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RESEARCH ARTICLE

Syntheses of Sceptrins and Nakamuric Acid and Insights into the Biosyntheses of Pyrrole–Imidazole Dimers

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Sceptrins and nakamuric acid are structurally unique antibiotics isolated from marine sponges. Recent studies suggest that the biosynthesis of these dimeric pyrrole–imidazole alkaloids involves a single-electron transfer (SET)-promoted [2+2] cycloaddition to form their cyclobutane core skeletons. We describe herein the biomimetic syntheses of racemic sceptrin and nakamuric acid. We also report the asymmetric syntheses of sceptrin, bromosceptrin, and dibromosceptrin in their natural enantiomeric form. We further provide mechanistic insights into the pathway selectivity of the SET-promoted [2+2] and [4+2] cycloadditions that lead to the divergent formation of the sceptrin and ageliferin core skeletons. Both the [2+2] and [4+2] cycloadditions are stepwise reactions, with the [2+2] pathway kinetically and thermodynamically favored over the [4+2] pathway. For the [2+2] cycloaddition, the dimerization of pyrrole–imidazole monomers is rate-limiting, whereas for the [4+2] cycloaddition, the cyclization is the slowest step.

Introduction

Sceptrin (**1a**)[1] and ageliferin (**3a**)[2] are the founding members of the dimeric pyrrole–imidazole alkaloids that have attracted synthetic chemists' attention for decades (Fig. 1).[3,4] Previously, the Baran and the Birman groups each developed a [2+2] photocycloaddition approach to accomplish the total synthesis of **1**.[5,6] The Baran group further demonstrated that **1** could be converted into **3** in a stereospecific manner.[7] We also used a biomimetic radical cyclization approach to complete the asymmetric synthesis of **1a** and **3**.[8] In addition, the Harran group achieved the synthesis of **3a** using a ring-expansion strategy,[9] and the Ohta group the synthesis of 12,12′-dimethylageliferin using a thermal Diels–Alder cycloaddition strategy.[10]

Although the biogenesis of these pyrrole–imidazole dimers has been a subject of long debates,[11] it is generally agreed that **1a** and **3a** are derived from hymenidin (**4a**) through formal [2+2] and [4+2] cycloadditions, respectively. Recently, Molinski and Romo have provided evidence through metabiosynthetic studies that the biogenic dimerization of **4** is promoted by an enzymatic single-electron transfer (SET) reaction.[12] A SET oxidation of **4** would give radical cation **4**•+ that is highly reactive toward [2+2] (*path a*) and [4+2] (*path b*) cycloadditions[13] with another molecule of **4** to give **1**•+ and **3**•+,

Sceptrin (**1a**): R,X,Y=***Ar***,H,H
Bromosceptrin (**1b**): R,X,Y=***Ar***,H,Br
Dibromosceptrin (**1c**): R,X,Y=***Ar***,Br,Br
Nakamuric acid (**2**): R,X,Y=CO₂H,H,H
(revised absolute stereochemistry)

Ageliferin (**3a**): X,Y=H,H
Bromoageliferin (**3b**): X,Y=H,Br
Dibromoageliferin (**3c**): X,Y=Br,Br
(revised absolute stereochemistry)

Hymenidin (**4a**): X=H
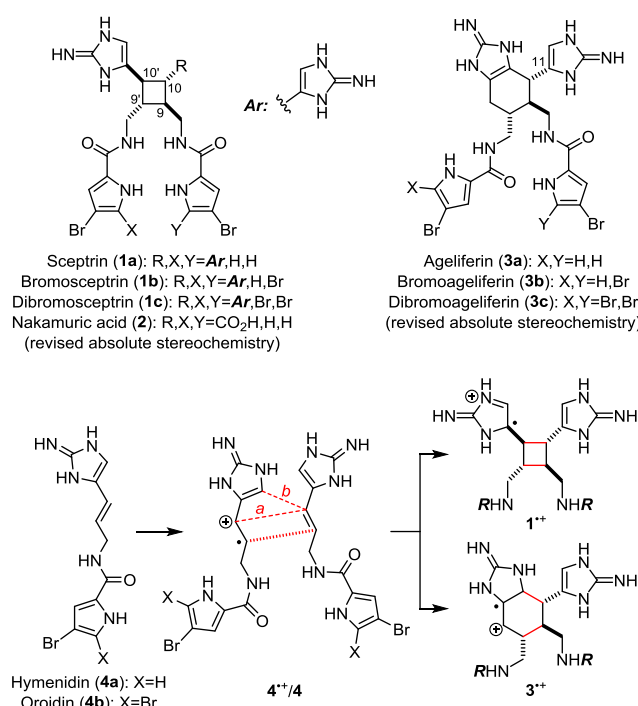Oroidin (**4b**): X=Br

4•+/**4**

Fig. 1. Sceptrins (**1**) and ageliferins (**3**) are formally the [2+2] and [4+2] cycloaddition products of hymenidin/oroidin (**4**). Nakamuric acid (**2**) is a pseudo-symmetric [2+2]-type pyrrole–imidazole dimer.

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correspondingly. Subsequent SET reduction would provide **1** and **3** after tautomerization. Guided by this biosynthetic hypothesis, we have developed an asymmetric approach to accomplish the syntheses of **1a** and **3**, and revised their absolute stereochemistries recently.[8e] We report herein the

syntheses of all members of sceptrins (**1**) and the pseudo-symmetric [2+2] dimer nakamuric acid (**2**)[5b,14]. Additionally, we provide a mechanistic understanding of the pathway selectivity of the cycloaddition of **4**[•+]/**4**.

