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An approach for the synthesis of nakamuric acid

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Abstract

The biosynthesis of dimeric pyrrole–imidazole alkaloids is likely mediated by enzyme-catalyzed reversible single-electron transfer (SET) cycloaddition. We now show that Ir(ppy)₃ can promote SET-mediated formal [2+2] and [4+2] cycloaddition reactions of pyrrole–imidazole alkaloids-related substrates under photolytic conditions. This biomimetic approach is useful for the construction of the core skeleton of nakamuric acid and sceptrin.

Keywords

Single-electron transfer; Radical; Cyclization; Imidazole; Pyrrole

1. Introduction

Dimeric pyrrole–imidazole alkaloids have attracted synthetic chemists' attention for decades because of their unique molecular architectures.¹ Nakamuric acid (**1**) is a unsymmetrical family member isolated from Sponge *Agelas nakamurai* by Proksch in 1999 (Fig. 1).² It is structurally related to the C₂-symmetric sceptrin (**2**), the first pyrrole–imidazole dimer discovered in nature by Faulkner and Clardy in 1981.³ Although the cyclobutane core of **1** and **2** could be derived from a [2+2] photocycloaddition reaction, there was not enough light at where the producing sponges lived. Attempts to induce the photo-dimerization of hymenidin (**3**) failed to give **2** under various conditions.^{3,4a} Similarly, abiotic experiments suggests that ageliferin (**4**)⁵ is not a thermal [4+2] cycloaddition reaction product of **3**.⁶ Currently, there is only one report of the synthesis of **1**,^{4b} and two reports of the synthesis of **2**.^{4,7}

Recently, Molinski and Romo have provided evidence for the involvement an enzyme-catalyzed single-electron transfer (SET) in promoting the dimerization of **3**.⁸ A biogenic SET-oxidation of **3** will give rise to **3**^{•+} that is highly reactive toward [2+2] cycloaddition

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(path *a*) to generate **2** after back-SET. We also believe that **4** arises from SET-promoted formal [4+2] cycloaddition (path *b*) and have previously reported an asymmetric synthesis of **4** using a radical cyclization reaction to mimic the biogenic dimerization of **3**.⁹ We now describe the use of photoredox chemistry to induce the formal [2+2] cycloaddition for the synthesis of the core skeleton of **1** and **2**.

2. Results/Discussion

To study the biomimetic dimerization of **3**, we would need a model system that allows us to carry out the SET-promoted formal [2+2] cycloaddition efficiently. We anticipate that the reaction efficiency can be improved significantly by tethering **3** and **3**^{•+}. Selective SET-oxidation of one of the two involving olefin group can also be achieved by suppressing the oxidation of one olefin by replacing the adjacent aminoimidazole group with an alkyl group to increase the redox potential. We thus envision that **5** is a biogenically relevant and synthetically amenable model system for **3**^{•+}/**3**. Radical cation **5** can undergo a 5-*exo* followed by a 4-*exo* (path *a*) or a 6-*endo* (path *b*) cyclization to afford the nakamuric acid/sceptrin core **6** or the ageliferin core **7** (Fig. 2).

We started our study by evaluating the feasibility of generating **5** via SET-oxidation and examining the radical characteristics of **5**. A more practical system would be replacing the aminoimidazole group with an imidazole group for chemical stability reasons. In addition, the 2-position of imidazole is reactive and should be masked. With these considerations, we chose **8** as the model system for studying the SET-promoted [2+2] cycloaddition reaction. Our computational work suggests that **8**^{•+} is a proper model system of **3**^{•+}/**3**. First, DFT calculations (UB3LYP/6-311⁺G**) confirm that the HOMO orbital of **8** resides on vinylimidazole (Fig. 3). Therefore, the SET-oxidation of **8** should selectively occur at this site. Second, after SET-oxidation, the resulting **8**^{•+} has high computed spin density at the desired C-9 position (hymenidin numbering). Consequently, the radical cyclization reactions should proceed with the anticipated regioselectivity.

