrrole-imidazole alkaloids not observed in nature before.

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Key words: alkaloids, diversity, imidazole, marine natural products, pyrrole

1 Introduction

Pyrrole-imidazole alkaloids are exclusively found in marine sponges, mainly the Agelasidae, Axinellidae, and Halichondridae families. Constantly, novel pyrrole-imidazole alkaloids with unprecedented molecular architecture are discovered. The pyrrole-imidazole alkaloids are fascinating due to their biogenetic relationship leading to a large, structurally diverse family based on a common key metabolite, oroidin (1). There are surprisingly few, advanced key building blocks in natural products biosynthesis.1

With this article we give an account on the research performed in the field over the past 30 years. By the end of 2002, there was about 70 papers published each on the synthesis and on the structure elucidation of the pyrrole-imidazole alkaloids. An additional 40 contributions deal with special issues of biological activity. The interest of organic chemists in the total synthesis of the pyrrole-imidazole alkaloids has strongly increased over the past five years. One third of the contributions have appeared since 1999. A detailed mechanistic consideration on the biogenesis of cyclized and dimerized pyrrole-imidazole alkaloids starting from the non-cyclized precursor oroidin was published by Al Mourabit and Potier.2 There has been no comprehensive review on the synthesis of the pyrrole-imidazole alkaloids.

About 90 pyrrole-imidazole alkaloids have been characterized, some of which occur in high concentrations of more than 1% of the sponge dry weight, or as low as 10−4%. Oroidin (1) and the dimeric sceptrin (9, Figure 3) are the most abundant members of the family. Although it is possible to isolate enough material for initial biological testing, the problem of supplying larger quantities has to be solved by synthesis. There is no work on molecular biology related to the pyrrole-imidazole alkaloids.

1.1 Alkaloid Economy

Efficiency is a decisive criterium both for organic chemistry and for living organisms. Since the biosynthesis of alkaloids consumes valuable amino acids, it should be an evolutionary advantage to be able to generate a maximum degree of molecular diversity, and presumably function, on the basis of a common building block. It would be even better, if that building block would in itself be life saving. This is the case for oroidin (1), which secures the chemical defense of sponges of the genus Agelas against predation by reef fish (see chapter 1.3). The system of cyclized and dimerized pyrrole-imidazole alkaloids appears to be the answer to yet unknown questions of biological function.
In the following, pyrrole-imidazole alkaloids possessing the skeleton of oroidin without any further cyclization are termed ‘non-cyclized’, although, of course, oroidin itself contains the heterocycles pyrrole and imidazole. The atom positions in the basic building block are numbered according to Figure 1.

Non-cyclized members of the pyrrole-imidazole alkaloid family almost always occur together with the cyclized or dimerized sponge metabolites.6–9,c,11,12,13a,b,c,f Six modes of intramolecular cyclization of the C_{11}N_{4} building block represented by oroidin (1) have been observed in sponges, beginning with dibromophakellin (5),6,9,12,13a,c,f,19a which was discovered first by Sharma in 1971. The skeletons of cyclooroidin (2),8 hymenialdisine (3),9,12,14b,19a agelastatin B (4),10 dibromoagelaspongin (6),11 and dibromoisophakellin (7),12,13 were found subsequently (Figure 2). Cyclooroidin (2) and hymenialdisine (3) are tricyclic, while the other cyclized pyrrole-imidazole alkaloid monomers are tetracyclic.

Among the five groups of (‘dimerized’) pyrrole-imidazole alkaloids consisting of two non-cyclized subunits (Figure 3), the sceptrin (9),9d,9l,13c,e,14,19a was discovered first by Faulkner in 1981, later followed by mauritiamine (8),15 ageliferin (10),13c,e,14,c,f,16 and axinellamine (11).17 An additional mode of dimerization of the 2-amino-4(5)-

(3-aminopropenyl)-portion of oroidin is observed for the bromotyrosine-derived marine alkaloid archerine which lacks the pyrrole part.18

The most complex pyrrole-imidazole alkaloids are represented by the hexacyclic palau’amine (12),19,20 and stylloguanidine (13),19,c,20 exhibiting the phakellin or isophakellin cyclization modes in addition to the intramolecular formation of ring E (Figure 4). In addition to pyrrole-imidazole alkaloids containing the complete building block of 1, several metabolites possibly being fragments have been isolated from marine sponges,3,4,12,13,21,22 Pyrrole-imidazole alkaloids assembled from three or more subunits have not been observed, yet.

Table 1 summarizes the number of pyrrole-imidazole alkaloids isolated thus far, sorted by the above modes. The numbers of publications reporting completed total syntheses are given.

The pyrrole-imidazole alkaloids vary with regard to the oxidation, reduction, or hydrolysis state of the 2-amino-4(5)-vinylimidazole unit. The pyrrole-2-carboxamide moiety can be non-, mono-, or dibrominated in the 2- and 3-positions (numbering according to Figure 1). Bromination of the pyrrole 4-position or of the imidazole part has not been observed.

Biographical Sketches

Holger Hoffmann (born 1968) studied chemistry at the Technical University of Darmstadt, Germany. In 1996, he received his Diploma with a thesis on the synthesis of dicyclopenta-cyclooctanes under the guidance of Klaus Hafner. He then moved to Heidelberg for doctoral studies on the total synthesis of the pyrrole-imidazole alkaloids, together with Thomas Lindel. After obtaining his PhD degree in 1999, he joined the research group of George R. Pettit (Cancer Research Institute, Tempe, Arizona, USA), working on the isolation and partial synthesis of marine alkaloids. After a second postdoc with Manfred Wiessler at the German Cancer Research Center, Heidelberg, Holger Hoffmann became a research scientist at Aventis Pharma, Frankfurt, Germany, in 2001. His current research focuses on the discovery of biologically active natural products.

Thomas Lindel (born 1966) studied chemistry at the University of Münster, Germany, where he received his PhD degree in 1992 with Burchard Franck for research on the enantioselective total synthesis of terpene epoxides. For postdoctoral studies, he joined the group of William Fenical at the Scripps Institution of Oceanography (La Jolla, California, USA) exploring the isolation, structure elucidation and biological activity of new marine natural products. In 1995, he started his independent work in the laboratories of Richard Neidlein at the Institute of Pharmaceutical Chemistry, University of Heidelberg, where he obtained his habilitation for organic chemistry in 2000. Since 2001, Thomas Lindel has been an associate professor at the Department of Chemistry, University of Munich, Germany. In 2001, he received the first Dechena Young Investigator Award for Natural Products Research. He is co-editor of the Zeitschrift für Naturforschung B: Chemical Sciences. His research interests cover the synthesis of the pyrrole-imidazole alkaloids, the chemistry of peptoid sandwich complexes, the structure elucidation of new marine natural products, and the development of computational tools for HMBC-based structure elucidation.
The regioisomeric pyrrole-imidazole alkaloids palau'amine (12) and styloguanidine (13) differ by the orientation of the pyrrole ring. Absolute stereochemistries are unknown. The currently known pyrrole-imidazole alkaloids represent only a limited number of all possible derivatives that are theoretically accessible from the key building block 1 (see chapter 6).

### 1.2 Biosynthesis

Bromination of marine alkaloids is frequently observed. Catalyzed by haloperoxidases, halogenide anions from sea-water are oxidized. Halogenation itself can occur via specific halogenases.23

The only experiment on the biosynthesis of the pyrrole-imidazole alkaloids published thus far has been reported by Kerr et al. who observed low incorporation (0.022–0.026%) of the amino acids [U-14C]proline, [U-14C]histidine, and [C5-14C]ornithine into stevensine (190, hymenialdisine mode).24 When a cell culture of the marine

### Table 1  Pyrrole-Imidazole Alkaloids, Grouped by Modes

<table>
<thead>
<tr>
<th>Mode</th>
<th>Isolated Compounds</th>
<th>Publ. on Total Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-cyclized</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>hymenialdisine</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>cyclooroidin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>agelastatin</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>phakellin</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>agelaspongin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>isophakellin</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>mauritiamine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>sceptrin</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>ageliferin</td>
<td>10</td>
<td>0p</td>
</tr>
<tr>
<td>axinellamine</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>palau’amine</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>styloguanidine</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>partial structures</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>total</td>
<td>93</td>
<td>40</td>
</tr>
</tbody>
</table>

*a* Enantiomer: cantharelline.

*b* A total synthesis of a closely related derivative has been reported.

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**Figure 2** Modes of intramolecular cyclization of the C11N4 key building block (bold), represented by the natural products 2–7.

**Figure 3** Modes of intermolecular reaction of two non-cyclized C11N4 key building blocks (bold) to the natural products 8–11. The absolute stereochemistry of 10 and 11 is unknown.

**Figure 4** The regioisomeric pyrrole-imidazole alkaloids palau’amine (12) and styloguanidine (13) differ by the orientation of the pyrrole ring. Absolute stereochemistries are unknown.
sponge *Teichaxinella morchella* was used, [U-14C]arginine was not incorporated.