Results and discussion

We are interested in using total syntheses to examine the biosynthetic hypotheses for the pyrrole–imidazole dimers.[8] The prior syntheses of **1**/**2** by the Baran group and the Birman group involve the use of a [2+2] photocycloaddition to build the cyclobutane core with a formation of the C9/C10 and C9'/C10' linkages.[5,6] Recent development in photoredox chemistry by Yoon and others[15,16] has inspired us to explore the possibility of using a SET-promoted [2+2] cycloaddition to establish the C9/C9' and C10/C10' linkages of **1**/**2** in a biomimetic fashion.

Our study started with the design of a SET-promoted [2+2] cycloaddition to assemble the core skeleton of **1** and **2**. After exploring various substrate systems, we decided to use radical cation **5** to mimic **4**[•+]/**4**. We envisioned that **5** would undergo a formal [2+2] and a [4+2] cycloaddition to give **6** and **7**, correspondingly (Fig. 2). Initial studies using **8** as the model substrate led to the identification of a suitable photoredox catalyst. Irradiation of **8** in the presence of a catalytic amount of Ir(ppy)$_3$ gave the [2+2] cycloadducts **9** and the [4+2] cycloadduct **10** smoothly.[8f]
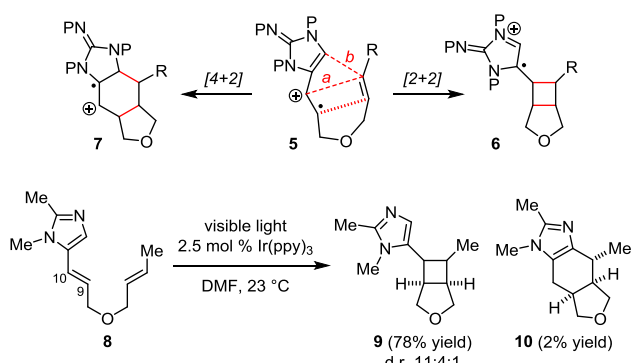

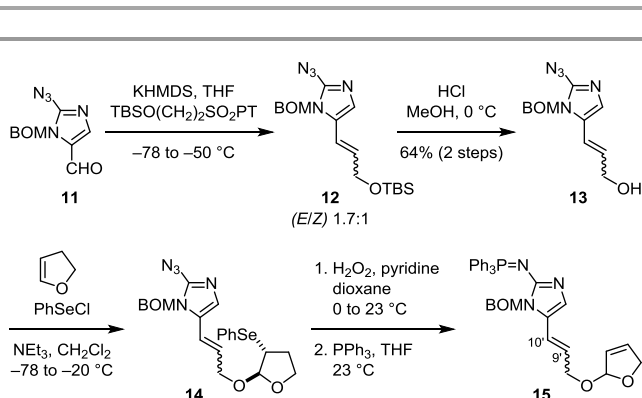**Fig. 2.** Design and proof-of-concept of our biomimetic synthetic strategy.

Fig. 3. Preparation of the [2+2] cycloaddition precursor.

With this success, we went on to study the synthesis of nakamuric acid (**2**). Starting from aldehyde **11**,[8c,d] a Julia–Kocienski olefination gave allylic ether **12** with a modest *E*/*Z* selectivity (Fig. 3). Subsequent deprotection yielded allylic alcohol **13**, which was coupled with 2,3-dihydrofuran to provide **14** through alkoxy senelylation. Next, oxidation of the phenylselenide, elimination of the resulting phenylselenoxide, and reduction of the azido group afforded **15**.

Recently, the Yoon group has developed a remarkably mild method to promote SET-mediated [2+2] cycloadditions.[16] Following their protocols, we irradiated **15** with visible light in the presence of 3 mol % Ir(ppy)$_3$ and obtained the desired [2+2] cycloadduct *meso*-**16** together with its C10' epimer (d.r. 1.8:1) (Fig. 4). Attempts to induce the [2+2] cycloaddition prior to the Staudinger reduction failed under various conditions presumably due to the high oxidative potential of vinylazidoimidazole. Reduction of the azido group gave a phosphine imide-protected vinylaminoimidazole that is more electron-rich and can be readily oxidized by a photoredox catalyst. Because Yoon has found that iridium(III)-complexes could also promote [2+2] cycloadditions via an energy-transfer mechanism,[16g] we irradiated **15** with a catalytic amount of 9-fluorenone that has a triplet energy (E_T = 55 kcal/mol)[17] the same as that of Ir(ppy)$_3$ in order to probe the mechanism of the Ir(ppy)$_3$-catalyzed [2+2] cycloaddition of **15**. As no reaction occurred with 9-fluorenone, we believe that **16** was produced via a SET mechanism. Notably, isomerization of the C9'-10' olefin of **15** was observed during the reaction, indicating that the cycloaddition of **15**[•+] instead of the SET oxidation of **15** was the rate-limiting step.
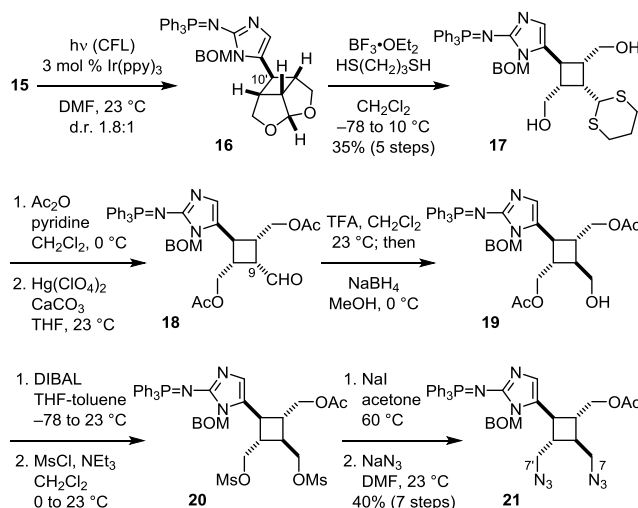

Fig. 4. Construction of the cyclobutane core skeleton.

