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Marine Natural Products

The Pursuit of Palau’amine

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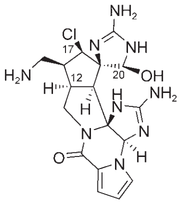
Since its discovery in 1993, the marine natural product palau’amine has intrigued natural product chemists. Its exotic molecular architecture and purported bioactivity made it an ideal target for synthesis. However, as the years went by and related marine alkaloids were isolated, a skeptical eye was cast on the structure of palau’amine; recently these suspicions were confirmed and the structure of palau’amine revised. This Minireview gives a careful overview of the structural revision and its ramifications to both its biogenesis and total synthesis.

1. Introduction

The isolation, synthesis, and biological evaluation of marine natural products often lead to grand and lasting lessons for science.[1] Although too numerous to list here, prime examples include brevetoxin,[2] palytoxin,[3] ecteinascidin,[4] and salinosporamide.[5] In 1981, Faulkner, Clardy, and co-workers revealed the structure of the first dimeric pyrrole–imidazole alkaloid, sceptrin (**2**, Scheme 2),[6] thus opening a new chapter in marine natural products chemistry. Perhaps because it was published back-to-back with the isolation of brevetoxin B,[2a] this unique cyclobutane-containing alkaloid was virtually ignored by chemists for more than two decades. In 1993, Scheuer and co-workers reported the structure of palau’amine (**1**, Scheme 1),[7] an architecturally interesting alkaloid from the same family. Since then, the pyrrole–imidazole alkaloid family (Scheme 2) has been steadily growing, with the isolation of many analogues of sceptrin (**3**–**7**),[8] the ageliferins (**8**–**10**),[9] the nagelamides (**11**–**13**),[10] the axinellamines (**14**–**17**),[11] massadine (**18**),[12] the styloguanidines (**19**–**22**),[13] the konbu’acidins (**23** and **24**),[14] brominated palau’amines (**26** and **27**),[7b] and the stunning tetrameric stylissadines (**28** and **29**).[15] Recently, the structure of palau’amine was called into question and was revised based on a combination of advanced spectroscopic analysis, computation, and even biosynthetic considerations.[15b,16]

2. Isolation of the Styloguanidines and Structural Revision of the Palau’amines

The story of structural revision begins with one of the defining features of the structure originally reported for palau’amine: the relative configuration of the two bridgehead carbon atoms of the central 3-azabicyclo[3.3.0]octane moiety. The coupling constant of the two protons H11 and H12 was the primary argument used to assign the junction as *cis* fused.[7] The spirolactone leucodrine (**30**, Scheme 3)[17] was used as a comparison: “The bicyclo[3.3.0]azaoctane must be *cis* fused, which is supported by the coupling constant (14.1 Hz) between H11 and H12. Although this seems large for a *cis*-fused bicyclo[3.3.0] system, comparable values are observed in similarly rigid spiroannulated five-membered rings.” The coupling constants for **30** were assigned as 8.3 Hz for H8/H9, and 12.4 and 7.8 Hz for H4/H3 + H3′. Since H8 and H9 are *trans* fused, the large coupling constant for H4/H3 was assigned as having a *cis* relationship. As **30** bears only a superficial structural resemblance to palau’amine (**1**), and a difference of almost 2 Hz in the relevant coupling constant, the analogy between the two structures is tenuous. Nevertheless, the *cis*-fused structure was



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Scheme 1. The previously accepted structure of palau’amine, as proposed in 1993 by Scheuer and co-workers.[7a]

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universally accepted for well over a decade, and was only recently called into question after three separate reports on two new palau'amine congeners: tetrabromostyloguanidine[16a] (**22**, also carteramine A[16b]) and konbu'acidin B (**24**).[15b] In these studies, the configuration at C17 (with chlorine substitution) and at C12 was inverted, which leads to a *trans*-fused 3-azabicyclo[3.3.0]octane moiety compared to the original structure of palau'amine (**1**). To discuss the differences between the old and the new configurations of the palau'amines, tetrabromostyloguanidine (**22**) will be used as a model in the following discussion.

The advent of powerful computational techniques in recent years complements NMR spectroscopy in the ability to unambiguously assign structures of compounds that fail to crystallize. Many of these techniques[18] were employed in the structural assignment of tetrabromostyloguanidine (**22**).[16a] Perhaps one reason that the incorrect structure of palau'amine persisted for so long is the intuitive image of a *cis*-fused 5,5-bicycle as being thermodynamically more stable. Indeed, calculations have shown that the *cis*-fused system of **22** is energetically favored by approximately 27.3 kJ mol^{-1} over the *trans*-fused system.[19] *Trans*-fused annulated five-membered rings are quite rare.[20] Figure 1 shows the distance against the dihedral angle between the two bridgehead protons for the crystal structures of bicyclo[3.3.0]octane (top) and 3-azabicyclo[3.3.0]octane (bottom) that have been reported.[21] Only 10 out of over 2000 bicyclo[3.3.0]octane structure fragments have a *trans* junction. Only 1 out of 121 crystal structures of the 3-azabicyclo[3.3.0]octane moieties is *trans* fused; for this molecule, (1*R**,4*S**,8*R**,11*S**)-3-(*p*-nitrobenzenesulfonyl)-3-azatricyclo[6.2.1.0^{4,11}]undecan-9-one (Figure 2), no explicit assignment of the ^{1}H NMR coupling constants was reported.[22]

