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Total Synthesis of Ageliferin via Acyl N-amidinylium Ion Rearrangement†

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Abstract

Ageliferin is a marine natural product having antiviral and antimicrobial activities. These functions remain to be characterized at a molecular level. Ageliferin is also thought a biosynthetic intermediary linking oroidin type alkaloids to more complex polycyclic derivatives. This scenario has the amino tetrahydrobenzimidazole motif in ageliferin serving as a reduced progenitor of oxidized, ring-contracted spirocycles. Here we describe the reverse. Namely, a concise synthesis of ageliferin which features ring expansion of a spirocyclic precursor – itself derived from reduction. The pathway also provides access to unique isosteres of the axinellamine ring system, allowing new synthetic additions to the growing family of pyrrole / imidazole alkaloids.

Ageliferin (**1**, Figure 1) is a pyrrole / imidazole alkaloid discovered in extracts of *Agelas coniferin*. It has since been identified in numerous *Agelas* sponges; routinely alongside isomers such as sceptrin and nagelamides.¹ The molecule is a prototype oroidin dimer and features prominently in discussions as to how, or if, its structure is biosynthetically intermediate en route to more complex relatives.² Regarding the origin of **1** itself, two pathways have been advocated; 1) a net two-carbon ring expansion of sceptrin³ and 2) formal Diels–Alder dimerization of hymenidin followed by tautomerization.^{1b} Both constructions have been emulated in the laboratory. Baran has synthesized **1** by executing the former, while Ohta has prepared a dimethylated congener (unnatural) using a variant of the latter.^{4,5} Chen’s recent asymmetric synthesis of **1** is not aligned with either pathway.⁶

The aminotetrahydrobenzimidazole motif in ageliferin is thought a reduced precursor to ring-contracted spirocycles such as those observed in palau’amine, konbu’acidin, axinellamines and massadine.² Several laboratories have adopted similar logic for converting ageliferin synthons into congeners of dehydro ‘pre-axinellamine’ (i.e. **2**, X = Cl).⁷ Our own observations have led us to pursue the reverse outcome. Namely, we find that C_2 -symmetric dimers of the natural product dispacamide readily isomerize to oxidized precursors of **2**; wherein X = H (vide infra). We recently discovered methods to partially reduce these materials^{8b}, and herein demonstrate novel ring expansion of the resultant hemiaminals to ageliferin. Depending upon intermediate stereochemistry, we also create previously unknown structural isomers of the axinellamine ring system.

The assembly of C_2 -symmetric spiroaminals **6** requires twelve steps beginning with γ -butyrolactone, thiourea and carbohydrazide **5** (Scheme 1). As we’ve shown previously,^{8b} the amina units in **6** are moderately stable to acid, but not base. In fact, all diastereomers of this

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structure are susceptible to a base mediated rearrangement cascade; funneling ultimately to alkylidenes **7** following degradation of the oxadiazine rings. In earlier studies, we advanced individual isomers of **7** to axinellamine structures.^{8b} In the current work, separation is not necessary. Geometric isomers of each C14 epimer of **7** can be reduced as a mixture; initially to alkylidene aminoimidazolines **8**. These subsequently tautomerize to aminoimidazoles **9**.

A valuable finding was made while experimenting with **9**. The structure is isolated as a mixture of four diastereomers. It turns out the stereochemistry at C10 and C14 can be equilibrated. This is achieved simply by heating salt forms of **9** in water. For example, microwave heating an aqueous solution of pure **9a** (bis-TFA salt, 180°C, 1.0 mM) converts it fully to **9c** and its C14 epimer **9d** (65% isolated by HPLC, d.r. ~2:1) within 15 minutes (Scheme 1). A similar result is observed when the experiment is repeated on pure **9d**, a mixture of **9a** and **9b**, or a mixture containing **9a**, **9b** and **9d**. In each case, the system converges on C10, C11 trans diastereomers **9c** and **9d**, wherein **9c** predominates in roughly a 2:1 ratio.⁹ Mechanistic details are not yet known, although data is consistent with reversible cleavage of the C10,C14 bond.¹⁰