If histidine (17) is a biogenetic precursor, the natural product clathramide A (18) from the oroidin source *Agelas clathrodes* could be a biogenetic intermediate (Scheme 1). The missing carbon atom would be incorporated into the histidine-derived portion via methylation of the imidazole 5-position, followed by conversion of 18 to a cyclopropane and subsequent ring opening.

![Scheme 1](image)

Scheme 1 Possible biosynthetic pathways leading to the key pyrrole-imidazole alkaloid oroidin (1).

Ornithine (16) might, as well, provide the five contiguous carbon atoms of the imidazole section, as proposed by Kitagawa and Braekman. Ornithine would also be incorporated into proline, which then could be oxidized to the pyrrole-2-carboxylic acid moiety of the pyrrole-imidazole alkaloids.

The isolation of the homoarginine derivative 15 by Köck et al. indicates the existence of a biosynthetic pathway via an open chain intermediate (Scheme 1). We proposed that hydroxylation of 15 at the δ-position, followed by oxidation and cyclization generates 2-aminohomohistidine which then undergoes oxidative decarboxylation and isomerization of the resulting double bond, eventually forming 1. Our hypothesis is supported by a similar occurrence of homoarginine and 2-aminoprop(en)ylimidazoles in the case of the aplysinamisines I and II from the sponge *Aplysina* sp. Following a similar pathway, the biogenesis of the arginine-derived amino acid enduracididine occurs which is the imidazoline analog of aminohistidine.

The facile synthesis of the homoarginine derivative 15 starts from lysine methyl ester (19) and makes use of the regioselective guanidinylation of the ε-amino group with the pyrazole 20. The introduction of the pyrrole moiety is followed by a widely used method by Bailey and Johnson employing the trichloromethyl ketone 21.

We wondered if 6-hydroxylysine (22), component of collagen could be converted in a process resembling our biogenetic proposal. Indeed, the amino acid aminohomohistidine (24) could be obtained from 22 in five steps and 48% overall yield (Scheme 2). The oxidative decarboxylation of 24 is currently under investigation. Compound 24 may be of interest in the area of drug development, because it resembles arginine with regard to its binding and steric properties.

![Scheme 2](image)

Scheme 2 Synthesis of the homoarginine derivative 15, isolated from the marine sponge *Agelas wiedenmayeri* by Köck et al. Conversion of 6-hydroxylysine (22) to 2'-aminohomohistidine (24).

The pKₐ values of 2-aminimidazolium (26) and of its methyl substituted derivatives 27 and 28 in aqueous solution range from 8.4 to 9.2 (Figure 5), their pKₐ being much closer to that of imidazolium (25, pKₐ 7.1) than the pKa of guanidinium (30, pKₐ 12.5). Incorporation into strained ring systems also reduces basicity of guanidine moieties, impressive examples constitute the pyrrole-imidazole alkaloid dibromophakellin (5, pKₐ 8.0) and the potent marine toxin saxitoxin (29). The latter case, Rapoport et al. showed that the 2-aminimidazolone part is deprotonated first (pKₐ 1.8.2), while the corresponding 6-ring is almost as basic as guanidine (pKₐ 11.3).
1.3 Biological Activity

Not all of the biological activities of the pyrrole-imidazole alkaloids have been described along with their isolation, therefore, the current picture is incomplete. The pyrrole-imidazole polyamides, artificial molecules originally inspired by the natural product distamycin, which specifically interact with DNA, are not covered in the article.\(^{36}\)

Antimicrobial and antiviral activities have been described for sceptrin (9) and ageliferin (10).\(^{14c}\) Oroidin (1) and mauritiamine (8) inhibited larval metamorphosis of the barnacle *Balanus amphitrite* with ED\(_{50}\) values of 15 µg/mL and 19 µg/mL.\(^{15}\) Agelastatin (4) exhibited potent activity against brine shrimp (LC\(_{50}\) 1.7 ppm) and insecticidal activity against larvae of beet army worm, *Spodoptera exigua* and corn rootworm, *Diabrotica undecimpunctata*.\(^{10c}\)

Interestingly, the non-cyclized pyrrole-imidazole alkaloids oroidin (1), clathridin and keramadine (90) show antagonistic activity against serotonergic and cholinergic receptors\(^{37}\) whereas dispacamidine A (101), B and taurodispacamide (139) show antihistaminic activity on the guinea pig ileum.\(^{44d}\) α-Adrenoceptor blocking activity has been described for those cyclized pyrrole-imidazole alkaloids with an azepine ring system.\(^{38}\) Oroidin (1) has been subject to binding studies with artificial receptor molecules.\(^{39}\)

One of the first interesting cytotoxic compounds was gjerrilline (RP-49532),\(^{22a}\) which showed potent in vitro and in vivo antitumor activity.\(^{40}\) Potent antitumor activity was also found for cycled and dimeric pyrrole-imidazole alkaloids like agelastatin (4), dibromophakellin (145) and palau’amine (12). Palau’amine (12) also showed significant immunosuppressive activity in the mixed lymphocyte reaction (IC\(_{50}\) < 18 ng/mL).

Structural changes in the imidazole part can alter the cytotoxicity. When the guanidine moiety of dibromophakellin (5) is replaced by a urea function, the inhibitory activity against human cancer cell lines increases up to a 100-fold (e.g. ED\(_{50}\) 110 ng/mL against both the KM20L2 (colon) and the SK-MEL-5 (melanoma) cell lines).\(^{78}\) The alkylidene glycococamidine hymenialdisine (3) and the corresponding alkylidene hydantoin axinohydantoin differ also with regard to the imidazole partial structure. In this case, hymenialdisine (3) with the guanidine moiety shows cytotoxicity against the cell line 60178y (ED50 3.9 g/mL) whereas axinohydantoin with the urea moiety was inactive.\(^{9h}\) Table 2 summarizes the current knowledge on the biological activities of the pyrrole-imidazole alkaloids.

Hymenialdisine (3) was found to be a potent inhibitor of cyclin-dependant kinases (e.g. CDK5: IC\(_{50}\) 28 nM), glycogen synthase kinase-3β (GSK-3β: IC\(_{50}\) 10 nM) and casein kinase 1 (CK1: IC\(_{50}\) 35 nM).\(^{41}\) Due to these activities hymenialdisine has been identified as a kinase inhibitor with promising potential applications for treating neurodegenerative disorders like Alzheimer’s disease. Debromohymenialdisine showed inhibition of the G\(_{2}\) DNA damage checkpoint (IC\(_{50}\) 8 M) and of protein kinases Chk1 and Chk2 (IC\(_{50}\) 3 and 3.5 µM, respectively).\(^{42}\) Recently, a Raf/MEK-1/MAPK cascade inhibitor activity-directed fractionation of the sponge *Stylissa massa* led to the isolation of (E)/(Z)-hymenialdisine. Both showed significant enzyme inhibitory activity (IC\(_{50}\) 3 nM and 6 nM, respectively).\(^{43}\) Secondary assays identified these compounds as potent MEK-1 inhibitors.

Hymenialdisine (3) has recently been characterized as an inhibitor of protein kinase C and the proinflammatory transcription factor, nuclear factor B (NFB) activation.\(^{45–48}\) NFB is believed to be involved in the regulated gene expression of the inflammatory enzyme, cyclooxygenase (COX-II). Together, these proteins play important roles as mediators of inflammation associated arthritis. In addition, debromohymenialdisine has been shown to slow joint deterioration and cartilage degradation associated with osteoarthritis in animal models and is currently under development as a promising new drug candidate.\(^{49}\)

Oroidin (1) is one of the quite few natural products a biological function has been assigned to. Intrigued by the question why sponges of the genus *Agelas* were not being fed on by predatory reef fish, an ecoassay-guided fractionation led to 1 and to 4,5-dibromopyrrole-2-carboxylic acid as responsible chemicals.\(^{50}\) Later, other pyrrole-imidazole alkaloids were identified as being feeding deterrents.\(^{50b,c}\) The average concentration of 1 is about (1.4±1.1 mgmL\(^{-1}\)) of sponge volume (*Agelas clathrodes*). In the same concentration, oroidin was active in the feeding assays.

Figure 6 summarizes the current knowledge on the structure-activity relationships regarding the fish feeding deterrency by oroidin-like molecules.\(^{51}\) The pyrrole part is required for activity, but of itself is not sufficient. The imidazole section is not a feeding deterrent on its own, but enhances the activity of the pyrrole part.
2 Reactivity of Partial Structures

2.1 2-Aminoimidazole

Despite its simple structure, there are relatively few publications dealing with the functionalization of 2-aminoimidazole (31). Most of the knowledge on the reactivity of 2-aminoimidazole has been gained in conjunction with the synthesis of the pyrrole-imidazole alkaloids. There is extensive literature available on the chemistry of 2-anobenzimidazole and of imidazole, which is not covered in this review.52

Scheme 2 gives a few examples of the reactivity of the electron-rich 4,5-double bond of 2-aminoimidazole. Via electrophilic substitution, treatment of 2-amino-4(5)-methyl-2-thyylimidazole (31) with isoamyl nitrite led to nitrosation of the 4-position with subsequent tautomeration to the oxime 32.53 Novikov et al. succeeded in preparing the dimeric marine natural product polycarpine (34) via reaction of the 2-aminoimidazole precursor 33 with S2Cl2, forming the disulfide bridge in an almost quantitative yield.55 This reaction also proceeds with the 2-deamino analog, but in a much lower yield (34%). The important attack of Cl+ or Br+ at the 2-aminoimidazole 4,5-double bond gives several opportunities for intra- and intermolecular reactions which have led to the synthesis of non-cyclized and cyclized pyrrole-imidazole alkaloids (see below).