In the following stage of the synthesis, the core skeleton of **2** was revealed by subjecting **16** to a transthioketalization reaction to provide **17**. Next, protection of the hydroxyl groups and removal of the dithiane protecting group gave **18**. Epimerization of the C9 stereogenic center followed by reduction of the C9 aldehyde yielded **19**. Consistent with Baran's prior observations,[5b] introduction of the N7 and N7' groups was challenging due to steric hindrance. Eventually, we

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realized this demanding transformation by applying the three-step procedure that we previously developed for the synthesis of ageliferin (**3a**).[8c,d] After removing one of the acetyl protecting groups of **19**, the resulting diol was mesylated to afford *rac*-**20**. Subsequent iodination and azidation gave **21** as a trifluoroacetic acid salt upon HPLC purification. Using pyridine instead of triethylamine[8c,d] as the base for the mesylation step effectively suppressed the side-reaction that led to the formation of the mesylaminoimidazolium salt of **20**.

To install the pyrrole groups, the azido groups of **21** were reduced to yield **22** (Fig. 5). Although this hydrogenolysis reaction proceeded more efficiently in methanol than in ethyl acetate, employing methanol as the solvent also led to the undesired formation of the methylamines of **22**. Diamine **22** was unstable and decomposed under various amidation conditions. We found that the carbodiimide-mediated amide coupling was the only effective method to introduce the pyrrole groups to give **23**. Subsequent removal of the acetyl group yielded alcohol **24**. Oxidation of the hydroxyl group to carboxylic acid was achieved by a Dess–Martin oxidation and a Lindgren oxidation in one-pot to provide **25**. To remove the benzyloxylmethyl protecting group, **25** was first treated with boron trichloride to cleave the benzyl group. The resulting hydroxymethyl group was then hydrolyzed by treating with ammonium hydroxide in situ to give **26**. Finally, the triphenylphosphine imide group was hydrolyzed under acidic conditions to afford *rac*-nakamuric acid (**2**). Because most aminoimidazole-containing intermediates in this synthesis were not stable and readily decomposed upon exposure to acid or air, this synthetic route was optimized to minimize the number of purification processes.
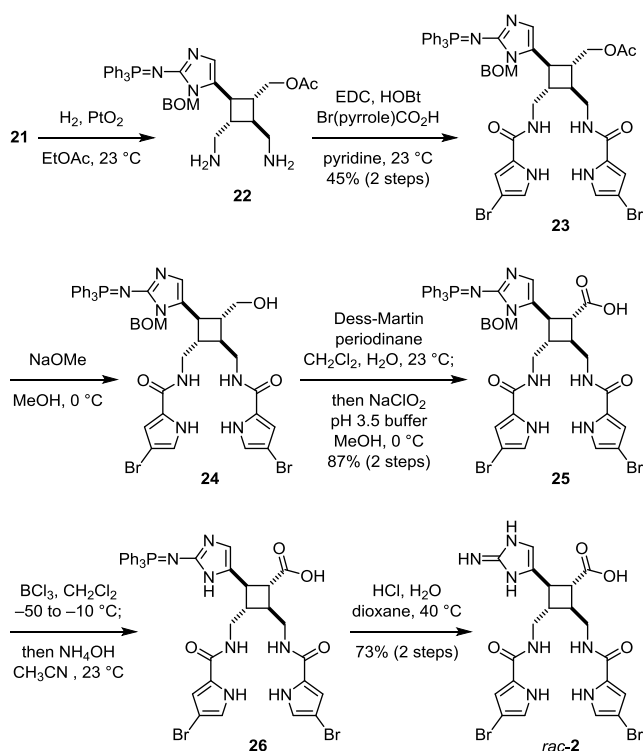

Fig. 5. Synthesis of *rac*-nakamuric acid (**2**).