The equilibration process converts four isomers of **9** to two, and the major isomer is used to synthesize ageliferin. **9c** is treated with excess SmI₂ in aqueous THF. This results in rapid debromination at C6' and C6'' followed by gradual reduction of the glycoeyamidine carbonyl. The resultant epimeric hemiaminals **10** (d.r. 1:1) are freed from samarium salts by preparative HPLC and exposed to trifluoroacetic anhydride (TFAA) in TFA.¹¹ This initiates ring-expanding rearrangement to a trifluoroacylated tetrahydrobenzimidazole, from which the racemic natural product (**1**) is isolated following hydrolytic (1N HCl) workup (Scheme 2).¹²

Each C1 epimer of **10** converts to **1** using this protocol, which we rationalize in terms of 1,2-alkyl migration occurring within an intermediate acyl N-amidinyliminium ion (**11**, X = H or COCF₃). The result is analogous to acylation-induced ring expansion of partially reduced 1,3-diazaspiro[4.4]nonan-2,4-diones.^{13,14} However, in the current complex, non-symmetric system, substrate stereochemistry provides for varying outcomes. For example, minor C14 epimer **9d** does not lead to ageliferin. Rather, upon SmI₂ reduction and TFAA/TFA treatment, this molecule gives polycycle **12**, wherein a putative N-amidinyliminium ion intermediate is trapped by the proximal, *cis*-disposed aminoimidazole (Scheme 3). When the original mixture of **9** is separated by HPLC rather than equilibrated, we observe a similar result beginning with major component **9a**. Like **9d**, the C14-C10 bond and the aminoimidazole substituent are oriented *cis* on the cyclopentane ring in **9a**. SmI₂ reduction and TFAA/TFA treatment of this material affords amina **13**.¹⁵

Structures **12** and **13** have inverted core topologies and represent new synthetic isosteres of the axinellamine ring system (Scheme 3). They exist at the oxidation state of ageliferin, yet this parameter is easily adjusted. For example, exposure of **13** to oxaziridine **14** (55°C, 2h, eq 1) in aqueous THF smoothly oxidizes the aminoimidazole ring (Figure 3).^{7b,8b} Following preparative HPLC, we isolate two hemiaminal epimers of pentacycle **15** (66%, d.r. ~1.4:1); a remarkable substance having two imbedded amina linkages sharing a common nitrogen atom. This unusual connectivity is assigned with the aid of HMBC spectra, wherein C1 and C5 amina protons correlate to C9. Relative to precursor **13**, a new long-range correlation linking C5H to C1'' and C3'' is reflective of the installed C9-N2'' bond.

One can envision numerous oxidative manipulations in this series, providing access to a range of designed congeners. When combined with a short and flexible synthesis of ageliferin, the chemistry provides a wide platform to explore biological functions of complex pyrrole / imidazole natural products; ideally while uncovering synthetic variants

having superior and/or more selective activity. Initial screens suggest moderate antibacterial activity for the group. We suspect other venues may be more fruitful. Particularly interactions with gated ion channels, for which there is intriguing precedent.¹⁶ Work along these lines is ongoing, as are attempts to exploit these key findings for total syntheses of palau'amine structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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9. Equilibration experiments conducted with **9a**, **9b** and **9d** uniformly **20** provide **9c** and **9d** in a ~2:1 ratio. In certain instances, competitive hydrolysis providing hydantoin derivatives of **9c** and **9d** is observed upon prolonged heating.
10. Thermolysis of **9a** in D₂O results in rapid tetradeuteration (as labeled, 95% D at each position as determined by ¹H NMR and MS) 25 concomitant with epimerization at C10 and C14. Data below reflects product mixture at ~75% conversion.