The third part of Scheme 2 concerns the hydroxyalkylation of 2-aminoimidazole. In their best example, Horne et al. obtained the hydroxypropylated compound 35 in the moderate yield of 42% by reaction of 2-aminoimidazole (31) with propionic aldehyde.56 As substantial side products, the dimers 26a,b were obtained, indicating the ability of the 4,5-double bond of 2-aminoimidazole to act as dienophile in Diels–Alder-type reactions. Apparently, a propionylimine intermediate is generated first which functions as the diene. A clearer picture is observed for the inverse Diels–Alder reaction of the very reactive 1,2,4,5-tetrazine 37 with N,N-dimethylaminoiminium-protected 2-aminoimidazole.57 The imida-
Pyrrole-imidazole alkaloids are synthesized from 2-aminoimidazole. The formation of 4,5-dihydropyridazine 38 occurs in a yield of 82% with loss of nitrogen. The 4,5-double bond of 2-aminoimidazole can undergo electrophilic addition reactions. Scheme 4 gives one of the first cases reported by Little and Webber who observed the formation of the 2-amino-4-hydroxyimidazoline 40 which is in equilibrium with the ring-opened guanidinium compound 41. On treatment of 39 with dry ethanolic HCl, the ethylated ketal 42 was obtained. Interestingly, this behavior was not observed for the corresponding cyclohexa homolog, which only gave the deacetylated aminoimidazole under the same reaction conditions.

2-Amino-4,5-dihydroxyimidazoline is formed on reduction of 2-(hydroxyamino)imidazole, obtained via reduction of the antibiotic 2-nitroimidazole (azomycin). The extended π-system of 2-amino-4(5)-vinylimidazole (43) occurs in several pyrrole-imidazole alkaloids and shows several modes of reactivity. Al Mourabit et al. outlined the ambivalent reactivity of the tautomers 43a–d (Scheme 5, iminoimidazole tautomers omitted). The complex equilibria between different tautomeric forms of 2-aminoimidazoles in different solvents have not yet been fully understood. Quantum mechanical calculations have been performed on 2-aminoimidazoles and on related nitrrenium forms. Compound 43 has also been isolated as a natural product.

The first study on the dimerization of 2-amino-4(5)-vinylimidazoles was reported by Braun and Büchi. The alkaloids pseudo- (45) and parazoanthoxanthin A (47) were obtained on treatment of the regioisomeric 2-amino-4(5)-hydroxyethylimidazoles 44 or 46 under dehydrating and oxidative conditions (Scheme 6). It was speculated that, after elimination of water, [6+4]-cycloaddition may take place between two molecules of 4(5)-vinylimidazoles. In a re-investigation of the problem, Horne et al. found that stepwise oxidative dimerization of 2-amino-4(5)-ethylimidazole (48) to parazoanthoxanthin A (47) can be achieved via the isolable synthetic intermediate 49 on
treatment with different equivalents of bromine in methanesulfonic acid.\textsuperscript{52} As the first step, oxidation of 48 to a diazafulvene intermediate is assumed. 1,3-Diazafulvene tautomers of 2-amino-4(5)-vinylimidazoles have rarely been characterized and, in most cases, are substituted in the 4- and the 5-positions.\textsuperscript{63} The zoanthoxanthins are bright yellow pigments exclusively isolated from various species of coelenterates of the order Zoanthidea and have been reviewed.\textsuperscript{64} No pyrrole-imidazole alkaloid corresponding to the dimerization modes of 45 or 47 has been isolated from natural sources, thus far.

Only a few cycloaddition reactions have been investigated with 4(5)-vinylimidazoles. In 1994, Walters and Lee reported the \([4+2]\)-cycloaddition of \(N\)-alkylated 5-vinylimidazoles to phenylmaleimide (50, Scheme 7), obtaining 52 after H-shift.\textsuperscript{65a} The behaviour of 1-methyl-5-vinylimidazole (51) as an electron-rich diene was in accordance with semiempirical calculations. Recently, Lovely et al. re-investigated that reaction in more detail employing 4-vinylimidazoles such as 53. It was possible to isolate the non-aromatized diastereomer 54 in a yield of 93%.\textsuperscript{65c} It is noteworthy that even in dichloromethane at room temperature, the Diels–Alder reaction is complete after 48 hours. If oroidin (1) would undergo \([4+2]\)-cycloaddition under such mild conditions, it would be difficult to isolate it. The Diels–Alder reaction is even more rapid and also reversible, if \(N\)-phenylmaleimide (50) is replaced by 4-phenyl-1,2,4-triazoline-3,5-dione (55). Koomen et al. reported the cycloaddition of 55 and 56 to 57 at a temperature of 0 °C.\textsuperscript{55b}

The natural product sceptrin (9, Figure 3) bearing a 2-amino substituent has not yet been synthesized. Scheme 8 shows the formation of a sceptrin-like cyclobutane ring on irradiation of allyl urocanate (58) without participation of the allyl groups in high yield (72%).\textsuperscript{66} D’Auria and Racioppi observed excellent regio- and stereocontrol of the dimerization. PM3-RHF-CI semiempirical calculations of the frontier orbitals were found to be in very good agreement with the observed head-to-head regiochemical outcome. The \(trans–trans\) relative stereochemistry is observed as the greatest thermodynamic stability is seen with this isomer. Earlier, Morrison et al. investigated the photochemical \([2+2]\)-dimerization of urocanic acid and its immunosuppressant (\(Z\))-isomer.\textsuperscript{67} Chemoselective Diels–Alder reaction at the vinyl double bond of urocanic acid methyl ester with cyclopentadiene as diene component has been reported by Ikeda et al.\textsuperscript{68}
2.2 Pyrrole-2-carboxamide

The pyrrole ring as the second heterocycle of the pyrrole-imidazole alkaloids generally participates as a nucleophile in the intramolecular cyclization reaction. In certain cases such as the biogenesis of the hymenialdisine-type pyrrole-imidazole alkaloids, radical processes may be involved.

![Diagram showing intramolecular hydroxyalkylation and Michael additions of pyrrole-2-carboxamide derivatives leading to the marine natural products longamide A (68), B (71), and hanishin (72).](image)

Among the simple heterocycles, free or N-methylated pyrrole exhibits a relatively strong nucleophilicity at C-2 which rivals even nucleophilic solvents. Pyrrole is less nucleophilic than indole, but much more nucleophilic than furan (Mayer nucleophilicity parameters 5.9 vs. 6.9, 2.5 respectively). In the pyrrole-imidazole alkaloids, positions N-1 and C-4 of the pyrrole part (altered position numbering, see Figure 1) usually participate in intramolecular cyclizations of the pyrrole-imidazole alkaloid key building block. Position C-5, which is the most nucleophilic in free pyrrole has only rarely been quaternized.

A study by Brimble et al. and the syntheses of the natural products longamide A (68), B (71), and hanishin (72) from the marine sponges Agelas longissima and Homoaxinella sp. give some insight into the behavior of the pyrrole-5-carboxamide moiety (Scheme 9) with respect to intramolecular cyclizations. Longamide A (68) can be obtained via kinetically favored lactamization of the α-amidoaldehyde 65 on treatment of the acetal 60 (R = -CH₂CH₂- or R = Et) with aqueous HCl. The enantio- mers can be separated via chiral HPLC, but racemize within minutes. Their tendency to cyclize is governed by the chain length, for the homologous β-amidoaldehyde 66 the equilibrium favors the open-chain compound 66 which can be isolated and characterized.

If the α-amidoaldehydes 68 or 69 or their acetal precursors 66 or 61 are treated under more drastic conditions for prolonged reaction times in the presence of POCl₃, BF₃, TiCl₃, CSA, or MeSO₃H, the thermodynamically favored C-hydroxyalkylation of the pyrrole ring is observed, followed by elimination of water leading to the homologous compounds 63 or 64 (Scheme 9). The carboxylic acid corresponding to 66 can be cyclized to the marine pyrroleazepinone aldinsine by employing P₂O₅/polyphosphoric acid.

It is possible to react the lactal longamide A (68) or its de-brominated analog 69 with Wittig–Horner or Wittig reagents, leading to a chain-elongation by three carbon atoms. Via intramolecular Michael additions of the deprotonated pyrrole nitrogen, two approaches to the natural products longamide B (71) and hanishin (72) resulted.

3 Non-Cyclized Pyrrole-Imidazole Alkaloids

The development of reliable synthetic pathways to the non-cyclized pyrrole-imidazole alkaloids such as oroidin (1) is the basis of any progress in understanding their biomimetic cyclizations and dimerizations. In the following, the approaches are subdivided into those starting from an already assembled imidazole ring and those making use of an open-chain precursor. Although lacking the pyrrole unit, the antitumor marine natural product girolline (104) is included which is based on the 2-amino-4(5)-aminopropyl partial structure of the pyrrole-imidazole alkaloids.