With the computational supporting evidence, we set out to study the SET-promoted cycloaddition of **8**. We first prepared **8** in three steps from commercially available 1,2-dimethyl-1*H*-imidazole-5-carbaldehyde (**9**) (Fig. 4). A Horner–Wadsworth–Emmons reaction of **9** with methyl (triphenylphosphoranylidene)acetate gave **11** with excellent (*E*)/(*Z*) selectivity. No (*Z*)-enoate product was observed in the crude ¹H NMR spectra of the crude reaction mixtures. Reduction of **10** then provided alcohol **11**. Coupling of **11** with crotyl bromide yielded **8**.

We first attempted to generate the radical cation of **8** using the single-electron oxidation reagents developed by Bauld.¹⁰ However, no reaction occurred when treating **8** with a catalytic amount of triarylaminium salt. Increasing the amount of the oxidant or extending the reaction time led to complete decomposition. Due to the sensitive nature of **8**, we decided to turn our attention to photocatalytic SET reactions.¹¹

Yoon and co-workers recently reported that visible light could activate Ru(bpy)₃²⁺ to catalyze [2+2] cycloaddition reactions through radical cation intermediates.¹² However,

irradiating **8** with $\text{Ru}(\text{bpy})_3^{2+}$ under various conditions resulted in complete decomposition only. We suspected that the cationic ruthenium catalyst bound to the basic imidazole group leading to undesired redox chemistry. We therefore switched to using the neutral $\text{Ir}(\text{ppy})_3$ catalyst.¹³ Consistent with our hypothesis, irradiating **8** with 2.5 mol % of $\text{Ir}(\text{ppy})_3$ gave the desired [2+2] cycloaddition product **12** in 53% yield (Fig. 5). We also obtained the C-10' epimer **13** in 20% yield. These results suggest that cycloaddition of **8** is a stepwise instead of a concerted process, similar to the Mn(III)-promoted oxidative [4+2] cycloaddition reaction that we developed for the ageliferin synthesis.⁹ We further observed *cis-trans* isomerization of the C-9/10 olefin of **8** during the reaction, indicating that the first cyclization instead of SET-oxidation is the rate-limiting step. The scrambling of this olefin geometry also resulted in the formation of the C-10 epimer **14** in 5% yield. Additionally, we obtained **15** that bears the ageliferin skeleton in 2% yield. The ratio of **12:13:14:15** did not change over the course of the reaction. Therefore, we believe that **12** was formed directly from **8** instead of through rearrangement of **13–15**.¹⁴

The use of an ether tether is important for the intramolecular cycloaddition reactions of **8**. Attempts to carry out the SET-induced cycloaddition reactions with a carbonate or a silyl tether failed to provide the [2+2] and [4+2] cycloaddition reaction products. Additionally, we were not able to induce the homodimerization of **11** or its derivatives under various conditions.

The Baran group previously found that sceptrin (**2**) and ageliferin (**4**) were always co-isolated from marine sponges, and thus proposed that **4** was derived from **2** via skeletal rearrangement.¹⁵ In collaboration with the Houk group, they further showed that thermolysis of **2** gave **4** stereospecifically through a diradical mechanism.¹⁶ The formation of **12–15** from **8** made us suspect that **2** and **4** are formed independently from **3**. We hypothesize that the radical cation $3^{*\cdot+}$ reacts with **3** through a [1e+2e] cycloaddition to give $2^{*\cdot+}$ and a [3e+2e] cycloaddition to give $4^{*\cdot+}$. This process is in contrast to Bauld's SET-promoted [4+2] cycloaddition that operates through a [4e+1e] mechanism with the radical cation residing on the olefin.¹⁰

3. Conclusion

We have developed a biomimetic strategy to construct the core skeleton of nakamuric acid (**1**), sceptrin (**2**), and ageliferin (**4**). Visible light-mediated catalytic photoredox chemistry was used to promote the intramolecular [2+2] and [4+2] cycloaddition of **8**. SET-oxidation of the vinylimidazole group of **8** gave a radical cation species that is highly reactive toward [1e+2e] and [3e+2e] cycloaddition reactions. Subsequent SET-reduction provide the formal [2+2] and [4+2] cycloaddition products **12–15**. These atypical cycloaddition reactions are likely involved in the biogenic production of **1–3**.