As regards the coupling constant discrepancy, both relative configurations of **22** were computationally optimized.[16a] The coupling constants between H11 and H12 were calculated for both optimized structures of **22** by rotating the dihedral angle (H11-C11-C12-H12) in 5° increments from −180° to +180° according to the empirical equation published by Hassnot, de Leeuw, and Altona[23] (Figure 3). The two maxima in this graph clearly indicate a dihedral angle of 180°, which is given by a *trans*-fused orientation of the 3-azabicyclo[3.3.0]octane system.[24] In addition, these calculations show a difference of 1.5 Hz between the *trans* and the *cis* coupling constants. The calculated coupling constant of 13.1 Hz is still 1.3 Hz smaller than the experimental value. Since the experimentally obtained H11/H12-coupling constants of the palau'amine congeners are between 14.1 and 14.5 Hz (almost the maximum possible coupling constant in organic systems), it is very unlikely that this coupling constant arises from a *cis* arrangement. Unfortunately, the number of coupling constants for *cis*- or *trans*-fused bicyclo[3.3.0]octanes that have been reported is very limited because the protons were often not assigned or the coupling constants could not be extracted from the multiplets.

To assign the relative configuration of **22**, Grube and Köck[16a] used interproton distances derived from ROESY spectra. To determine if a qualitative NOE or ROE analysis is

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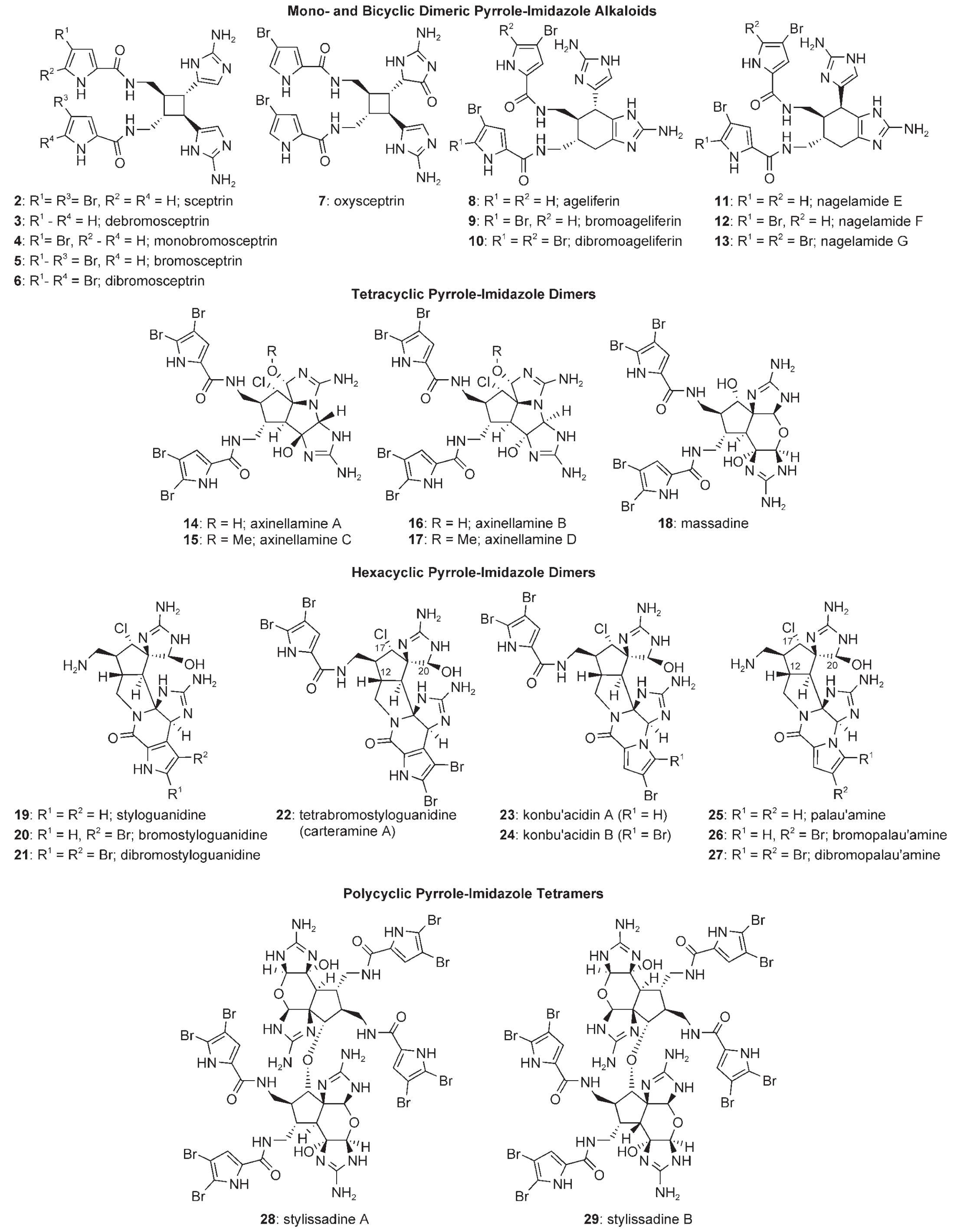