Among the pyrrole-imidazole alkaloids with a 2-aminoimidazole partial structure, only keramadine (90, Scheme 11) contains a trisubstituted imidazole ring while the corresponding imidazoles of the parent compound oroidin and of girolline are disubstituted. In the dispacamides (101, d. A) the 2-aminoimidazoline moiety is oxidized to an alkylidene glycocamidine, while midpacamide (98) contains an N-methylated hydantoin ring.

3.1 Starting from Imidazole

The structure of oroidin (1) was originally confirmed by synthesis of its monoacetylated derivative dihydrooroidin lacking the vinyl double bond. The first synthesis of the 2-amino-4(5)-vinylimidazole oroidin (1) was published by Ahond et al. in 1986. Key step of this and also of more recent approaches is a Wittig–Schweizer reaction employing a phosphonium salt which is prepared in situ
via nucleophilic attack of either phthalimide or trichloroacetamide to tributylvinylphosphonium bromide (Scheme 10).\textsuperscript{77}

Overall, conversion of 1-tritylimidazole-4-carbaldehyde (73) to the corresponding aminopropenyl imidazoles 74 or 77 was achieved in good yields. While in the phthalimide case the \((E)\)-isomer apparently had been formed exclusively, reaction with the trichloroacetamide-derived reagent predominantly provided the \((Z)\)-isomer 77 (6:1). The introduction of the imidazole 2-amino substituent was somewhat more difficult. While 2-aminimidazole itself can be prepared by reaction of the diazonium salt of \(p\)-bromoaniline with imidazole and hydrogenation, more complex imidazole derivatives often yield colorfull, intractable product mixtures.

An alternative is the introduction of an azide functionality, at the imidazole 2-position, after lithiation. While the use of phenyl azide generated the triazene \((Z)\)-isomer apparently had been formed exclusively, reaction with the trichlorooacetamide-derived reagent provided the \((Z)\)-isomer apparently had been formed exclusively, reaction with the trichlorooacetamide-derived reagent predominantly provided the \((Z)\)-isomer 77 (6:1). The introduction of the imidazole 2-amino substituent was somewhat more difficult. While 2-aminimidazole itself can be prepared by reaction of the diazonium salt of \(p\)-bromoaniline with imidazole and hydrogenation, more complex imidazole derivatives often yield colorfull, intractable product mixtures.

An alternative is the introduction of an azide functionality, at the imidazole 2-position, after lithiation. While the use of phenyl azide generated the triazene 75 in low yield, employment of tosyl azide\textsuperscript{79} gave the azide 78, satisfactorily. Interestingly, Ahond et al. could carry out the azidation in the presence of an unprotected pyrrole ring and obtained the oroidin precursor 78 in three steps from 77. Reduction of the azide function with propane-1,3-thiol and removal of the trityl group under acidic conditions completed the synthesis of oroidin (1) in six steps and 6\% overall yield. The older pathway\textsuperscript{75} via the triazene 75 provided oroidin (1) within five steps, but in an overall yield of only 1.8\%. Ahond et al. also synthesized keramadine (90) which exhibits an \(N\)-methylated imidazole ring and a \((Z)\)-double bond.\textsuperscript{76} Regioselective methylation of a 1-\(N\)-trityl-4-vinylimidazole precursor was possible, but the corresponding \(N\),\(N\)‘-dimethylimidazolium salt formed as a side product. Another problem was the partial isomerization of the \((Z)\)-double bond on reduction of the azid group.

Scheme 11 \((Z)\)-selective alkyne pathway to keramadine (90).\textsuperscript{80}

Synthesis 2003, No. 12, 1753–1783 © Thieme Stuttgart · New York
We wondered if the (Z)-double bond of keramidine (90) could be masked as an alkyne throughout the synthetic sequence (Scheme 11). Simultaneous hydrogenation of the triple bond and of an imidazole-2-azido group would yield stereochemically pure keramidine (90). While the (Z)-vinyl double bond of the N-methylated keramidine was known to be stereochemically stable, it was unclear if the hitherto unknown (Z)-oroidin (89) would isomerize to the naturally occurring (E)-form 1.

Pd-catalyzed Sonogashira coupling81 of 8082 or 8583 with Boc-protected propargylic amine 7984 gives the alkynylimidozoles 82 and 86, respectively, in high yields (Scheme 11). After azidation of the imidazole 2-position of 82 employing n-BuLi/tosyl azide and removal of the Boc protecting groups the pyrrole moiety was introduced via coupling with the 4,5-dibromopyrrolyltrichloromethyl ketone 83.31 The overall sequence to 89 concludes with the double hydrogenation of the 5-alkynyl-2-azimidazole 84. In the synthesis of keramidine (90), the desired imidazole substitution pattern is achieved via treatment of the alkynylated imidazole 86 with trimethylsilyl tetrafluoroborate yielding 87 after methanolation, followed by azidation providing 88, which is converted to 90. (Z)-oroidin (89) and keramidine (90) were obtained in 30% (five steps) and 25% (six steps) overall yields, respectively.

Clean conversion of (Z)- to (E)-oroidin is observed under acidic conditions [6 N aqueous HCl–MeOH (1:1) at 60 °C, Scheme 2]. When the analogous experiment was performed in an NMR tube in DCl–D2O, no incorporation of deuterium into 9 or 10 of the resulting (E)-oroidin ([E]-1) was observed.85 Probably, the isomerization proceeds via an oxazoline intermediate formed by intramolecular attack of the carbonyl oxygen at C-9.

Direct reduction of the 2-azido-4-alkynylimidazole 82 to the (E)-2-amino-4-alkynylimidazole 91 is possible with NaAlH4(Ο₂Cl₂Ο₂CH₂ΟΜe) (Red-Al). A short synthesis of the pyrrole-N-methylated natural product sventrin (93)34 resulted (Scheme 12). Clean detritylation of the 2-aminomidazole part without amide hydrolysis was possible by refluxing in formic acid.85

Carboni et al. assembled the vinylimidazole portion via Suzuki cross-coupling between the boronate 94 and 4-iodo-1-tritylimidazole (80, Scheme 12).86 Detritylation of the 2-azimidazole 96 after acylation is more facile than in the amino case.

The racemic midpacamide (98) from Agelas mauritiana and the dispacamides (101, d. A) from Agelas dispar contain oxidized imidazole moieties. In those cases, the condensation of the isolable, yet sensitive aldehyde 65 (Scheme 13) and hydantoin-type compounds is superior to the oxidation of imidazole derivatives. The reactivity of the nucleophilic 5-position decreases in the order 2-thiohydantoin > hydantoin > glycoxyamidine. In fact, hydantoin is already not reactive enough to obtain good yields of condensation product with 65 and must be replaced by the phosphonate 97.97 On reaction with the aldehyde 65, an alkylidene hydantoin is formed which can be regioselectively dimethylated at the most acidic positions. Chemoselective hydrogenation to 98 is possible if Ru/Al2O3 is used as a catalyst, while debromination occurred when Pd catalysts were employed.72

Condensation of 2-thiohydantoin (99) with the aldehyde 65 provided the alkylidene thiohydantoin 100 which can be converted to the alkylidene glycoxyamidine dispacamide A (101) in one step by treatment with an aqueous solution of ammonia in the presence of tert-butylhydroperoxide.88 This procedure is more facile than the two-step sequence via S-methylation and ammonolysis in a sealed tube which led to the formation of side products. Bergman et al. and Ireland et al. applied the TBHP-procedure to the syntheses of the marine natural products leucentamine B (103) and polyandrocarpamine A.89

Girolline (104) from the marine sponge Cymbastela cantharella (previously Pseudaxinyssa cantharella) was discovered by Ahond et al.22a and exhibits potent in vitro cytotoxicity and in vivo antitumor activity.40 Girolline (104) lacks the pyrrole part. The vinyl double bond present in oroidin (1) is oxidized to the chlorohydrin (Figure 7). The only other pyrrole-imidazole alkaloid containing a chlorohydrin moiety is the isophakellin-type
The relative and absolute stereochemistry ($S,S$; threo) of girolline (104) was elucidated by a series of total syntheses published by Ahond et al. 90 and Commerçon et al. 91,92 In their initial approaches, both groups started from the allylic alcohol 106, which is accessible from 4(5)-hydroxymethylimidazole 93 in three steps (Scheme 14). After TBS-protection the monosubstituted double bond can be regioselectively carbamatoxygenylated to the synthetic intermediate 107 (moderate de 59%). Chromatographic separation, Appel reaction, and deprotection furnished the threo racemate 108. Diazotization and hydrogenolysis of 108 were possible, but in the very low yield of 2% over two steps.

Scheme 14 Syntheses of the diastereomeric precursors 108 and 111 of the marine natural product girolline (104).