After completing the synthesis of nakamuric acid (**2**), we turned our attention to the synthesis of sceptrin (**1a**). Starting with alcohol **24**, we adapted the method developed by Stoltz for the dragmacidin synthesis[18] to construct the second aminoimidazole group. A Dess–Martin oxidation of **24** followed by a Henry reaction with nitromethane gave **27** after reduction of the nitro group using the Carreira's conditions,[19] and protection of the resulting amino group as a *tert*-butylcarbamate (Fig. 6). Notably, no debromination of the 4-bromopyrrole occurred when the reduction of the nitro group by zinc was performed at 4 °C. Subsequent oxidation of the hydroxyl group yielded ketone **28**. The benzyloxymethyl and *tert*-butylcarbamate protecting groups were then removed to provide aminoketone **29**. The aminoimidazole group was constructed by condensing **29** with cyanamide[20] to furnish *rac*-sceptrin (**1a**). The triphenylphosphine protecting group was also hydrolyzed under these reaction conditions.
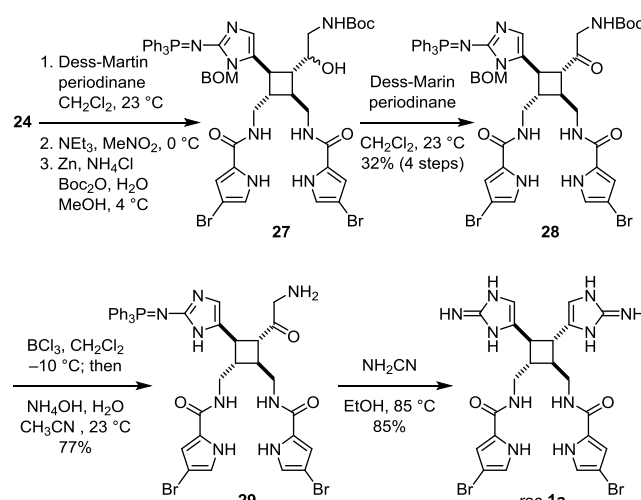

Fig. 6. Synthesis of *rac*-sceptrin (**1a**).

To achieve the asymmetric synthesis of **1**, we first attempted to desymmetrize **17** or its derivatives. However, we could only obtain products with low optical purities. Equally frustrated was the resolution of **21** or its derivatives. The formation of imidazolium salts with L-menthol chloroformate proceeded with low efficiency. Separation of the two diastereomeric salts on HPLC was also difficult. Despite some success on small scales, this method is far from being practical. Therefore, we turned our attention to the chiral-pool approach that we developed for the asymmetric syntheses of **3**.[8a–e]

Previously, we took advantage of the stereocenter at the C11 position to control the stereoselective formation the core skeleton of **3**. We thus decided to use this strategy for the stereoselective establishment of the sceptrin core skeleton. In contrast to using D-serine as the source of chirality for **3**, we started our synthesis of **1** from D-glutamic acid (**30**). Diazotization of **30** led to the formation of **31** (Fig. 7).[21] Reduction of the carboxylic acid group of **31** provided alcohol **32**.[22] Subsequent protection of the hydroxyl group and reduction of the lactone yielded hemiacetal **33**, which was dehydrated to afford dihydrofuran **34**.[23] Coupling of fragments

13 and **34** through alkoxy selnenylation[24] proceeded with excellent stereoselectivity. Episelenium formation with **34** occurred on its less hindered face, allowing alcohol **13** to approach from the more hindered face to give **35** as the only diastereomeric product. Subsequent oxidative elimination of the phenylselenide group provided **36**. Staudinger reduction of the azido group gave 8,11-*cis*-**37** that underwent a smooth intramolecular [2+2] cycloaddition under photoredox conditions. Irradiation of **37** with visible light in the presence of 3 mol % Ir(ppy)$_3$ yielded **38** as a 1.8:1 mixture of C10′ diastereomers.
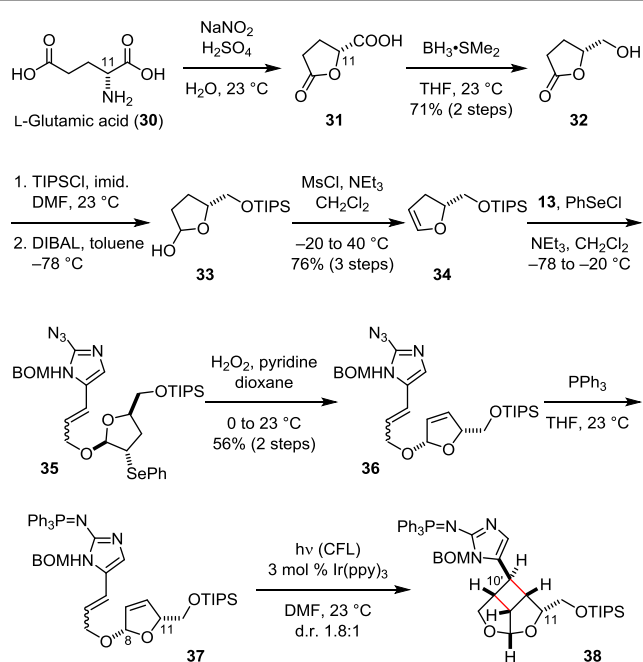

Fig. 7. Construction of the core skeleton of *nat*-sceptrins (**1**).

To complete the synthesis of **1**, the sceptrin core of pseudosymmetric **38** was revealed by transthioketalization to give **39** (Fig. 8). The hydroxyl groups were then protected and the dithiane group was hydrolyzed. Epimerization at the C9 stereocenter, reduction of the aldehyde group, and removal of the acetate protecting groups yielded **40**. Subsequently, mesylation, iodination, azidation, and desilylation delivered **41**. To construct the second aminoimidazole group, the hydroxyl group of **41** was oxidized and the resulting mesyl aldehyde was condensed with Boc-guanidine to give **42**. Hydrolysis of the Boc protecting group occurred during HPLC purification. Next, reduction of the azido groups of **42** yielded diamine **43**. Carrying out the reduction in *tert*-butanol provided improved efficiency. Coupling of **43** with 4-bromopyrrole-2-carboxylic acid or 4,5-dibromopyrrole-2-carboxylic acid gave **44a** or **44c**, correspondingly. Sequential coupling of **43** with these two acids gave **44b**. Finally, deprotection of **44** afforded sceptrins in its natural enantiomeric form (*nat*-**1**) as indicated by CD analyses (Fig. 9).[25] This result is consistent with our previous work that using