Mono- and Bicyclic Dimeric Pyrrole-Imidazole Alkaloids

2: $R^1 = R^3 = Br$, $R^2 = R^4 = H$; sceptrin
3: $R^1 - R^4 = H$; debromosceptrin
4: $R^1 = Br$, $R^2 - R^4 = H$; monobromosceptrin
5: $R^1 - R^3 = Br$, $R^4 = H$; bromosceptrin
6: $R^1 - R^4 = Br$; dibromosceptrin
7: oxysceptrin
8: $R^1 = R^2 = H$; ageliferin
9: $R^1 = Br$, $R^2 = H$; bromoageliferin
10: $R^1 = R^2 = Br$; dibromoageliferin
11: $R^1 = R^2 = H$; nagelamide E
12: $R^1 = Br$, $R^2 = H$; nagelamide F
13: $R^1 = R^2 = Br$; nagelamide G

Tetracyclic Pyrrole-Imidazole Dimers

14: R = H; axinellamine A
15: R = Me; axinellamine C
16: R = H; axinellamine B
17: R = Me; axinellamine D
18: massadine

Hexacyclic Pyrrole-Imidazole Dimers

19: $R^1 = R^2 = H$; styloguanidine
20: $R^1 = H$, $R^2 = Br$; bromostyloguanidine
21: $R^1 = R^2 = Br$; dibromostyloguanidine
22: tetrabromostyloguanidine (carteramine A)
23: konbu'acidin A ($R^1 = H$)
24: konbu'acidin B ($R^1 = Br$)
25: $R^1 = R^2 = H$; palau'amine
26: $R^1 = H$, $R^2 = Br$; bromopalau'amine
27: $R^1 = R^2 = Br$; dibromopalau'amine

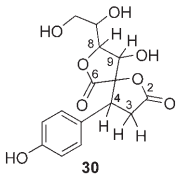
Polycyclic Pyrrole-Imidazole Tetramers

28: stylissadine A
29: stylissadine B

Scheme 2. Structures of dimeric (**2**–**27**) and tetrameric (**28** and **29**) pyrrole–imidazole alkaloids.

sufficient, the theoretical interproton distances for the cyclopentane ring of tetrabromostyloguanidine (**22**) in both relative configurations must be compared. To avoid potential complications,[25] only the 1,3-interactions (H11/H17, H11/H18, and H12/H17) and not the 1,2-interactions (H11/H12, H12/H18, and H17/H18) were considered. All six distances for both relative configurations are between 2.20 and 4.00 Å and can, in principle, be observed in both NOESY and ROESY experiments. Therefore, a quantitative approach was required to unambiguously distinguish between the two or more diastereomers. In Figure 4, the 1,3-interproton distances for the central cyclopentane ring of both relative configurations in comparison to the experimental values are shown. These results clearly support the revised structure.

When considering interproton distances, one must evaluate the differing conformations of the cyclopentane ring for the two relative configurations of **22**. In other words, in the context of a complex molecule, it would be too simplistic to assume that changing both centers in a 1,3 relationship would not change their distances. To be sure, the cyclopentane ring



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Scheme 3. Leucodrine (**30**) which served as a reference for the coupling constants between the two bridgehead protons H11 and H12 in the original palau'amine study.[7a] The coupling constants reported for leucodrine are 8.3 Hz for H8/H9, and 12.4 and 7.8 Hz for H4/H3 + H3'.