The erythro-diastereomer 111 was obtained as a racemate via electrophilic attack of Cl⁺ at the double bond. Treatment of 106 with DBU and trichloroacetonitrile first led to the formation of a trichloroacetimidate which immediately underwent an azoxa-Claisen rearrangement to the trichloroacetylated 3-amino-2-propenylimidazole 109. Commerçon report an interesting, competing Claisen rearrangement to a 5-aminoimidazoline, which, unfortunately, was not characterized. In situ-generated hypochloric acid induced a 6-endo closure to the dihydrooxazine 110 with defined stereochemistry, followed by acidic hydrolysis to 111. Horne’s work on the total synthesis of the dimeric pyrrole-imidazole alkaloid mauritiamine A (8, chapter 4.2) shows that the direct conversion of the natural product 2-amino-(4S)-(3-aminoprop-1-enylimidazole (43) to girolline (104) via intermolecular attack of NCS/
water has little chance to be high-yielding. *threo*-Girolline (104) was formed only as a very minor side product.110

The enantioselective synthesis of girolline (104) by Commerçon92 and shortest synthesis of rac-girolline (104) by Al Mourabit et al.95

Büchi et al. developed a short and high-yielding pathway to dihydrooroidin (120) originally starting from citrulline methyl ester, which was later replaced by ornithine methyl ester (119).96 Scheme 16 outlines this approach as part of the study by Horne et al. on the oxidation of dihydrooroidin (120) to either oroidin (1), dispacamide A (101) or dihydrodispacamide (122).97 Ornithine methyl ester is reduced to the aldehyde, by the Akabori process,98 which is then condensed with cyanamide. Reaction with the trichloromethyl ketone 83 provides dihydrooroidin (120) in three steps and 40% overall yield. Büchi and Horne made the important discovery that trans-dioxygenation of the 4,5-double bond occurs on treatment of 2-aminoimidazole with NBS in the presence of alcohols. Thus, the dimethoxy adduct 121 could be obtained in good yield. On elimination of methanol, a mixture of oroidin (1) and the alkylglycocyamidine 122 was formed. The latter could be oxidized to dispacamide A (101). Overall, oroidin (1)
was obtained from ornithine methyl ester (119) in 5 steps and 15% yield. An alternative approach to dispacamide A (101) started from dihydrooroidin (1) by treatment with bromine in DMSO. Probably, DMSO first attacks as a nucleophile, followed by elimination of dimethyl sulfide. A different synthesis of oroidin (1) was reported by Little and Webber who started from the α,β-unsaturated ketone 123 (Scheme 17).\(^5^8\) Bromination of the α-methyl group and condensation of 124 with acetylguanidine (125), followed by hydrazinolysis of the phthalimide and acetyl protecting groups furnished the natural product 43. The direct use of guanidine was not possible due to its basicity. The subsequent acylation of 43 to oroidin (1) proceeded in a surprisingly low yield.

Fresneda et al. reported a synthesis of midpacamide (98) by Fresneda et al.\(^9^9\) Fresneda et al. reported a synthesis of midpacamide starting from the amide 126, which was aminated in the α-position via azidation and Staudinger reduction. Trisyl azide proved to be more efficient than tosyl azide. An overall sequence of 7 steps resulted (Scheme 17).\(^9^9\) In a similar manner, dispacamide A (101) was obtained.

The imidazole portion is also assembled in one of the girolline syntheses. Ahond et al. used D(-)-arabinose (128) as chiral pool starting material, providing the contiguous C5-fragment present in 129 and in the natural product 104 (Scheme 18).\(^9^9\) After deprotection of 129, Appel reaction, and nucleophilic displacement of the primary chlo-

The non-biomimetic syntheses of the slagenins (136, s. A, Scheme 19) are included in this section, although these pyrrole-imidazole alkaloids are formally tricyclic. This is, because the third ring is not formed by an intramolecular cyclization of the key building block, but with participation of a hydroxy group at C-9. Nevertheless, the alternative biomimetic approach to the slagenins (136) is discussed in chapter 4.1, because the synthetic precursor used by Horne et al. also lead to the truly tricyclic hymenin (159).

The monosaccaride L-xylose (132) is the starting point of an enantioselective synthesis of the slagenins by Jiang et al. (Scheme 19).\(^1^0^0\) The sugar is transformed into the methylfuran partial structure of the slagenins. After protection of 132 and Barton–McCombie deoxygenation the ketal 133 is obtained. The benzoyloxy group is substituted by an azide moiety in three steps, followed by methanolysis of the ketal unit. After Dess–Martin oxidation the keto 134 resulted which was deprotected and condensed with urea under acidic conditions. A 1:1 mixture of the diastereomeric imidazolones 135a,b was obtained in a high yield of 75%. Surprisingly, slagenin A (136) was formed as a single diastereomer after subsequent hydrogenolysis and condensation with the trichloromethyl ketone 21. As soon as the hydroxy groups of 135a,b are methylated, both diastereomers are retained during the final two steps, leading to slagenins B and C. Overall, Jiang et al. needed 12 steps to assemble slagenin A (136) in an overall yield of about 20%. A very similar synthesis was published by
Gurjar and Bera, who start from L-arabinose and proceeds via the TBS analog of the ketone 134. Not all of the non-cyclized pyrrole-imidazole alkaloids have been synthesized, yet. In particular, mauritamide (137), tauro'acidin (138), and taurodispacamide (139) containing a taurine side chain remain open (Figure 8).

Figure 8 Taurine side chains in mauritamide (137), tauro'acidin (138), taurodispacamide (139), which have not been synthesized, yet.

4 Biomimetic Syntheses

The syntheses of the cyclized monomeric and the ‘dimeric’ pyrrole-imidazole alkaloids can be subdivided into two approaches, those which start from fully assembled C_{11}N_{4}-building blocks (biomimetic) and into all other (non-biomimetic) pathways. Knowledge of the behavior of the various precursors in biomimetic syntheses is especially valuable with regard to the challenging extension of the known pyrrole-imidazole alkaloid system by new modes of cyclization and dimerization.

4.1 Cyclized Monomers

The first biomimetic synthesis of a cyclized marine pyrrole-imidazole alkaloid was reported in a pioneering study by Foley and Büchi (Scheme 20). With the exception of a similar synthesis of rac-dibromophakellstatin (145) by Horne et al., Büchi's work has remained the only biomimetic cyclization of a linear pyrrole-imidazole alkaloid.

Scheme 20 Biomimetic cyclization of dihydrooroidin (120) to rac-dibromophakellstatin (5) and to the novel tetracycle 142 by Foley and Büchi and conversions of 5 to 143 and dibromoisophakellin (7).
rac-Dibromophakellin (5) was obtained by an oxidative cyclization of dihydrooroidin 120. Treatment of 120 with bromine in acetic acid and subsequent reaction of the precipitate with potassium tert-butoxide in 2-butanol gave racemic dibromophakellin (5). The precipitate was highly unstable and could not be fully characterized but the authors considered the formation of the spiro-imidazole 140 as a possible intermediate. This is very likely, because 140 can be quenched with methanol in an intermolecular reaction leading to methoxylation at C11 of the imidazole.102 Later, Horne found that the use of NBS in TFA followed by evaporation and quenching with Et₃N–THF (1:1) gave better yields of racemic dibromophakellin (5).

Another cyclization of the spiro-intermediate 140 was observed on treatment with DMSO or DMF in the absence of base. The tetracyclic dilactam 142 is formed diastereoselectively in a high yield of 66% in one of the, among the pyrrole-imidazole alkaloids, rare cases of nucleophilic attack by C2 of the pyrrole ring.95 Compound 142 exhibits a mode of cyclization which has not (yet) been discovered among the naturally occurring pyrrole-imidazole alkaloids. Horne et al. found that the phakellin skeleton can be converted to the thermodynamically more favored isophakellin mode. Heating of dibromophakellin (5) in the presence of potassium carbonate caused an N to C rearrangement to dibromoisophakellin (7). Earlier evidence for this isomerization was provided by the model studies with longamide (section 2.2). The oxidized compound 143, was obtained by Sharma and Magdoff–Fairchild on treatment of dibromophakellin (5) with nitric acid.34

The oxo-analog 144 of dihydrooroidin (120) behaved in the same manner (Scheme 21). Oxidation with NBS/TFA at 0 °C for 5 minutes followed by evaporation and addition of Et₃N–THF (1:1) led to the formation of rac-dibromophakellstatin (145) and the spiro adduct 147 in 45% and 40% yields, respectively. Apparently, the reaction proceeds via a cationic intermediate. Compound 147 does not undergo ring closure to dibromophakellstatin (145) under the reaction conditions.