L-glutamic acid as the source of chirality for this synthetic sequence gave *ent*-**1a**, affirming the notion[8e] that the absolute stereochemistry of sceptrins and ageliferins should be revised to those of **1** and **3** as shown in Fig. 1.
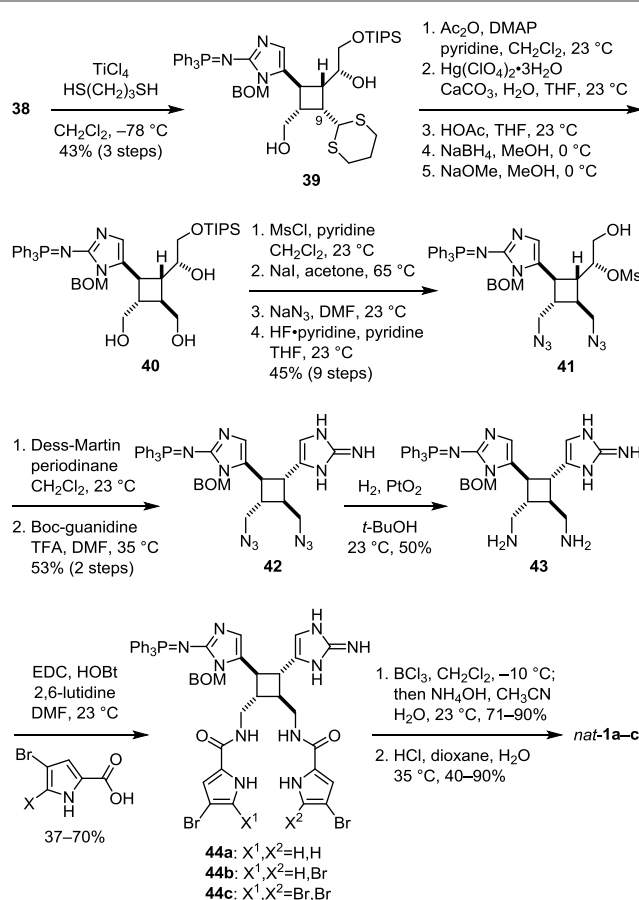

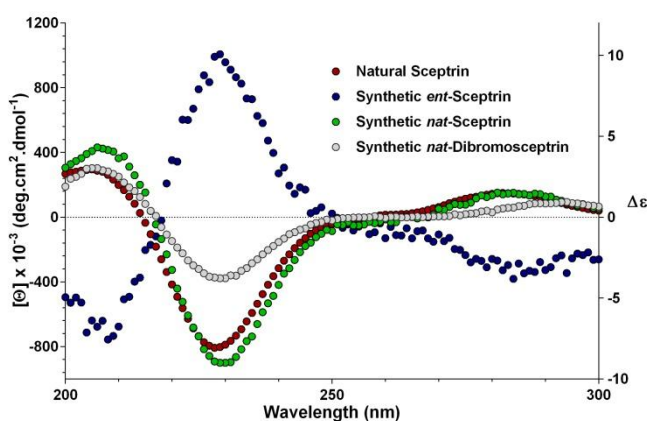**Fig. 8.** Synthesis of *nat*-sceptrin (**1a**).

Fig. 9. Comparison of the CD spectra of sceptrins in water. Red, natural sceptrin•TFA in methanol;[26b] Blue, synthetic sceptrin•TFA from L-glutamic acid in water; Green, synthetic sceptrin•TFA from D-glutamic acid in water; Grey, synthetic dibromosceptrin•TFA from D-glutamic acid in water.
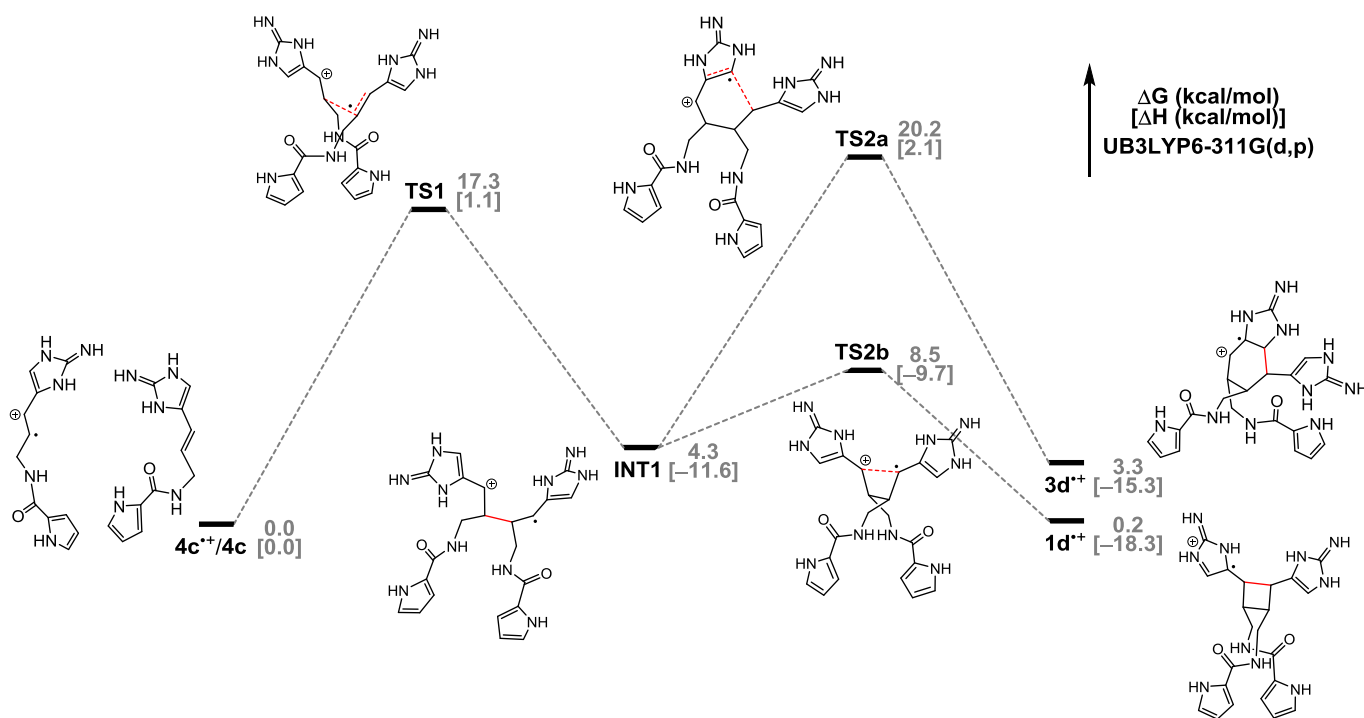
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Fig. 10. Energy diagram for the [2+2] and [4+2] cycloadditions of **4c•⁺/4c**.