4. Experimental Section

General Procedures

All reactions were performed in glassware under a positive pressure of argon. The normal-phase flash column chromatography was performed on EMD silica gel 60 (230–400 mesh

ASTM). TLC analyses were performed on EMD 250 μm Silica Gel 60 F254 plates and visualized by quenching of UV fluorescence ($\lambda_{\text{max}} = 254 \text{ nm}$), or by staining ceric ammonium molybdate. ^1H and ^{13}C NMR spectra were recorded on Varian Inova-600, Inova-500, or Inova-400. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in ppm (δ) relative to the ^1H and ^{13}C signals in the solvent (CDCl_3 : δ 7.26, 77.00 ppm). Mass spectra were acquired on Agilent 6120 Single Quadrupole LC/MS. Preparative HPLC was performed using a Waters Atlantis dC18 OBD 5 μm column with a dimension of 19 $\times$ 150 mm or Eclipse XDB-C18 5 μm column with a dimension of 9.4 $\times$ 250 mm.

Synthesis of 10

To a solution of methyl (triphenylphosphoranylidene)acetate (273 mg, 1.5 mmol, 1.5 equiv) in tetrahydrofuran (5.0 mL), *n*-butyllithium (2.5 M in hexanes, 0.56 mL, 1.44 mmol, 1.4 equiv) was added at -78°C . After stirring for 30 min, **9** (114 mg, 1.0 mmol, 1.0 equiv) in tetrahydrofuran (5.0 mL) was added. The reaction mixture was then stirred at 0°C for 1 h followed by quenching with saturated ammonium chloride, extracted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered, and concentrated to afford crude **10**, which was used for the next step directly.

Synthesis of 11

To a solution of crude **10** (1.0 mmol) in methylene chloride at 0°C was added diisobutylaluminium hydride (1 M solution in toluene, 2.5 mL, 2.5 mmol, 2.5 equiv) slowly. After stirring for 2 h, the reaction was quenched with 10% Rochelle salt aqueous solution, extracted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered, and concentrated to afford the crude **11**, which was used for next step directly.

Synthesis of 8

To a solution of crude **11** (81 mg, 0.533 mmol, 1.0 equiv) in *N,N*-dimethylformamide (1.5 mL) at 0°C was added sodium hydride (60% in mineral oil, 26 mg, 0.640 mmol, 1.2 equiv) slowly. After stirring for 30 min, 1-bromo-2-butene (65 μL , 0.640 mmol, 1.2 equiv) was added and the reaction was stirred at 23°C for 16 h. The reaction was then quenched with saturated ammonium chloride, extracted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (1% triethylamine in 5% methanol/ethyl acetate) to afford **8** (85 mg, 77% yield).

8: ^1H NMR (400 MHz, CDCl_3) δ 7.02 (s, 1H), 6.36 (d, $J = 8.0 \text{ Hz}$, 1H), 6.14–6.05 (m, 1H), 5.78–5.54 (m, 2H), 4.08 (dd, $J = 5.6, 1.2 \text{ Hz}$, 2H), 3.97–3.93 (m, 2H), 3.49 (s, 3H), 2.37 (s, 3H), 1.72 (dd, $J = 7.0 \text{ Hz}$, 3H); MS(ES) $^+$ calcd for $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 207.2, found 207.1.