Dibromophakellstatin (145) from the marine sponge Phakellia mauritiana and dibromophakellin (5) differ only by the presence of a guanidine function in 5 instead of a urea function in 145. Interestingly, dibromophakellstatin (145) exhibited significant inhibitory activity against human cancer cell lines [e.g., ED₅₀ 110 ngmL⁻¹ against both the KM20L2 (colon) and the SK-MEL-5 (melanoma) cell lines] whereas dibromophakellin (5) was almost inactive.7b

We wondered if it would be possible to combine the cyclization of an open-chain pyrrole-imidazole alkaloid analog with the introduction of functionality into ring C of the phakellin system. In that way it could be possible to study cycloadditions with participation of ring C, e.g. to the pyrrole-imidazole alkaloid palau’amine (12, section 1.1). Ideally, a bromine substituent could be introduced as a precursor to a double bond. We studied the cyclization of the vinyl bromide 148 (Scheme 22) which was accessible via bromination/dehydrobromination of the corresponding alkylidene hydantoin.72 Indeed, treatment of the N-protected 148 with bromine in acetic acid induced a biomimetic cyclization forming the spiro-hydantoin 149 showing germinal dibromination in ring C. The tribenzylated alkylidene hydantoin 151 led to the formation of the diastereomERICALLY pure spiro-hydantoin 152 with the nitrogen atom of ring C and the bromo substituent on opposite sides.103 Compounds 149 and 152 are the first examples with a functionalized ring C.

2-Aminoimidazoles and imidazolines such as 153 containing a free amine in the side chain not capable of intramolecular cyclizations can be methoxylated in the aliphic position by treatment with NCS in MeOH (Scheme 23).97 First, the C4–C5 double bond is dimethoxylated, presumably followed by double elimination of MeOH and addition of MeOH to a diazafulvene intermediate. If the free amine 154 is treated with TFA, MeOH is eliminated yielding a 4-vinylimidazolone in modest yield (35%). If, on the other hand, the pyrrolylcarbonyl moiety has been introduced prior to TFA exposure, the intermediate carbocation is attacked in an intramolecular cyclization generating the spiro compound 155 (60%) and the pyrroloazepinone 156 (10%).104 As in the earlier, base-free cyclization by Büchi,96 the higher nucleophilicity of the C2-position of the pyrrole ring dominates over attack of C3 at the cationic benzylic position of the imidazolone. When, debromo analogs of 154 were subjected to the cyclization conditions, a 2–3 fold yield increase in yield of azepinones was observed. The pyrroloazepinone 156 can be oxidized to the axinohydantoins, which are closely related to the pharmacologically interesting hymenialdisines.

The oxazoline 157 (Scheme 23) can be obtained from the amine 154 in three steps of which treatment with methanesulfonic acid induces the intramolecular cyclization with participation of the amide carbonyl oxygen atom.105 Formally, this sequence moves the oxygenation one car-

\[ \text{Scheme 21 Biomimetic cyclization of the imidazolone 144 to rac-dibromophakellstatin (145) by Horne et al.} \]

Synthesis 2003, No. 12, 1753–1783 © Thieme Stuttgart - New York
bon away from the imidazolone into the homoallylic position. Subsequent cleavage of the oxazoline yielded the racemic β-hydroxy imidazolone 158. Treatment with NCS in methanol gave a diastereomeric mixture of cis-fused tetrahydrofuro[2,3-d]imidazolidin-2-ones which was converted to the natural product slagenin A (136) on heating with acid. This biomimetic approach to the slagenins from Agelas nakamurai occurs in 8 steps from ornithine methyl ester in an overall yield of about 10%.

The exploration of pyrrole-imidazole alkaloid chemistry has to include studies on their interconversion and functionalization. Horne et al. investigated the conversion of the natural product hymenin (159) to the hymenialdisines.106,107 These are tricyclic natural products and they share a fused bicyclic pyrrolo[2,3-c]azepin-8-one ring system bearing either a 2-aminoimidazole, a glycocyamidine or a hydantoin appendage. Hymenialdisine (3) and axinohydantoin are the only metabolites among the pyrrole imidazole alkaloids that contain a monobromo pyrrole moiety in which the bromine atom is situated in the α-position.

Oxidation of hymenin (159) with two equivalents of bromine in an acetate buffer afforded (Z)-3-bromohymenialdisine (160) as a single isomer in multigram quantities in a high yield of 85%.108 Treatment of the same compound 159 with bromine in trifluoroacetic acid cleanly afforded 4′-bromohymenin (161), which was hydrolyzed to 3-bromo-4,5′-dihydrohymenialdisine (162, both diastereomers). On heating in MeSO₃H in the presence of catalytic amounts of HBr, regioselective protodebromination of 162 occurred at the pyrrole ring with concomitant oxidation to the alkylidene glycocyamidines (Z)-hymenialdisine (3) and its fully debrominated analog 163. In a similar manner, several hymenialdisine-type pyrrole-imidazole alkaloids can be interconverted.

Pietra et al. studied the derivatization of the cytotoxic ageastatins from Agelas dendromorpha.10b,109 After regioselective dehydration of agelastatin A (164) to the imidazolone 155 as a versatile precursor of cyclized pyrrole-imidazole alkaloids of the axinohydantoin and slagenin types. The novel cyclization to the spiro-compound 155 has not been observed in a naturally occurring pyrrole-imidazole alkaloid.
4.2 Dimeric Pyrrole-Imidazole Alkaloids

Until now, the antifouling mauritiamine (8) and, recently, $N,N'$-dimethylageliferin (177) constitute the only dimeric pyrrole-imidazole alkaloids obtained by total synthesis. The latter 177 is not exactly the natural product, but has only been isolated as the unmethylated derivative. In their biomimetic approach, Horne et al. oxidized the eastern part 43 of oroidin (1) with $N$-chlorosuccinimide/TFA, followed by heating the product mixture in MeOH/$m$-xylene while allowing MeOH to evaporate (Scheme 26).\textsuperscript{110} The major product was the alkylidene glycocyamidine (42%) representing the eastern part of dispacamide A (101). The immediate synthetic precursor 172 of the dimeric rac-mauritiamine (8) was obtained in a yield of 23%, while erythro-girolline [170, diastereomer of the natural product girolline (104)] was formed as the third product in 12% yield.

Scheme 26 NCS-oxidation of the vinylimidazole 43 by Horne et al.,\textsuperscript{110} partially leading to formation of the dimeric precursor 172 of the pyrrole-imidazole alkaloid rac-mauritiamine (8).

Several intermediates may be formed initially. The 1,2-adduct 168 would lead to the girolline isomer 170, while the trifluoroacetylated enol form 169, generated from the 1,4-adduct, could be the precursor of the alkylidene glycocyamidine 171. With regard to the dimerization, several mechanisms are possible. One proposal was made by Fusetani et al. when mauritiamine was first isolated from Agelas mauritiana, initial addition of hypohalogenite to
the imidazole 4,5-double bond of one partner would be followed by the attack of the nucleophilic 4-position of the other and quenching of the cation by water. Elimination of HX and dehydration would lead to the dimer 8. In Horne’s experiment, the enol intermediate 171 might undergo a second addition of Cl⁺ and trifluoroacetate making the quaternary position susceptible to nucleophilic attack by a second aminomidazole.

The first Diels–Alder dimerization of 5-vinylimidazoles was achieved by Ohta et al. in 2002. In the key reaction, the N-methylated 5-vinyl-2-phenylsulfanylimidazole 173 was diastereoselectively transformed to the bicyclic 174 simply by refluxing in xylene for 30 hours (55%, Scheme 27). The diastereomer 174 exhibits the relative stereochemistry of ageliferin (10), which was first isolated by Kobayashi et al. as the parent compound representing this mode of cyclization. Starting from the monomer 173, Ohta et al. obtained the new derivative 15,15’-dimethylageliferin (177) in 10 steps and an overall yield of 1.3%. The phenylsulfanyl group appears to be necessary for the dimerization, because later it is removed by desulfurization with NiCl₂·6H₂O/NaBH₄ in methanol (formation of nickel boride and hydrogen), followed azidation of nickel boride and hydrogen), 112 followed azidation of the free imidazole 2-position.

Dilley and Romo found an entry into the spirocyclic palau’amine group of pyrrole-imidazole alkaloids, which is based on a spiro ring contraction of one of the Diels–Alder products 180 and 181 (Scheme 28). Reaction of the vinylimidazolone 179 with the α,β-unsaturated pyrroglutamic acid derived lactam 178 needed, prolonged reaction times (4 d) and elevated temperatures (95 °C).

Both 180 and 181 are endo products with 181 being the predominant regiosomer. Three new stereogenic centers are formed during the reaction. According to a proposal on the biosynthesis of palau’amine (12) by Scheuer et al., the Diels–Alder cycloaddition of a hitherto unknown dehydrophakellin (184) and the eastern half 43 of oroidin (1) would be the initial step. The cycloaddition would be immediately followed by attack of Cl⁺ and spiro rearrangement (Scheme 29) via an intermediate iminium ion reacting with nucleophilic water.

Indeed, it is possible to achieve such a ring contraction on treatment of the major Diels–Alder product 181 with dimethylidioxirane and reductive work-up. Reaction of the resulting carbinal urea 182 with NCS in the presence of cyclohexene gave the spirocyclic system 183 in high yield. Cyclohexene is added, as an ‘alkene buffer’, to prevent otherwise substantial aromatization of the starting material.

5 Non-Biomimetic Approaches

5.1 Completed Syntheses

Syntheses of cyclized pyrrole-imidazole alkaloids, which do not follow the presumable biosynthetic pathway have been developed for several hymenialdisine-type alkaloids and for the agelastatins.

