Cascade Reactions

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Regiocontrol in Mn^{III}-Mediated Oxidative Heterobicyclizations: Access to the Core Skeletons of Oroidin Dimers**

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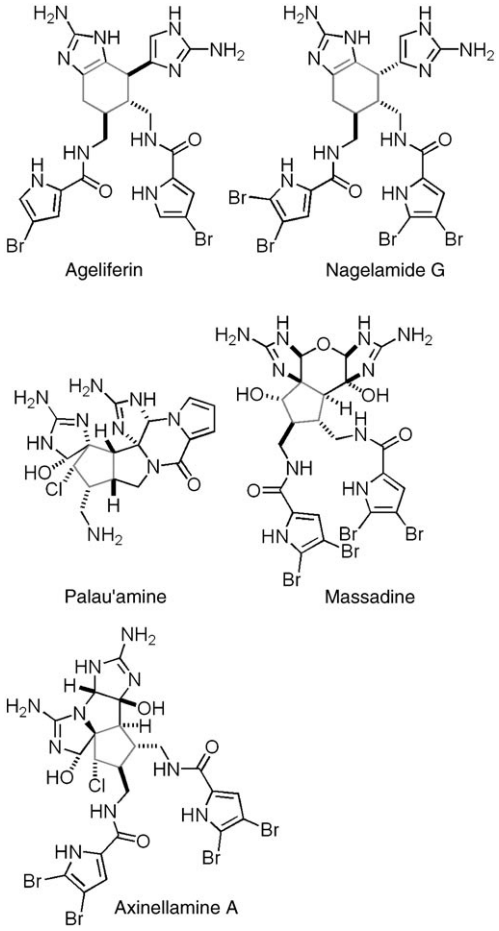
Dedicated to Professor Tien-Yau Luh on the occasion of his 60th birthday

Pyrrole–imidazole alkaloids, also known as oroidin-family natural products, possess diverse molecular skeletons (Scheme 1) and many important biological properties, such as antibiotic, antiproliferative, and immunosuppressive activities.[1] The synthesis of polycyclic oroidin dimers remains a significant challenge.[1,2] To address this issue, we devised a radical cascade cyclization[3] strategy to construct the central cyclopentyl and cyclohexenyl core skeletons (**4** and **5**) of two classes of oroidin dimers, ageliferin/nagelamide and massadine/palau'amine/axinellamine. Herein, we describe two types of Mn^{III}-promoted cyclization cascades of allylic β-imidazolinonyl-β-ketoesters **1**, wherein two C–C bonds and three or four contiguous stereogenic centers are established in a single operation (Scheme 2).

Manganese(III) acetate is well known as an effective oxidant for enolizable carbonyl compounds.[4] Since the initial report of Corey and Kang on the intramolecular Mn^{III}-promoted oxidative cyclizations of β-dicarboxylates,[5] the reaction has grown in popularity and scope.[6,7] However, despite extensive investigations, applications of this method to unsaturated N-heterocyclic systems[8] and allylic β-ketoesters[9] are rare.



Scheme 1. Structures of oroidin dimers.

As outlined in Scheme 2, our strategy involves the oxidation of β-ketoester **1** with Mn^{III}, thus initiating a radical cascade cyclization reaction to give the ageliferin/nagelamide core skeleton **4** or the massadine/palau'amine/axinellamine core skeleton **5** after decarboxylation. With the controlling element X = H, the reaction proceeds through a 5-*exo*/6-*endo* cyclization pathway. On the other hand, the reaction can be directed to the 5-*exo*/5-*exo* cyclization pathway when X = Cl or CN. We have also developed an oxidative rearrangement reaction of **2** and **4** as an alternative approach to **3** and **5**.[10]

Our initial efforts focused on the 5-*exo*/6-*endo* cyclization of **1** (**1**→**2**). β-Ketoester **6**, which bears an α-methyl group, was oxidized cleanly by $[Mn(OAc)_3]$ in HOAc at 60 °C to give the ageliferin skeleton **7** in 63 % yield of the isolated product (Table 1, entry 1). No monocyclization products and other diastereomers were observed in the ^1H NMR spectra of the crude product.[11] We found that $[Mn(OAc)_3]$ was the best oxidant and HOAc the optimal solvent. Addition of Cu-

