*Natural Product Synthesis*

# Sceptrin as a Potential Biosynthetic Precursor to Complex Pyrrole–Imidazole Alkaloids: The Total Synthesis of Ageliferin**

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The isolation and characterization in 1981 of the first dimeric pyrrole-imidazole alkaloid, sceptrin (**1**, Scheme 1) by Faulkner, Clardy, and co-workers[1] was a milestone event in marine

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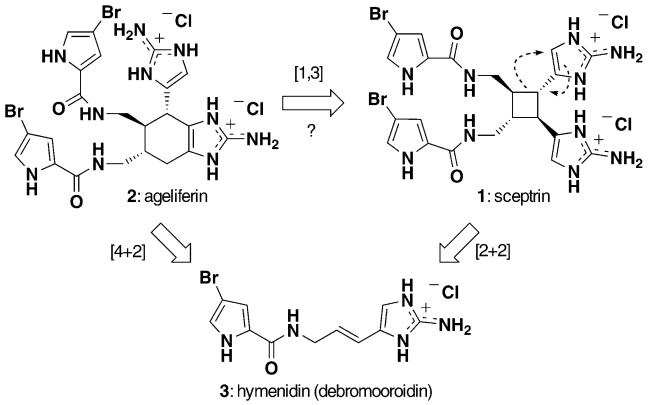



***Scheme 1.*** Structures of ageliferin (**2**), sceptrin (**1**), and debromooroidin (**3**) as well as retrosynthetic analysis of **1** and **2**.

natural product research as these compounds have extraordinary biological activity and stunning molecular architectures.[2] Indeed, they have inspired a flurry of research in chemistry.[2] Recently, the long-standing synthetic challenge posed by sceptrin (**1**) was solved with a concise sequence that proceeds in approximately 24% overall yield, can be conducted on a preparative scale, and does not necessitate chromatography.[3]

Ageliferin (**2**),[4] isolated in 1986 from *Agelas conifera* by Rinehart, is an antiviral agent[4b] and may be a useful chemical tool for mechanistic studies of actin–myosin contractile systems.[4c] It has been the subject of numerous synthetic efforts,[5] all of which are based upon a widely accepted biosynthetic hypothesis[6] wherein **2** is derived from two molecules of hymenidin (debromooroidin, **3**) by an enzymatic "Diels–Alderase" (Scheme 1). We were compelled to question this proposal upon noticing that in every instance in which **2** was isolated, **1** was by far the major constituent (see Figure 1 for an example).[7] We reasoned that if **1** and **2** were derived from **3** by a divergent pathway (as is proposed[6]), then the observed ratio of **1** and **2** after isolation should be reversed, solely on thermodynamic grounds. Thus, to explain this apparent discrepancy, we envisioned an alternative scenario wherein **1** rearranges to form **2**. Although such a rearrangement should not proceed thermally in a concerted fashion (see below), it would constitute an "allowed" event if the reaction proceeded in a stepwise fashion (radical or ionic processes) or through photochemical means.[8,9]

Herein, we report the remarkable thermal conversion of sceptrin (**1**) into ageliferin (**2**). We also present an alternative biogenetic hypothesis commencing from **1** rather than **3** for other complex dimeric pyrrole-imidazole alkaloids, including the axinellamines[10] and palau'amines.[11]

Our explorations began with several unsuccessful attempts to effect photochemical [1,3] sigmatropic rearrangement of **1**. Thus, exposure of **1** to a 450-W Hanovia lamp (quartz or pyrex filter) for several days led only to gradual decomposition. Similarly, decomposition was observed when sceptrin (**1**) was heated in methanol at temperatures as high as 150 °C in a microwave. We also found the free base of **1** to be extremely unstable and to decompose into a variety of products which have not been fully characterized. However, when **1** was dissolved in water and heated to 195 °C for 1 minute by using microwave irradiation (Scheme 2), we obtained ageliferin ((±)-**2**) in 40% yield and identical in all respects to a natural sample, along with recovered (±)-**1** (52%). An NMR spectroscopic comparison of synthetic **1**, synthetic **2**, natural **2**, and the products of this reaction is