The same experiment carried out on **9c** results in tetradeuteration and loss of stereochemical integrity at C14. The ratio of C14 epimers is ~2:1, comparable to that produced from **9a**, suggesting equilibrium has been established. No C10 epimers (e.g. **17**) are observed. Yields refer to isolated material following preparative reverse phase HPLC. See Supporting Information for details.

11. Desalted hemiaminals **10** show diagnostic (see ref. 8b) C1 methine ¹H resonances at δ 5.23 and 5.14 (500 MHz, CH₃OH-*d*₄). Because the materials degrade readily, seemingly through auto-oxidation, they are reacted with TFAA/TFA immediately after isolation.
- 12 (a). ¹³C NMR data for synthetic (**1**) is identical to that reported for natural ageliferin, except for a 3.8 ppm discrepancy in chemical shift for C11 (Scheme 2). The same phenomenon is observed by Baran (ref. 2) and Chen (ref. 6). We attribute the difference to the natural product being purified and characterized as an acetate salt, whereas we isolate **1** by preparative HPLC eluting with 0.1% TFA in CH₃CN / H₂O. For further discussion see: Pugmire RJ, Grant DM. *J. Am. Chem. Soc.* 1968; 90:697.; Olofson A, Yakushijin K, Horne DA. *J. Org. Chem.* 1998; 63:5787. [PubMed: 11672177]
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14. The analogous SmI₂ mediated reduction on model 2-imino-1,3-diazaspiro[4.4]nonan-4-one provides 2-amino-1,3-diazaspiro[4.4]non-1-en-4-ol which undergoes efficient ring expanding rearrangement to 2-aminotetrahydrobenzimidazole (See Supporting Information).
15. Based on results for **9a**, **9c** and **9d**, we anticipated the remaining series diastereomer, namely **9b**, would lead to nagelamide E (i.e. C10 epi-**1**) upon SmI₂ reduction and ring expansion. Interestingly, a mixture (as yet inseparable) of **9b** and its C14 epimer (i.e. **9a**) gives only **13** and ageliferin following these two operations. To the extent **9a** leads only to **13** (Scheme 3), the ageliferin produced is derived from **9b**. This implies C10 epimerization occurs during and/or prior to ring expansion. Note: thermal equilibration of **1** and nagelamide E has been demonstrated (See ref. 2 and O'Malley DP. Ph.D. Dissertation. 2008the Scripps Research InstituteUMI #3313886
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Figure 1.
Pyrrole/imidazole alkaloids: monomer oxidation state and the interrelatedness of derived dimers.

Figure 2.

Spirocycles **9** are prepared in 12 steps from γ -butyrolactone, utilizing thiouron **4** and carbohydrazide **5** as key building blocks.

Figure 3.

A *Reagents and conditions:* **14**, THF, 60°C, 2h, 66%, d.r.~1.4:1. **B** Partial HMBC data for **15** (500 MHz, CH₃OH-*d*₄); Key correlations: H5–C1'', H5–C3'', H5–C9 and H1–C9.

Scheme 1.

Trifluoroacetate salt forms of diastereomers **9** thermally equilibrate in water. *Reagents and conditions:* (a) *e.g.* pure **9a**, H₂O, 180°C (microwave), 15 min, 42% of **9c**, 23% of **9d**.

Isolated yields for variations of this experiment are detailed in the Supporting Information and in ref. 10.

Scheme 2.

Reagents and conditions: (a) **9c**, excess SmI_2 , $\text{THF} / \text{H}_2\text{O}$, -40°C to RT, 37%; (b) TFAA / TFA , THF , 70°C ; aq. 1N HCl , 38% from **10**.

Scheme 3.

Reagents and conditions: (a) TFAA / TFA, THF, 60°C; aq. 1N HCl. Products **12** and **13** isolated as bistrifluoroacetate salts (22 and 13% respectively over two steps, >95% purity) following two rounds of preparative reverse phase HPLC. Lowered yields reflect competing air oxidation of intermediates during isolation.