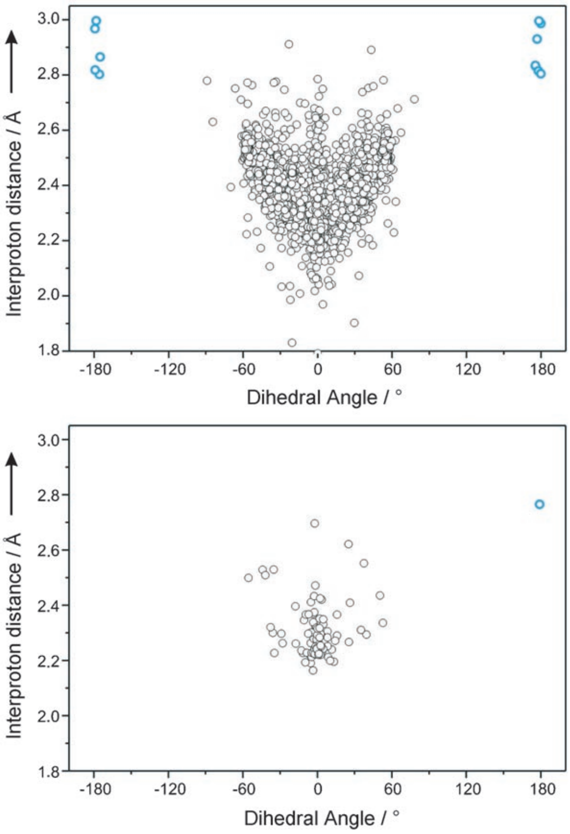


Figure 1. Parameters for the crystal structures of bicyclo[3.3.0]octanes (top) and 3-azabicyclo[3.3.0]octanes (bottom).[21] The graphs show the distance (Å) versus the dihedral angle between the two bridgehead protons (H11/H12 in the case of tetrabromostyloguanidine (**22**)).

in the new relative configuration adopts an envelope conformation whereas in the old relative configuration is twisted (Figure 5). This explains the differences in the expected against the actual values of the 1,3 distances (Table 1). For the pair H12/H17 in which the configurations of both centers are changed, no difference in the interproton distance would be expected between the two relative configurations only if the conformation of the central cyclopentane ring remains the same. In reality the difference between the two relative configurations is about 1.70 Å.

Of the studies dealing with this issue,[15b,16] only that of tetrabromostyloguanidine (**22**)[16a] presented a quantitative analysis of the ROESY spectra. Using the interproton distances in unison with computation, the results clearly confirm the new relative configuration.

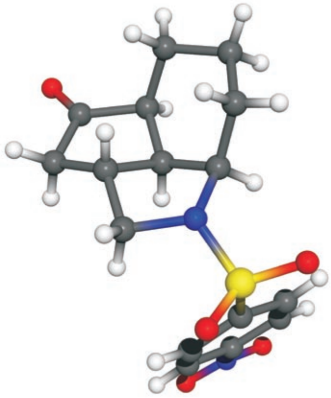


Figure 2. Graphical representation of (1*R**,4*S**,8*R**,11*S**)-3-(*p*-nitrobenzenesulfonyl)-3-azatricyclo[6.2.1.0^{4,11}]undecan-9-one, the only compound in the Cambridge Structural Database (CSD) with a *trans*-fused 3-azabicyclo[3.3.0]octane substructure.

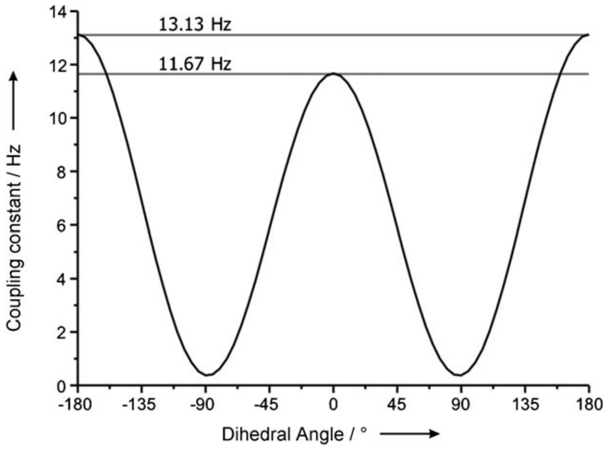


Figure 3. Dependence of the H11/H12-coupling constant on the dihedral angle of tetrabromostyloguanidine (**22**). The dihedral angle (H11-C11-C12-H12) was rotated in 5° increments from −180° to +180° and the subsequent coupling constant was calculated according to the empirical equation from Ref. [23].