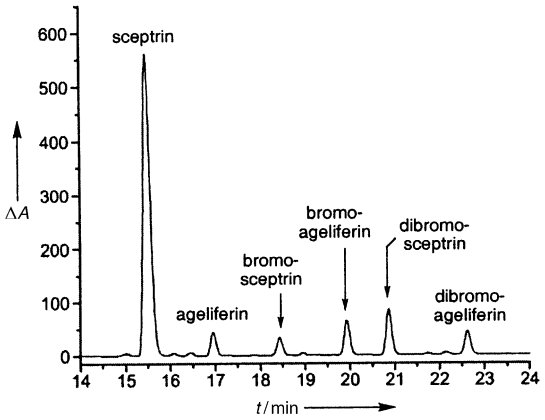
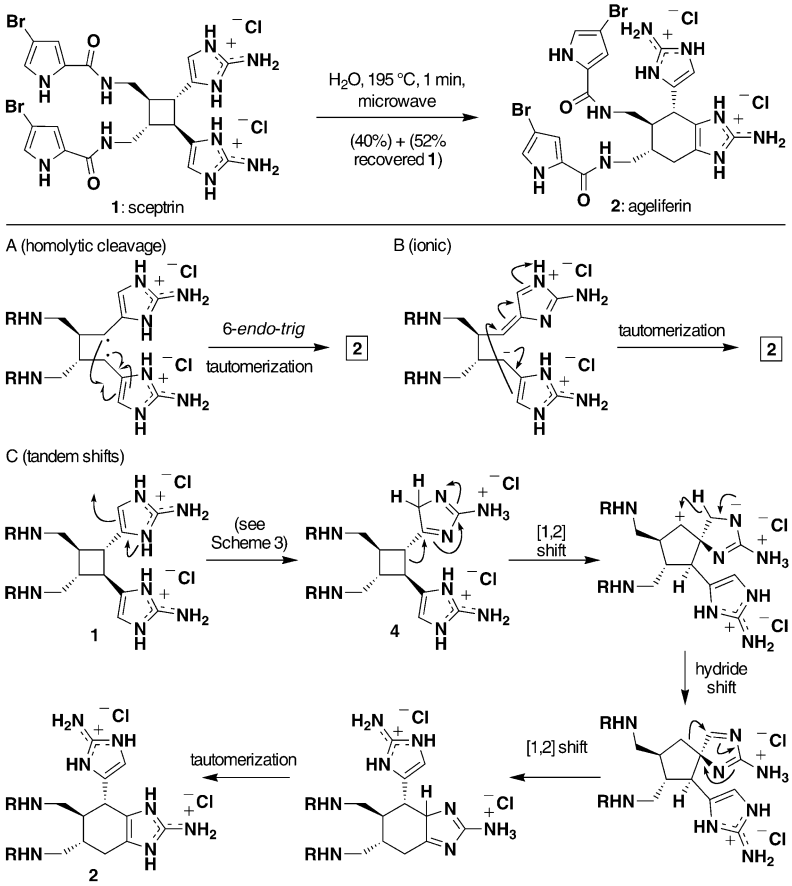



***Figure 1.*** HPLC chromatogram from the extracts of *Agelas conifera*. Reproduced from Ref. [7].




***Scheme 2.*** Remarkable conversion of sceptrin (**1**) into ageliferin (**2**) and mechanistic analysis.

shown in Figure 2. Given the thermal instability of sceptrin[3] and ageliferin, it is quite surprising that this reaction proceeds cleanly and reproducibly. In fact, decomposition begins after only 90 seconds at 195 °C. If the reaction is performed at 195 °C without a microwave, only sceptrin and decomposition products are observed.