To gain insights into the biogenic dimerization of **4**, we analyzed the energy profiles of the SET-promoted [2+2] and [4+2] cycloadditions of clathrodin (**4c**) by DFT calculations at the (U)B3LYP-6-311G(d,p) level (Fig. 10). Both the Gibbs free energies and the enthalpies of the reaction intermediates and transition states were evaluated. Consistent with our experimental results on the model systems,[8d,f] these cycloadditions are most likely stepwise radical addition reactions, as we were not able to locate the transition states corresponding to the concerted cycloadditions. These reactions start from the formation of **INT1** from **4c•⁺** and **4c**, with an activation enthalpy of 1.1 kcal/mol. Formation of **INT1** is exothermic by 11.6 kcal/mol. Then, bifurcation from **INT1** to give either [2+2] or [4+2] cycloadduct takes place. For the formation of **1d•⁺**, the first step via **TS1** with an activation enthalpy of 1.1 kcal/mol is a bimolecular process, whereas the second step of converting **INT1** to **1d•⁺** with an activation enthalpy of 1.9 kcal/mol is a unimolecular process. Therefore, the first step of the [2+2] pathway is the rate-determining step when considering the entropy penalty in **TS1** with respect to reactants **4d•⁺** and **4d**.

DFT calculations also found that the [2+2] pathway is highly favored because **TS2b** to **1d•⁺** is lower in free energy than **TS2a** to **3d•⁺** by 11.7 kcal/mol (ΔΔH‡, 11.8 kcal/mol). Consistently, our model studies showed the same pathway selectivity. SET-promoted cycloaddition of **8** gave the [2+2] cycloaddition product predominantly, with a pathway selectivity of nearly 40:1 (Fig. 2). It is likely that, in ageliferin-producing sponges, the oxidoreductase promoting the SET-dimerization reaction stabilizes **TS2a** to facilitate the formation of **3**. In nature, **1a** is one of the most abundant pyrrole–imidazole alkaloid.[26] When

1a and **3a** were isolated from the same sponges, **1a** is always by far the major constituent.[1b,2b,14]

Conclusions

We demonstrate herein that SET can promote [2+2] and [4+2] cycloadditions of oroidin/hymenidin/clathrodin (**4**) to give sceptrins (**1**) and ageliferins (**3**) as proposed by Molinski, Romo, and us. Following this hypothesis, we completed the biomimetic syntheses of scetprins (**1**) and nakamuric acid (**2**), using photoredox chemistry to promote SET in assembling the core skeleton of these pyrrole–imidazole dimers. We also confirmed that the original absolute stereochemistry of **1** determined by crystallographic studies was incorrect. Whereas X-ray analysis has been regarded as an "unambiguous" way to establish the structure of small molecules in the field of organic chemistry, cautions are still needed to avoid misinterpretation of the diffraction data.[27] Finally, our computational studies provided direct support that SET can promote cycloadditions of **4** to give **1** and **3**. Importantly, the relative natural abundance of **1** and **3** is consistent with the pathway selectivity of the SET-promoted but not the thermal cycloadditions.

Acknowledgements

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Notes and references

1 (a) R. P. Walker, D. J. Faulkner, D. V. Engen and J. Clardy, *J. Am. Chem. Soc.*, 1981, **103**, 6772–6773; (b) M. Assmann and M. Köck, *Z. Naturforsch., C: Biosci.*, 2002, **57**, 157–160.

2 (a) J. Kobayashi, M. Tsuda, T. Murayama, H. Nakamura, Y. Ohizumi, M. Ishibashi, M. Iwamura, T. Ohta and S. Nozoe, *Tetrahedron*, 1990, **46**, 5579–5586; (b) P. A. Keifer, R. E. Schwartz, M. E. S. Koker, R. G. Hughes, Jr., D. Rittschof and K. L. Rinehart, *J. Org. Chem.*, 1991, **56**, 2965–2975.