Finally, there has been some disagreement with regards to the stereochemistry of the C20-hemiaminal center. The relative configuration of this center in the palau'amine congeners differs within the first four reports.[7,13,14] In the original studies of palau'amine (**1**, 1993), styloguanidine (**19**, 1995), and konbu'acidin A (**23**, 1997) the configuration at C20 was assigned as *R* (reference center C6 was *R* configured). In the second study on palau'amine (**1**, 1998) the configuration at C20 was inverted. The justification for this curious inversion of configuration was solely based on a small NOE effects.[26] The use of quantitative NMR spectroscopy and computation clearly indicates that the first assignment of C20 was correct.[16a]

In summary, a reexamination of the palau'amine structure prompted by the isolation of tetrabromostyloguanidine (**22**)

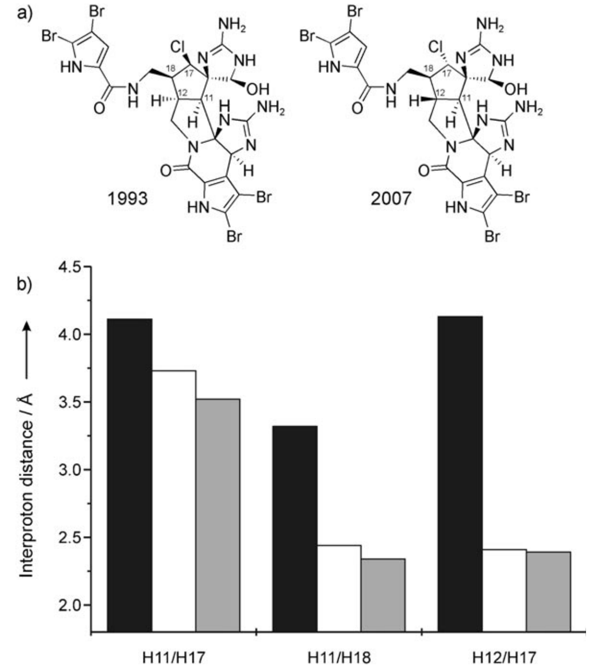


Figure 4. Comparison of the 1,3-interproton distances of tetrabromostyloguanidine (**22**) for both relative configurations (palau'amine structures from 1993 and 2007); black bars: the original proposed configuration; white bars: the revised configuration; gray bars: the experimental values.

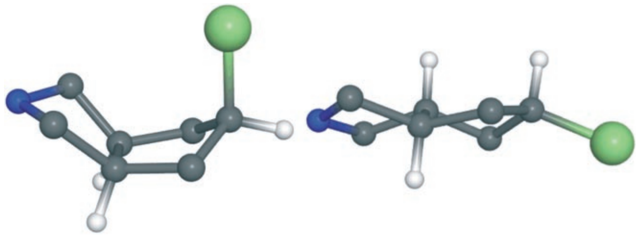


Figure 5. Structural conformations of the central 3-azabicyclo-[3.3.0]undecane moiety in the original palau'amine configuration (left) and revised configuration (right).

Table 1: Comparison of the possible 1,3-interproton distances [Å] for tetrabromostyloguanidine (**22**).

Proton pair	**22** (relative configuration of palau'amine from 1993)	**22**	Expectation without conformational change
H11/H17	4.11	3.73	change expected
H11/H18	3.32	2.44	no change expected
H12/H17	4.13	2.41	no change expected

has led to revised structures for all of the palau'amine congeners (**19**–**27**).[16a] Two other research groups have also arrived at similar conclusions.[15b,16b] Thus, the structural assignment from 1993 with the relative configuration of 6*R*, 10*S*, 11*R*, 12*S*, 16*S*, 17*S*, 18*R*, 20*R* can now be stated as 6*R*, 10*S*, 11*R*, 12*R*, 16*S*, 17*R*, 18*R*, 20*R*.[27] It should be noted that the absolute configurations of many of the complex pyrrole–imidazole alkaloids are not known. Fusetani and co-workers used CD spectroscopy to tentatively assign the absolute configuration of massadine (**18**),[12] and the absolute configurations of sceptrin (**2**) and ageliferin (**8**), and these configurations have already been confirmed (the former by X-ray crystallography[6] and the latter by synthesis[28]).