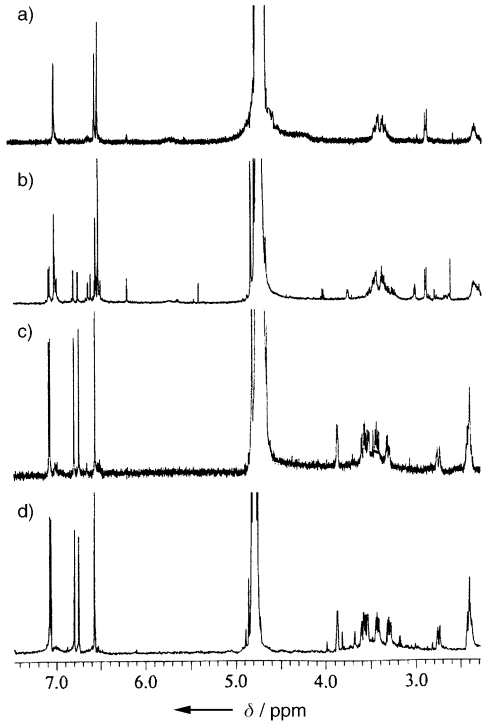


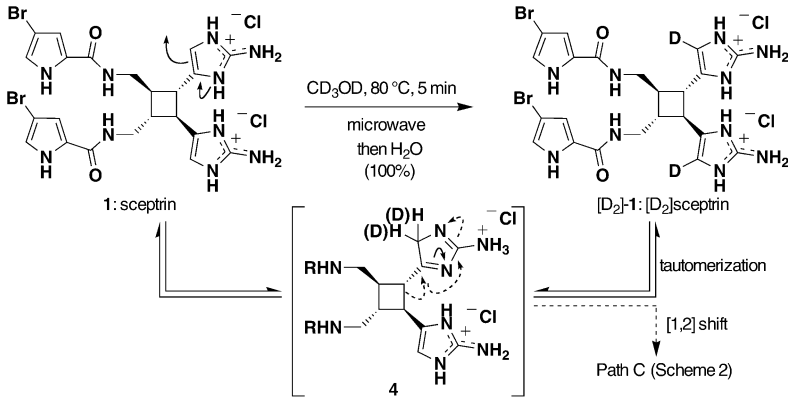

***Figure 2.*** Comparison of the $^1$H NMR spectra (600 MHz, $D_2O$) of a) synthetic sceptrin, b) sceptrin after 1 minute at 195 °C, c) synthetic ageliferin (trifluoroacetic acid salt), and d) natural ageliferin (HCl salt).

This conversion constitutes, to the best of our knowledge, the first vinyl cyclobutane rearrangement of a natural product. However, perhaps more importantly, it also raises the intriguing question as to whether nature employs an enzyme to catalyze a similar process. It is equally possible that we have unearthed a completely abiotic route to **2**; thermolysis of **1** may just lead to an intermediate that can either return to **1** or irreversibly transform into **2**.

Three selected mechanistic portraits are depicted in Scheme 2. In the first scenario (path A), the cyclobutane is ruptured in a homolytic fashion and this is followed by a 6-*endo-trig* closure. An ionic process, reminiscent of the currently proposed biosynthesis of **2** from **3**,[6] may also be invoked, as shown in path B. A series of concerted bond shifts, as depicted in path C, can also account for this structural reorganization. Thus, tautomerization to intermediate **4** followed by a thermal [1,2] shift (4→5-membered ring), a hydride shift, another [1,2] shift (5→6-membered ring), and a final tautomerization could lead to **2**. All three pathways could conceivably lead to the stereochemistry of **2** since the bromopyrrole-bearing carbon centers are incapable of epimerization and could therefore direct ring closure in paths A and B. It follows then that the conversion **1**→**2** should be the same whether racemic or optically pure **1** is employed. Notably, the "allowed" thermal concerted [1,3] sigmatropic pathway would require inversion (suprafacial) of configuration at the migrating carbon atom, while we observe retention.[8]

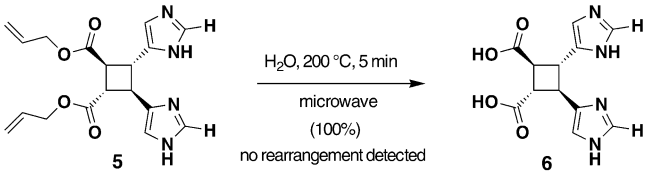
Although theoretical inquiries into the sigmatropic rearrangement of simple monocyclic vinyl cyclobutanes to cyclohexenes point to a radical mechanism,[9] we believe an ionic process (perhaps similar to paths B or C) is operative here. The ambivalent reactivity of the 2-aminoimidazole C4–C5 double bond contrasts sharply with that of previously studied olefins in this rearrangement.[12] For example, simply heating **1** at 80 °C in $CD_3OD$ for 5 minutes with microwave irradiation led exclusively to [$D_2$]sceptrin ([$D_2$]-**1**) in quantitative yield (Scheme 3). Incidentally, this appears to be the first report of deuterium exchange at a carbon center on a 2-aminoimidazole under neutral conditions. It is postulated that the tautomeric form of sceptrin (**1**), structure **4**, is involved in this proton-addition/proton-loss sequence. In principle, a [1,2] rearrangement could then occur (see dotted arrows, Scheme 3), thus leading to the events shown in path C (Scheme 2) with eventual arrival at ageliferin (**2**). There is ample precedent for this type of ring expansion of cyclobutanes.[13] Compelling evidence for the requirement of the 2-aminoimidazole subunit in this rearrangement was also garnered by submitting the known cyclobutane **5**[14] to extended microwave irradiation (200 °C, 5 min) only to obtain the diacid **6** in quantitative yield (Scheme 4).