Cycloaddition of 8

To a vial of **8** (60.0 mg, 0.291 mmol, 1.0 equiv) and $\text{Ir}(\text{ppy})_3$ (4.8 mg, 0.00728 mmol, 2.5%) under argon was added *N,N*-dimethylformamide (6.0 mL). The solution was degassed at 23°C for $3 \times 5 \text{ min}$. This reaction mixture was then irradiated with visible light using an 11 W compact fluorescent lamp (CFL) bulb. After stirring at 23°C for 20 h, the reaction solution

was diluted with ethyl acetate (20 mL) and washed successively with water and brine, and dried over sodium sulfate. The crude product was purified preparative HPLC (Eclipse XDB-C18, 9.4 × 250 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 10% B, T = 5 min: 10% B, T = 15 min: 20% B, 4.8 mL/min) to afford **15** (1.3 mg, 2% yield, retention time: 9.2 min), **12** (32.1 mg, 53% yield, retention time: 9.8 min), **13** (12.2 mg, 20% yield, retention time: 11.2 min), **14** (3.2 mg, 5% yield, retention time: 13.2 min).

12: ¹H NMR (500 MHz, CDCl₃) δ 7.15 (s, 1H), 4.01 (d, *J* = 9.6 Hz, 1H), 3.88 (d, *J* = 9.6 Hz, 1H), 3.59 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.50 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.48 (s, 3H), 3.32–3.25 (m, 1H), 3.16–3.07 (m, 1H), 2.65 (s, 3H), 2.52–2.46 (m, 1H), 2.46–2.38 (m, 1H), 0.79 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.2, 134.4, 116.1, 73.5, 72.8, 43.6, 39.9, 34.9, 34.5, 30.9, 16.8, 10.9; HRMS(ES)⁺ calcd for C₁₂H₁₉N₂O (M+H)⁺ 207.1492, found 207.1500.

13: ¹H NMR (400 MHz, CDCl₃) δ 7.12 (s, 1H), 4.19 (d, *J* = 10.0 Hz, 1H), 3.86 (d, *J* = 10.0 Hz, 1H), 3.55 (s, 3H), 3.47 (ddd, *J* = 14.2, 10.0, 5.3 Hz, 2H), 2.99 (q, *J* = 7.5 Hz, 1H), 2.92 (q, *J* = 5.6 Hz, 1H), 2.73–2.66 (m, 1H), 2.64 (s, 3H), 2.61–2.53 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.1, 137.6, 114.4, 72.1, 67.9, 42.3, 39.2, 38.4, 33.9, 31.4, 14.6, 11.0; HRMS(ES)⁺ calcd for C₁₂H₁₉N₂O (M+H)⁺ 207.1492, found 207.1502.

14: ¹H NMR (400 MHz, CDCl₃) δ 7.10 (s, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 3.51 (s, 3H), 3.50–3.34 (m, 3H), 3.29–3.09 (m, 2H), 3.03 (t, *J* = 8.3 Hz, 1H), 2.66 (s, 3H), 2.28 (q, *J* = 6.8 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), HRMS(ES)⁺ calcd for C₁₂H₁₉N₂O (M+H)⁺ 207.1492, found 207.1498.

15: ¹H NMR (500 MHz, CDCl₃) δ 4.10–3.97 (m, 2H), 3.62 (dd, *J* = 10.3, 4.8 Hz, 2H), 3.58 (s, 3H), 2.91–2.72 (m, 3H), 2.63 (s, 3H), 2.50 (dd, *J* = 11.9, 3.9 Hz, 1H), 2.34–2.24 (m, 1H), 1.36 (d, *J* = 7.0 Hz, 1H); HRMS(ES)⁺ calcd for C₁₂H₁₉N₂O (M+H)⁺ 207.1492, found 207.1493.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Structures of nakamuric acid (1), sceptrin (2), hymenidin (3), and ageliferin (4), and the Molinski–Romo biosynthetic hypothesis.

Fig. 2.
Design of the model system that mimics the biogenic dimerization of $3^{+\bullet}$ /3.

Fig. 3.
Evaluation of the model system **8** that mimics the biogenic dimerization of **3^{•+}/3**.

Fig. 4.
The synthetic route for **8**.

Fig. 5.
The biomimetic [2+2] and [4+2] cycloaddition of **8** induced by photoredox chemistry.