3. Biosynthesis of the Pyrrole–Imidazole Alkaloids

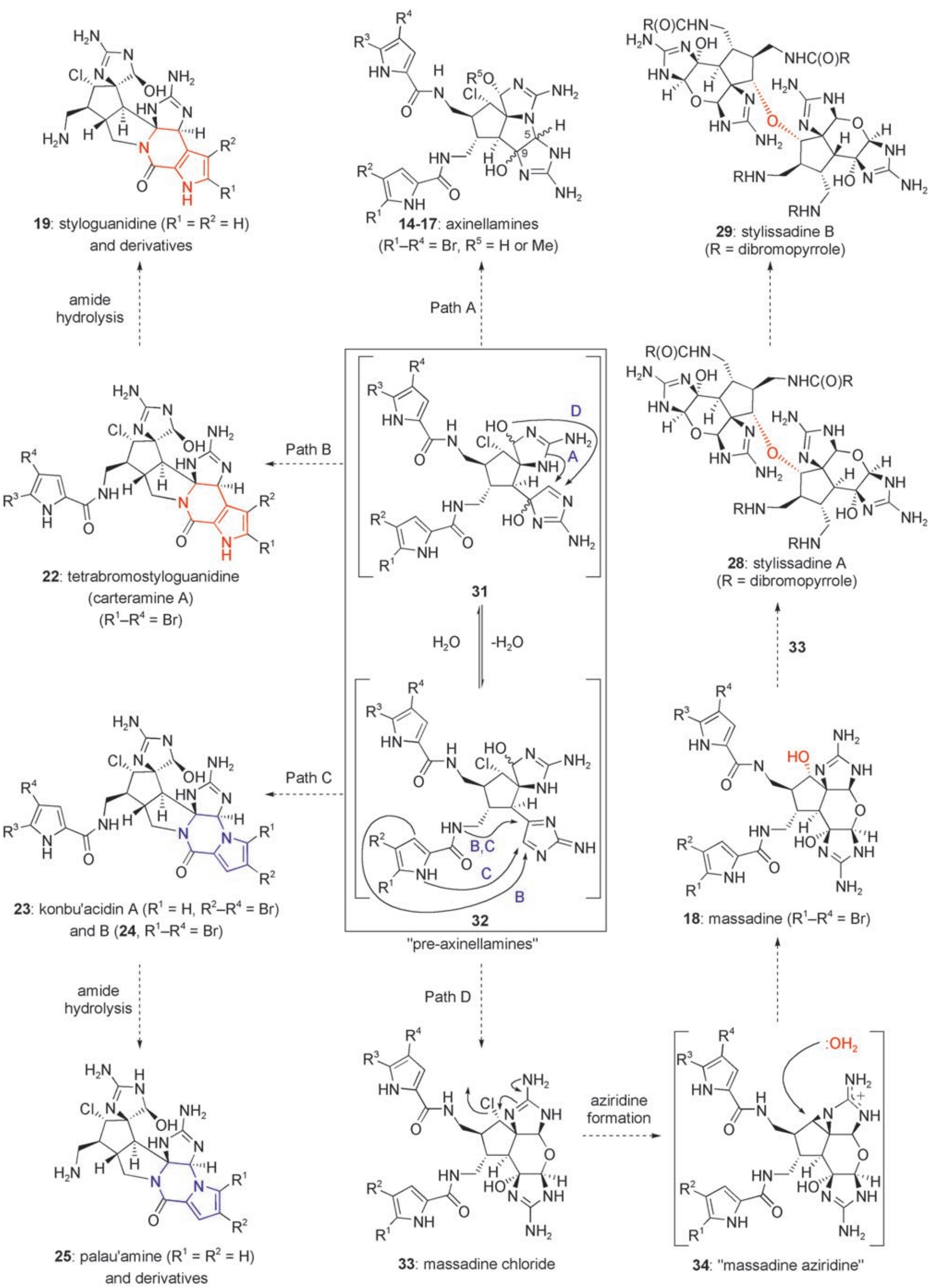
The corrected structure of palau'amine has important implications for the presumed biogenesis of cyclized dimeric pyrrole–imidazole alkaloids. As illustrated in Scheme 4, the proposition can be made that all of the members of the family come from a single precursor. This proposal bears resemblance to that of Al Mourabit and Potier[29] with the notable exception that the current hypothesis explains the conserved stereochemical relationships within the family. The hypothetical central intermediates, dubbed the "pre-axinellamines" (**31** and **32**) here for clarity, may follow one of four reaction pathways.

In reaction path A, closure of the spiro aminoimidazoline nitrogen atom onto the imine-containing amino imidazole leads to the axinellamines (**14**–**17**). Since the C5 and C9 atoms are part of an aminal and/or a hemiaminal, and have similar energies by molecular modeling, both *syn* diastereomers are observed. The reaction paths B and C describe straightforward closures of the neighboring pyrrole onto the oxidized, electrophilic aminoimidazole ring. The attack by the carbon or nitrogen atom of the pyrrole furnishes the phakellin framework of the styloguanidines (**19**–**22**) or the isophakellin framework that are found in the konbu'acidins (**23** and **24**) and the palau'amines (**25**–**27**), respectively.

The final reaction path D involves the formation of massadine chloride (**33**) by closure of the oxygen atom of the hemiaminal onto the adjacent aminoimidazole ring. Molecular models suggest that this alkyl chloride might be susceptible to an internal displacement to form "massadine aziridine" (**34**), which is poised to generate massadine (**18**) and the remarkable tetrameric stylissadines (**28** and **29**) by either opening by H_2O (leading to **18**) or by massadine itself (leading to **28**). Recently, we have isolated and characterized **33** and provided compelling indirect evidence for the existence of the fleeting aziridine **34**.[30]

Scheme 5 depicts three possible biosynthetic pathways to "preaxinellamine" (**31**). In the first proposal (linear), oroidin-like molecules **35** undergo an enantio- and diastereocontrolled dimerization to form **36**.[29] A hydration, reaction with an electrophilic chlorine source, and a cyclization lead via **39** to **42**. After tautomerization and oxidation of the remaining aminoimidazole, "preaxinellamine" (**31**) is formed.