Based on these findings, it would not be surprising if other complex dimeric pyrrole-imidazole alkaloids such as the palau'amines and axinellamines arise from sceptrin-type intermediates. Indeed, palau'amine (**9**), like ageliferin (**2**), was isolated along with sceptrin (**1**).[11] For the purpose of inspiring new synthetic approaches to these alkaloids, we propose an alternative biogenic hypothesis for the generation




***Scheme 3.*** Facile synthesis of [$D_2$]sceptrin ([$D_2$]-**1**) points to the potential viability of path C (see Scheme 2).

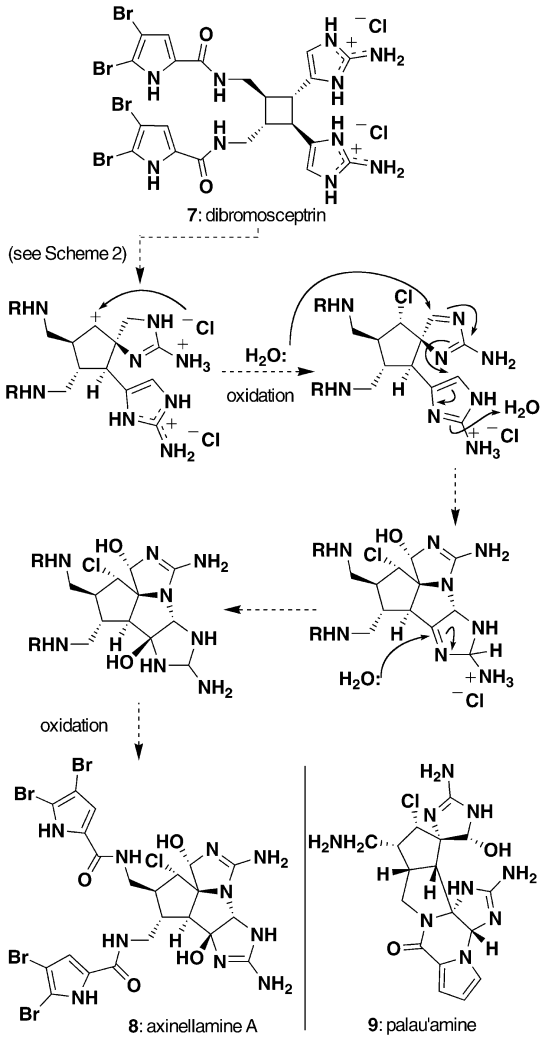
  




***Scheme 4.*** Even after 5 minutes at 200 °C, only hydrolysis (no rearrangement) is observed with the known cyclobutane **5**.

of these compounds: We have chosen to depict the proposed transformation of the known natural product dibromosceptrin (**7**) into axinellamine A (**8**) as an example (Scheme 5); a ring-expansion pathway from a sceptrin-type intermediate could also be drawn for palau'amine (**9**).[15] A ring-contraction pathway from an ageliferin-type structure could also lead to these alkaloids.[16]

In summary, we have completed the first total synthesis of ageliferin (**2**, Scheme 1), identified the first vinyl cyclobutane rearrangement of a natural product, and advanced an alternative biosynthetic hypothesis for the formation of complex pyrrole-imidazole alkaloids. The synthesis adds merely one additional step to the concise, practical, and analogue-friendly sceptrin synthesis developed in our laboratory,[3] and it can thus easily be scaled up to allow for a full evaluation of the biological potential and structure–activity relationships of these intriguing alkaloids. Efforts are underway to harness the innate symmetry and reactivity of **1** and related structures to effect conversion into other naturally occurring pyrrole-imidazole alkaloids.




***Scheme 5.*** Proposed conversion of dibromosceptrin (**7**) into axinellamine A (**8**) in nature and the related structure of palau'amine (**9**).

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**Keywords:** alkaloids · biosynthesis · microwave reactions · natural products · total synthesis

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