Several syntheses of hymenialdisin-type pyrrole-imidazole alkaloids by Horne et al. first assemble the pyrroloazepinone part and then introduce 2-aminoimidazole or imidazolone portions as nucleophiles. Although marine natural products consisting solely of the pyrroloazepinone core have been isolated, it is unlikely that they serve as biogenetic precursors. Therefore, the syntheses discussed in the following are considered ‘non-biomimetic’.

Scheme 27 First synthesis of an ageliferin analog via biomimetic [4+2]-cycloaddition of two vinylimidazole units by Ohta et al.
the analogous reaction with 2-imidazolone (186), which is prone to self-dimerization under acidic conditions is only 37%, but allows a mixture of stereoisomeric 3-bromo-axinohydantoins (187) to be synthesized after oxidation.\(^{104}\)

The electron-rich polarized double bond of 64 can also be converted to the O-methylated bromohydrin 188, which opens the possibility to conveniently access those hymenialdisine-type pyrrole-imidazole alkaloids with additional unsaturation in the 7-ring.\(^{107}\) Stevensine (190)\(^{9f}\) was obtained in two steps from 188 via reaction with 2-aminimidazole and elimination of HBr. By switching from MeSO\(_3\)H to TFA, the regioselectivity of the attack of 2-aminimidazole can be directed to the kinetically favored attack of the terminal amino group-forming compound 191 which has not been isolated as a natural product (Scheme 30).

![Scheme 28](image)

**Scheme 28** *Spiro contraction of the cycloaddition product 182 mimicking Scheuer’s proposal on the biosynthesis of palau’amine.*

![Scheme 29](image)

**Scheme 29** *Scheuer’s proposal on the biosynthesis of the spirocyclic palau’amine (12) via rearrangement of a Diels–Alder cycloaduct.*

![Scheme 30](image)

**Scheme 30** *Synthetic versatility of the olefin 64 leading to various pyrrole-imidazole alkaloids of the hymenialdisine type (Horne et al.).*
Alternatively, Annoura and Tatsuoka assembled the alkyldiene glycocamidine portion of (Z)-hymenialdisine stepwise (Scheme 31). The cyclization of the acid formed on reaction of pyrrole-2-carboxylic acid (192) with β-alanine regioselectively forms the pyrroloazepinedione 193 under thermodynamic control. Somewhat surprisingly, the preceding bromination occurs at C2 of 193 while in other cases C3 is clearly preferred. Wittig–Horner olefination was followed by α-oxidation via treatment of the enolate with 2-benzenesulfonyl-3-phenyloxaziridine, leading to the β,γ-unsaturated ester 194 after mesylation. For completion of the alkyldiene glycocamidine ring, free guanidine in DMF was used. Deprotection delivers stereochemically pure (Z)-hymenialdisine (3) in 9 steps and 3% overall yield.

![Scheme 31](attachment:scheme31.png)

Scheme 31 Synthesis of (Z)-hymenialdisine (3) by Annoura and Tatsuoka.

Among the pyrrole-imidazole alkaloids, agelastatin A (164, Scheme 25) represents an intriguing challenge due to its beautiful tetracyclic structure and its cytotoxic and insecticidal activities.

Weinreb et al. developed a diastereoselective total synthesis of agelastatin A (164) starting with the hetero-Diels–Alder cycloaddition of cyclopentadiene with the dienophile N-sulfanyl methyl carbamate (195, Scheme 32). Ring C of the product 203 completely stems from cyclopentadiene. After cleavage of the N–S bond of 196 by treatment with PhMgBr, a [2,3]-sigmatropic rearrangement of 197 leads to the oxygenation of the cyclopentene in the position later to become C11. After formation of the bicyclic carbamate 199 and Boc protection, refluxing with the new diSES sulfonylimide (200, SES = β-trimethylsilylthanesulfonyl) led to allylic amination via a second [2,3]-sigmatropic process (Sharpless–Kresze amination) affording 202. The N–S bond was reduced providing the intermediate 203.

The pyrrole ring was introduced into 203 via acylation with 204, followed by deprotection. Oxidation of the AC partial structure 206 of agelastatin A (164) set the stage for an intramolecular, diastereoselective Michael addition of the pyrrole nitrogen forming ring B (209). The synthesis finishes with the replacement of the TMS protecting group by bromine with NBS and the assembly of ring D with the help of methyl isocyanate. The synthesis requires 14 steps and provided racemic agelastatin A (164) in a yield of 7%.

Recently, Feldman and Saunders published the first enantioselective synthesis of agelastatin A (164). While the strategy introducing rings A, B, and D resembles that of Weinreb et al., Feldman uses a carbene insertion to build up ring C (Scheme 34). The enantioselectivity of the synthesis is ensured, by starting from the enantiomerically pure epoxy alkyne 211. Compound 211 was transformed into the alkynyl stannane 214 in three steps, which was treated with Stang’s reagent forming an alkynyliodonium triflate. Two reactions with the nucleophile sodium toluene sulfinate took place leading to the formation of the desired cyclopentene 216 via generation of the intermediates.
ate carbene 215 and insertion (34%), via nucleophilic substitution, of a sulfinated open-chain alkyne (41%). Diastereoselective, conjugate addition of \(\alpha\)-nitrobenzylamine to the \(\alpha,\beta\)-unsaturated sulfone 216 and acylation with pyrrole-2-carboxylic acid chloride (217) led to the intermediate 218 (Scheme 34). The oxazolidinone was chemoselectively decarbonylated in the presence of the urea moiety with Cs$_2$CO$_3$. Swern oxidation of 219 apparently passed through an unobserved cyclopentenone intermediate. After photochemical deprotection and bromination, (–)-agelastatin A (164) was obtained in 13 steps and 4% overall yield. The enantioselective total synthesis by Feldman confirmed the absolute stereochemistry of agelastatin A originally put forward by Pietra.

5.2 Under Construction

There are several still incomplete synthetic approaches to the pyrrole-imidazole alkaloids. Overman et al. report the syntheses of the molecules 221 and 222 designed as putative synthetic intermediates of the hexacyclic pyrrole-imidazole alkaloids of the styloguanidine (13) or palau’amine (12)/konbu’acidin (220) groups (Figure 9).\textsuperscript{122}

\begin{align*}
\text{Scheme 33} & \quad \text{Endgame to racemic agelastatin A (164) by Weinreb et al.} \textsuperscript{117} \\
\text{Scheme 34} & \quad \text{Enantioselective synthesis of (–)-agelastatin A (164) by Feldman and Saunders.} \textsuperscript{120}
\end{align*}
Scheme 35 outlines the approach to 221, which features an intramolecular 1,3-dipolar cycloaddition of the azomethine imine in 228 to a dehydro-amino acid moiety. The assembly of the precursor 227 takes eight steps starting from the allyl acrylate 223 and the sodium salt of glycine (224). Desilylation and condensation of the resulting α-ketone with thiosemicarbazide generates the azomethine imine 228 which diastereoselectively undergoes cycloaddition, followed by intramolecular acylation of the remaining amino group of 229. The product 230 contains three new stereogenic centers. Ester hydrolysis and reaction with phosphoryl isothiocyanate provided bis(thiohydantoin) 231. The exact mechanism of the concomitant reductive cleavage of the N–N bond has not been elucidated, yet. The DCEF analog 221 of konbu’acidin (220) has been assembled in 14 steps and about 18% overall yield starting from 223. Compound 222 (Figure 9) which contains the pyrrole section, but still lacks ring B, has been obtained in a similar manner.122b

The formation of ring B of the ABCD system of the phakellin- and isophakellin-type pyrrole-imidazole alkaloids has been addressed by Romo et al.123 and by us.124 Based on the facile cyclization of open-chain precursors to the AB system of the longamides and hanishins, we pursued the expansion of the strategy by the introduction of ring C, leading to unsymmetrical dipyrrolopyrazinones. Condensation of the pyrrolyltrichloromethyl ketone 83 with the ambident nucleophile L-prolinol 232 in acetonitrile gave the tertiary amide 233 as a major product without the need for any protecting group (Scheme 36). The only byproduct 234 resulted from additional acylation of the primary hydroxyl group and was recovered on conversion to 233 by saponification. Oxidation of the primary alcohol 233 was conveniently achieved employing IBX,125 immediately leading to an N,O-hemiacetal which was dehydrated to the unsymmetrically saturated ABC dipyrrolopyrazinone 235. On reacting 235 with MCPBA in the presence of water a diol was obtained which could be diastereoselectively converted to the monomethylated derivative 237 by refluxing in MeOH, probably via an intermediate acyliminium ion. In the absence of water, the
\( \alpha,\beta \)-unsaturated \( \alpha \)-aminoamide 236 was obtained. Compound 237 is a promising precursor of the phakellin-type pyrrole-imidazole alkaloids.