An alternative proposal was recently put forth which involves a ring expansion of the cyclobutane nucleus of sceptrin (**2**).[31] The proposition that **2** is a biosynthetic precursor of the other more-complex members of the family is supported by the extremely high concentrations of **2** found in many of the organisms that produce ageliferin (**8**)[8e,32] (compound **2** has also been isolated from the same organism as palau'amine (**25**)[7b]). Cation-initiated expansions of cyclobutanes to cyclopentanes have good precedent,[33] and have



Scheme 4. "Pre-axinellamines" as direct precursors to a range of pyrrole–imidazole alkaloids.

been implicated in the biosynthesis of hirsutene terpenes from illudanes.[34] It is therefore reasonable to propose that exposure of **2** to an oxidant leads to cation **37**. Attack by a chloride ion, possibly through the intermediacy of aziridine **40**, would then lead to **43**.

The third pathway (ring contraction) bears its conceptual roots in the earlier hypothesis for the genesis of palau'amine[7b] (**1**). Although ageliferin (**8**) was not used as a precursor by Scheuer and co-workers (presumably because of the *cis* relationship of the earlier structure of palau'amine (**1**)), the essence of the hypothesis remains valid. Thus, tautomerization of ageliferin (**8**) followed by reaction with an electrophilic chlorine source, ring contraction, and hydration leads to **31**. We have recently demonstrated that the ring-contraction pathway can lead to axinellamine-like structures from **8**.[35]

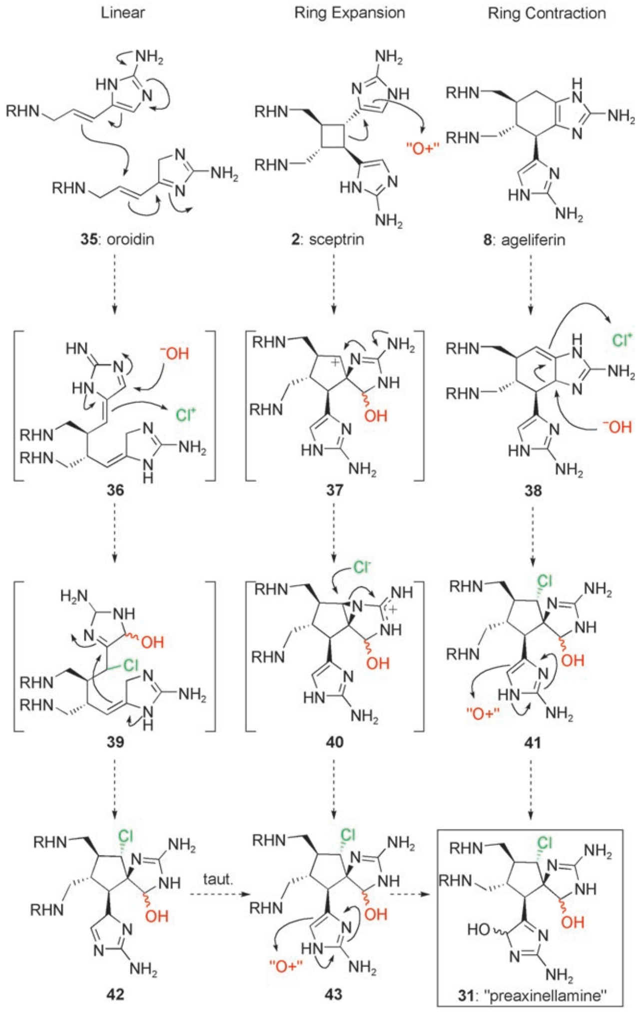
Although the postulation of biosynthetic origins might be dangerous without biochemical evidence, such ruminations often lead to innovative synthetic approaches. A classical example of this is the synthesis of strychnine by Woodward et al.,[36] which resulted from a conceptually brilliant biosynthetic postulate (the Woodward "fission") that was later proven to be false.

As an aside, it is interesting to draw a parallel between the marine-derived alkaloids and their terrestrial relatives, the terpenes. Nature generates libraries of terpenes by constructing certain favored carbon skeletons followed by oxidative manipulations and rearrangements.[37] These latter steps often lack chemoselectivity, thus creating large families of molecules. In the same way, nature has crafted a beautiful family of alkaloids by an enantioselective dimerization of a simple building block (oroidin) followed by a range of both selective and seemingly random oxidation/rearrangement cascades.