3 (a) H. Hoffmann and T. Lindel, *Synthesis*, 2003, **35**, 1753–1783; (b) D. E. N. Jacquot and T. Lindel, *Curr. Org. Chem.*, 2005, **9**, 1551–1565; (c) H. Du, Y. He, R. Sivappa and C. J. Lovely, *Synlett*, 2006, 965–992; (d) M. Köck, A. Grube, I. B. Seiple and P. S. Baran, *Angew. Chem. Int. Ed.*, 2007, **46**, 6586–6594; (e) S. M. Weinreb, *Nat. Prod. Rep.*, 2007, **24**, 931–948; (f) H.-D. Arndt and M. Riedrich, *Angew. Chem. Int. Ed.*, 2008, **47**, 4785–4788; (g) B. Heasley, *Eur. J. Org. Chem.*, 2009, 1477–1489; (h) B. Forte, B. Malgesini, C. Piutti, F. Quartieri, A. Scolaro and G. Papeo, *Mar. Drugs*, 2009, **7**, 705–753; (i) A. Al-Mourabit, M. A. Zancanella, S. Tilvi and D. Romo, *Nat. Prod. Rep.*, 2011, **28**, 1229–1260.

4 (a) X. Wang, Z. Ma, X. Wang, S. De, Y. Ma and C. Chen, *Chem. Commun.*, 2014, **50**, 8628–8639; (b) Y. Ma, S. De and C. Chen, *Tetrahedron*, 2014, **71**, 1145–1173.

5 (a) P. S. Baran, A. L. Zografos and D. P. O'Malley, *J. Am. Chem. Soc.*, 2004, **126**, 3726–3727; (b) D. P. O'Malley, K. Li, M. Maue, A. L. Zografos and P. S. Baran, *J. Am. Chem. Soc.*, 2007, **129**, 4762–4775.

6 V. B. Birman and X.-T. Jiang, *Org. Lett.*, 2004, **6**, 2369–2371.

7 (a) P. S. Baran, D. P. O'Malley and A. L. Zografos, *Angew. Chem. Int. Ed.*, 2004, **43**, 2674–2677; (b) P. S. Baran, K. Li, D. P. O'Malley and C. Mitsos, *Angew. Chem. Int. Ed.*, 2006, **45**, 249–252.

8 (a) X. Tan and C. Chen, *Angew. Chem. Int. Ed.*, 2006, **45**, 4345–4348; (b) Z. Ma, J. Lu, X. Wang and C. Chen, *Chem. Commun.*, 2011, **47**, 427–429; (c) X. Wang, Z. Ma, J. Lu, X. Tan and C. Chen, *J. Am. Chem. Soc.*, 2011, **133**, 15350–15353; (d) X. Wang, X.-L. Wang, X. Tan, J. Lu, K. W. Cormier, Z. Ma and C. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 18834–18842; (e) Z. Ma, X. Wang, X. Wang, R. A. Rodriguez, C. E. Moore, S. Gao, X. Tan, Y. Ma, A. L. Rheingold, P. S. Baran and C. Chen, *Science*, 2014, **346**, 219–224; (f) X. Wang and C. Chen, *Tetrahedron*, DOI: 10.1016/j.tet.2014.1010.1027.

9 H. Ding, A. G. Roberts and P. G. Harran, *Chem. Sci.*, 2012, **4**, 303–306.

10 (a) I. Kawasaki, N. Sakaguchi, N. Fukushima, N. Fujioka, F. Nikaido, M. Yamashita and S. Ohta, *Tetrahedron Lett.*, 2002, **43**, 4377–4380; (b) I. Kawasaki, N. Sakaguchi, A. Khadeer, M. Yamashita and S. Ohta, *Tetrahedron*, 2006, **62**, 10182–10192.

11 (a) Ref. 1a; (b) Ref. 2a; (c) Ref. 2b; (d) Ref. 7a; (e) A. Al Mourabit and P. Potier, *Eur. J. Org. Chem.*, 2001, 237–243; (f) B. H. Northrop, D. P. O'Malley, A. L. Zografos, P. S. Baran and K. N. Houk, *Angew. Chem. Int. Ed.*, 2006, **45**, 4126–4130.

12 (a) E. P. Stout, Y.-G. Wang, D. Romo and T. F. Molinski, *Angew. Chem. Int. Ed.*, 2012, **51**, 4877–4881; (b) E. P. Stout, B. I. Morinaka, Y.-G. Wang, D. Romo and T. F. Molinski, *J. Nat. Prod.*, 2012, **75**, 527–530.

13 (a) D. J. Bellville, D. D. Wirth and N. L. Bauld, *J. Am. Chem. Soc.*, 1981, **103**, 718–720; (b) N. L. Bauld and R. Pabon, *J. Am. Chem. Soc.*, 1983, **105**, 633–634; (c) D. W. Reynolds and N. L. Bauld, *Tetrahedron*, 1986, **42**, 6189–6194; (d) N. L. Bauld, *Tetrahedron*, 1989, **45**, 5307–5363; (e) W. Yueh and N. L. Bauld, *J. Am. Chem. Soc.*, 1995, **117**, 5671–5676.

14 C. Eder, P. Proksch, V. Wray, R. W. M. v. Soest, E. Ferdinandus, L. A. Pattisina and Sudarsono, *J. Nat. Prod.*, 1999, **62**, 1295–1297.