Crystal structure analysis of the diastereomeric Mosher esters of the \( N,O \)-acetal, formed on oxidation of 233, provided insight into their conformation in the solid state (Figure 10).\(^{126} \) While the carbinol proton and the trifluoromethyl group of the \( (R) \)-ester 239 were close to the expected w-shaped arrangement, the \( (S) \)-diastereomer 238 prefers a conformation with the carbinol proton and the trifluoromethyl group pointing to opposite sides. As a consequence, the magnetic shielding of the pyrrole ring would be very similar for both esters, while the pyrroline ring would experience different surroundings. In the \( (R) \)-ester 239, the phenyl ring is much closer to the methylene groups than in the \( (S) \)-ester 238. The differences in the NMR-chemical shifts correspond quite well with the observations in the crystal structure. Caution is advised with regard to Mosher stereochanical analysis on heterocycles.

Recently, Goetz et al. isolated the natural product ugi-bohlin (240) which possesses an open D-ring, compared with the isophakellin-type pyrrole-imidazole alkaloids (Scheme 37).\(^{13d} \) Earlier, Sharma et al. obtained the ABC-system 241 on acidic hydrolysis of dibromophakellin (5).\(^{34} \)

Given the 100-fold higher cytotoxicity of dibromophakellstatin (145, Scheme 21) over dibromophakellin (5) we wondered if a urea analog of 242 could be prepared.\(^{127} \) The behaviour of the olefin 235 under epoxidizing conditions led us to expect that aziridination would allow to introduce a nitrogen substituent at C10. Under Pellacani–Tardella aziridination conditions (TsONHCO\(_2\)Et)\(^{128} \), the olefin 235 was transformed to a vinyl carbamate which could be converted further to the urea analog 242 of the Sharma compound 241 by treatment with ammonia in a sealed tube (Scheme 37).

Romo et al. reported the diastereoselective functionalization of the diketopiperazine 243 of L-proline as a basis for an asymmetric desymmetrization strategy towards phakellin and phakellstatin (Scheme 38). They demonstrated that electrophilic additions to proline-derived diketopiperazine enolates with both alkyl halides and acyl halides proceed with high facial selectivity. Azidation of cyclo(Pro,Pro) (243) occurred smoothly by treatment with KHMDS followed by trisyl azide. Reduction and guanidinylation provided the model compound 246.

Figure 10 Crystal structures of the \( N,O \)-acetal Mosher esters 238 and 239.\(^{126} \)
While the dimeric pyrrole-imidazole alkaloids of the palau’amine (12) and styloguanidine (13) type possess one cyclized and one non-cyclized monomer unit, the pyrrole portions of the dimers of sceptrin (9), ageliferin (10), and axinellamine (11, a. A) do not participate in any cyclization. Carreira et al. reported a model synthesis of the fully substituted cyclopentane moiety of axinellamine A (11, Figure 11).129

The first steps of the sequence lead to the substituted cyclopentane moiety of axinellamine A (Figure 11).129

The six modes of cyclization of the pyrrole-imidazole alkaloid building block.

6 Cyclization Map

The six modes of cyclization of the pyrrole-imidazole alkaloid core structures are represented by the tricycles cycloooridin (2) and hymenialdisine (3), and by the tetracyclic natural products agelastatin B (4), dibromophakellin (5), dibromoagelaspongin (6), and dibromoophakellin (7). In order to estimate the biogenetic potential of the core building block of the pyrrole-imida-
The relative energy of the most favored diastereomer of every tetracycle is given. The cyclization modes ‘4–12, 7–11’ (isophakellin), ‘1–12, 7–11’ (phakellin), ‘1–9, 8–12’ (agelastatin), and ‘1–12, 7–12’ (agelaspongin) have already been found in marine sponges. The skeleton represented by isophakellin (7) is the thermodynamically most stable tetracycle of all possible modes of cyclization. The MM2 calculation is in accordance with what is observed experimentally, the greater stability of the isophakellin over the phakellin mode. For the agelastatin mode, four of the eight diastereomers show very similar enthalpies of formation. Among them Pietra’s diastereomer 166 (Scheme 25) can be found. Agelaspongin (6) is expected to be the least stable of the naturally occurring, tetracyclic pyrrole-imidazole alkaloids.

Figure 12 gives the energetically most favored diastereomers of all tetracycles based on the basic structure 257. If the α-position of the pyrrole ring is involved, the 2-pyrrolidone-containing analogs (cf. cpds. 257-4, -5, -6, -9) are shown. Agelaspongin (6) is not among them while the skeletons of isophakellin (257-1), phakellin (257-7), and epi-agelastatin (257-8) are listed. As expected, the unknown mode of isoagelastatin (257-2) is included. There are intriguing new pyrrole-imidazole alkaloids to be expected, including bridged molecules such as 257-4, 257-5, or 257-11. It can be hypothesized that the increasing knowlegde on the synthesis and reactivity of the pyrro-

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* Newly formed bonds are given in lines and columns, according to the position numbers of 257. Relative energies (kcal mol⁻¹) are given. Black areas indicate very stable modes of cyclization.

Table 3 Cyclization Map of the Tetracyclic Pyrrole-Imidazole Alkaloids*

Figure 12 Existing and hypothetical, tetracyclic pyrrole-imidazole alkaloids ordered by decreasing thermodynamic stability. The most strained naturally occurring pyrrole-imidazole alkaloid, agelaspongin (6), is not even on the board. See also Table 3.
imidazole alkaloids will lead to novel modes of cyclization in advance of their isolation from natural sources. Examples are the compounds 142 (Scheme 20) and 155 (Scheme 23) obtained by Büchi and Horne, respectively. On an even more fundamental level, new modes of cyclization are of interest with respect to the lysine-derived skeleton of the natural product 15 potentially underlying oroidin (1). Rearrangement of one of our synthetic intermediates led us to the novel tricyclic structure 260. The formation of 260 can be achieved on treatment of the ACD tricycle 258 with strong base. It is likely that an aziridine intermediate plays a role, which ring-opens in two different ways, leading to the functionalized ACD vinyl bromide 259 and to the pyrrolopyrazinone 260.

![Diagram](image)

Scheme 40  Ring-opening of the spiro-compound 258 via an intermediate aziridine on treatment with strong base.

7 Conclusion

As it is outlined in Table 1, there are several pyrrole-imidazole alkaloid skeletons, which have not yet been assembled, at all. Among the cyclized monomers, agelaspongin (6) remains a challenge. Here, it is necessary to achieve regioselective cyclization to the 6-ring and to avoid the apparently preferred 5-ring as it is observed in the phakellins (5) and isophakellins (7). Perhaps, rearrangement of the phakellin skeleton is possible as well.

The synthesis of ‘dimeric’ pyrrole-imidazole alkaloids formed by intermolecular reaction of two of the key building blocks has only in one case, mauritiamine (8), been achieved. In addition, the dimeric ageliferin skeleton has been assembled, but the methyl groups present in Ohta’s molecule 177 (Scheme 27) will be difficult to remove. Many others, in particular the cyclobutane sceptrin (9), still wait for their first total synthesis. Neither palau’amine (12) nor styloguanidine (13) have been synthesized, either.

Only three enantioselective total syntheses, agelastatin A (164), slagenin A (136), and very recently ent-dibromomopakellstatin (ent-145) exist. Furthermore, the absence of any identified radical process in the total syntheses of the pyrrole-imidazole alkaloids is apparent. The utilization of non-covalent interactions, e.g. to orientate two building blocks for proper dimerization, is completely unexplored.

A question that has not been touched to date concerns the isolation of enzymes or their genes from the readily available Agelas sponges. The optically active cyclobutane sceptrin (9) is formed by formal [2+2]-cycloaddition from two achiral dibromooroidin precursors. Ageliferin (10) is optically active as well, but no Diels–Alderase has been isolated from any of the sponges. The recent intense efforts on the synthesis of the pyrrole-imidazole alkaloids will lead to progress in the chemical biology of marine sponges. There is much more to discover.

Notes Added to the Proof

Very recently, Poullennec and Romo have completed the first chiral pool total synthesis of (+)-dibromophakellstatin (ent-145, Scheme 41), 133 Based on the results of their study (Scheme 38), desymmetrization of cyclo(Pro,Pro) (243) by mono-α-acylation was followed by aromatization of the remaining, α-unsubstituted pyrroolidine ring. The tricyclus 261 was chemoselectively reduced and epimerized. Three more steps led to compound 262 which, after ammonolysis, underwent an intramolecular Mitsunobu inversion installing the first nitrogen of ring D of (+)-dibromophakellstatin (ent-145). A tetracyclic intermediate is formed which is cleaved on treatment with ammonia. The second nitrogen at the quaternary center was elegantly introduced via Hofmann rearrangement of the amide 263 employing the hypervalent iodine reagent PhI(OCCF3)3. 134 Reduction of the N-O bond with TiCl3 set the stage for the closure to ring D via urea formation. Dibromination completed the synthesis, which takes 15 steps starting from 243 in an overall yield of about 2%.

![Diagram](image)

Scheme 41  Chiral pool synthesis of (+)-dibromophakellstatin (ent-145) by Poullennec and Romo. 133

Synthesis 2003, No. 12, 1753–1783 © Thieme Stuttgart · New York
Additionally Austin et al. reported a stereoregulated route via a transient N–O-linked Pauson–Khand Strategy for the synthesis of the deschloro cyclopentyl core of palau’amine (12) and styloguanidine (13).135

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