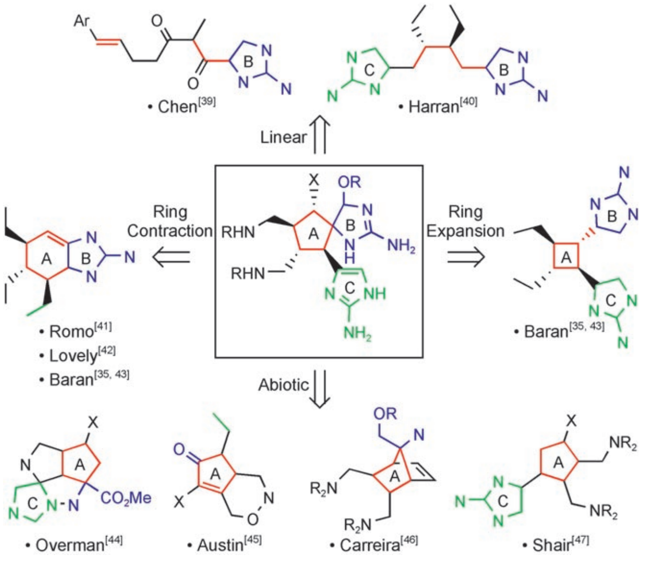
4. Towards the Synthesis of Palau'amine and Related Structures

Several approaches to this natural product family have already appeared, many of which are based on biosynthetic proposals (Scheme 6).

Most of the strategies reported so far have been reviewed elsewhere[38] and are flexible enough such that the revised structure of palau'amine (**25**) will not be a great setback. In fact, those research groups that are targeting the axinellamines (**14**–**17**) are now much closer to palau'amine (**25**). Although abiotic routes are likely to abound with interesting discoveries, the most direct pathway to this class of natural products will likely mimic aspects of their proposed biogen-



Scheme 5. Three hypotheses for the origin of "pre-axinellamine" (**31**).



Scheme 6. Previous synthetic approaches to the cyclized pyrrole–imidazole alkaloids.

esis. The corrected structure of palau'amine (**25**) brings a pleasing symmetry to the family that will hopefully translate to future total syntheses. Thus, it should be possible to design a synthetic pathway that will not only access the palau'amines (**25**–**27**) but also the axinellamines (**14**–**17**), the styloguanidines (**19**–**22**), massadine (**18**), and even the daunting stylissadines (**28** and **29**).

5. Conclusion

With their unusually high nitrogen content (N/C ≈ 1:2), exotic molecular architectures, and unusually oxidized skeletons, the dimeric pyrrole–imidazole alkaloids challenge the state-of-the-art methods in both isolation and synthetic chemistry. As a result of the scholarly studies of isolation chemists, the chemical structures of the palau'amines (**25**–**27**) and related family members (such as the konbu'acidins and styloguanidines) has now been revised. As a result of the difficulty in crystallizing these natural products, conclusive revision required the extensive use of both quantitative NMR experiments and computation.

These structural revisions make it possible to propose a unifying hypothesis for the biosynthesis that not only aids in the chemical rationalization of their structure but also may facilitate efforts towards their total synthesis. Indeed, we have recently isolated the elusive massadine chloride (**33**) and provided indirect evidence for the fleeting existence of "massadine aziridine" (**34**).[30]

The riveting story of the pyrrole–imidazole alkaloids continues to be expanded and has been enriched by the recent structural revision of some family members. The continued pursuit of palau'amine (**25**) and its relatives from isolation, biosynthetic, and synthetic angles holds promise for even more exciting discoveries, surprises, and inventions.

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[26] Ref. [7b] states: “Furthermore, H6 also shows a small NOE to H20, which confirms the configuration at C20 as shown.” and

"This is a correction of that suggested in our earlier communications. (this sentence referred to the 1993 publication and a conference contribution of 1992)". Also the structures in the study of 1998 were changed into the enantiomeric form compared to original publications (the reference center C6 was now *S* configured). Styloguanidine (1995) and konbu'acidin A (1997) were originally drawn with the same absolute configuration as palau'amine (1993). The research group of Quinn reported the change of three stereogenic centers[15b] because they used the structure from 1998[7b] as a reference, whereas the research group of Matsunaga[15b] as well as Grube and Köck[15a] reported only the change of two centers.

[27] Therefore, the relative configuration of both konbu'acidin B and carteramine A should read (according to Cahn–Ingold–Prelog) as: 6*S*, 10*R*, 11*S*, 12*S*, 16*R*, 17*S*, 18*S*, 20*S*. However, the stereogenic centers are given differently by both research groups: that of Matsunaga[16b] assigned the stereogenic centers in question to 12*S*, 17*S*, 20*S*, and that of Quinn[15b] to 12*R*, 17*S*, 20*S*. In the latter case center C12 was wrongly assigned according to CIP.

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