15 (a) D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 1239176; (b) T. P. Yoon, *ACS Catal.*, 2013, **3**, 895–902; (c) M. A. Ischay and T. P. Yoon, *Eur. J. Org. Chem.*, 2012, 3359–3372; (d) T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2010, **2**, 527–532; (e) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (f) J. W. Tucker and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 1617–1622; (g) J. J. Douglas, J. D. Nguyen, K. P. Cole and C. R. J. Stephenson, *Aldrichimica Acta*, 2014, **47**, 15–25; (h) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113; (i) J. Xuan and W.-J. Xiao, *Angew. Chem. Int. Ed.*, 2012, **51**, 6828–6838; (j) F. Teplý, *Collect. Czech. Chem. Commun.*, 2011, **76**, 859–917; (h) K. Zeitler, *Angew. Chem. Int. Ed.*, 2009, **48**, 9785–9789.

16 (a) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 12886–12887; (b) J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2009, **131**, 14604–14605; (c) M. A. Ischay, Z. Lu and T. P. Yoon, *J. Am. Chem. Soc.*, 2010, **132**, 8572–8574; (d) S. Lin, M. A. Ischay, C. G. Fry and T. P. Yoon, *J. Am. Chem. Soc.*, 2011, **133**, 19350–19353; (e) E. L. Tyson, E. P. Farney and T. P. Yoon, *Org. Lett.*, 2012, **14**, 1110–1113; (f) M. A. Ischay, M. S. Ament and T. P. Yoon, *Chem. Sci.*, 2012, **3**, 2807–2811; (g) Z. Lu and T. P. Yoon, *Angew. Chem. Int. Ed.*, 2012, **51**, 10329–10332; (h) J. Du, K. L. Skubi, D. M. Schultz and T. P. Yoon, *Science*, 2014, **344**, 392–396; (i) A. E. Hurtley, Z. Lu and T. P. Yoon, *Angew. Chem. Int. Ed.*, 2014, **53**, 8991–8994.

17 (a) D. Valentine, Jr. and G. S. Hammond, *J. Am. Chem. Soc.*, 1972, **94**, 3449–3454; (b) F.-C. Chen, S.-C. Chang, G. He, S. Pyo, Y. Yang, M. Kurotaki and J. Kido, *J. Polym. Sci., Part B: Polym. Phys.*, 2003, **21**, 2681–2690.

18 N. K. Garg, R. Sarpong and B. M. Stoltz, *J. Am. Chem. Soc.*, 2002, **124**, 13179–13184.

19 A. Breder, G. M. Chinigo, A. W. Waltman and E. M. Carreira, *Chem. Eur. J.*, 2011, **17**, 12405–12416.

20 (a) Ref. 5b; (b) L. H. Foley and G. Büchi, *J. Am. Chem. Soc.*, 1982, **104**, 1776–1777.

21 (a) O. H. Gringore and F. P. Rouessac, *Org. Syn.*, 1985, **63**, 121–126; (b) A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3278–3284; (c) A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3284–3289; (d) A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3593–3603; (e) M. Taniguchi, K. Koga and S. Yamada, *Tetrahedron*, 1974, **30**, 3547–3552.

22 U. Ravid, R. M. Silverstein and L. R. Smith, *Tetrahedron*, 1978, **34**, 1449–1452.

23 A. Takle and P. Kocieński, *Tetrahedron*, 1990, **46**, 4503–4516.

24 A. P. Kozikowski, K. L. Sorgi and R. J. Schmiesing, *J. Chem. Soc., Chem. Commun.*, 1980, 477–479.

25 (a) Ref. 7b; (b) J. Muñoz, C. Moriou, J.-F. Gallard, P. D. Marie and A. Al-Mourabit, *Tetrahedron Lett.*, 2012, **53**, 5828–5832; 6865.

26 (a) Ref. 1a; (b) F. Cafieri, R. Carnuccio, E. Fattorusso, O. Taglialatela-Scafati and T. Vallefuoco, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2283–2288; (c) M. Assmann, E. Lichte, J. R. Pawlik and M. Köck, *Mar. Ecol. Prog. Ser.*, 2000, **207**, 255–262; (d) E. Richelle-Maurer, M. J. De Kluijver, S. Feio, S. Gaudêncio, H. Gaspar, R. Gomez, R. Tavares, G. Van de Vyver and R. W. M. Van Soest, *Biochem. Sys. Ecol.*, 2003, **31**, 1073–

1091; (e) M. Assmann, E. Lichte and M. Köck, *Boll. Mus. Ist. Biol. Univ. Genova*, 2004, **68**, 187–193.

27 (a) P. G. Jones, *Chem. Soc. Rev.*, 1984, **13**, 157–172; (b) D. Rogers, *Acta Cryst.*, 1981, **A37**, 734–741; (c) H. D. Flack and G. Bernardinelli, *J. Appl. Cryst.*, 2000, **33**, 1143–1148; (d) H. D. Flack and G. Bernardinelli, *Chirality*, 2008, **20**, 681–690; (e) H. D. Flack, *Acta Chim. Slov.*, 2008, **55**, 689–691; (f) R. W. W. Hooft, L. H. Stravera and A. L. Spek, *J. Appl. Cryst.*, 2008, **41**, 96–103; (g) A. L. Thompson and D. J. Watkin, *Tetrahedron Asymmetry*, 2009, **20**, 712–717; (h) H. D. Flack, *Chimia*, 2014, **68**, 26–30.

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