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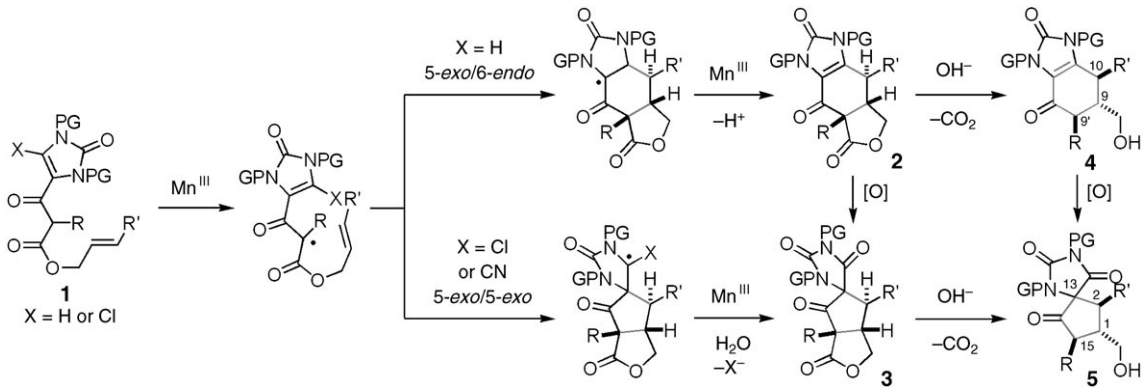
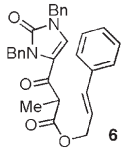
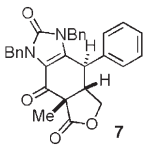
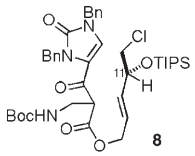
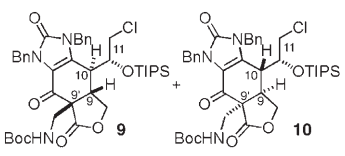
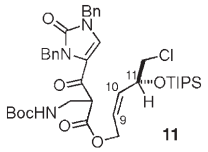
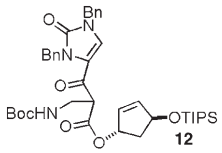
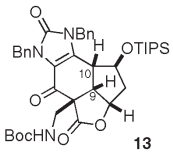


Scheme 2. Synthetic approach to the oroidin dimers.

Table 1: Mn^{III}-promoted 5-*exo*/6-*endo* radical cyclization reactions.[a]

Entry	Substrate	Product(s)	Yield [%]
1	 **6**	 **7**	63
2	 **8**	 **9** + **10**	59 (2.1:1)
3	 **11**	**9** + **10**	50[b] (1:1.5)
4	 **12**	 **13**	60

[a] Reaction conditions: $[Mn(OAc)_3]$ (3.0 equiv), HOAc, 60 °C. [b] 80 °C.

$(OAc)_2$ or $[Yb(OTf)_3]$ (Tf = trifluoromethanesulfonyl) has no significant effects.

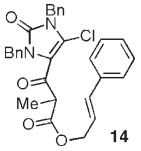
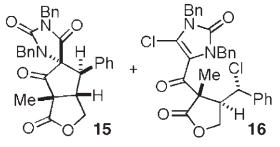
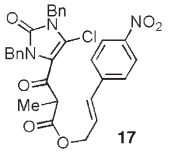
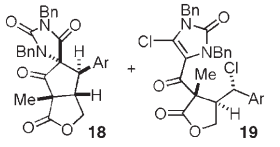
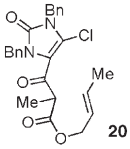
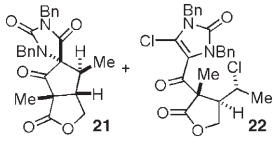
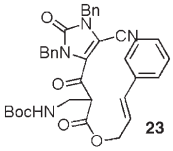
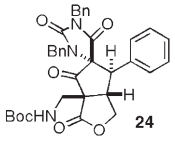
We next explored the scope of this radical cascade reaction. (*E*)-Allylic β-ketoester **8**, bearing all the necessary functional groups for the ageliferin synthesis, was oxidized cleanly to **9** and **10** in 59% yield (d.r. = 2.1:1; entry 2). Only two out of eight possible diastereomers were obtained. The C11 stereogenic center controlled the diastereoselectivity of this transformation through a moderate $A^{1,3}$ strain.[12] The α-radical of β-ketoester **8** added to the olefin preferentially from the less-hindered β face to give **9** as the major diastereomer. Lactones **9** and **10** contain the proper configurations at C9, C9′, and C10 for the ageliferin and *ent*-ageliferin synthesis. It is interesting to note that the oxidation of (*Z*)-**11** proceeded with "epimerization" at C10 and also afforded **9** and **10** (d.r. = 1:1.5; entry 3).[13,14] Constraining the (*Z*)-olefin in a cyclic system not only improved the diastereoselectivity but eliminated the issue of stereospecificity. Lactone **13** was obtained as the only product from the oxidation of **12** with $[Mn(OAc)_3]$ (entry 4).

We then turned our attention to the synthesis of the massadine/palau'amine core skeleton and introduced a Cl atom as X to direct the second cyclization toward the 5-*exo* pathway (**1**→**3**). Oxidation of **14** proceeded through a 5-*exo*/5-*exo* cyclization to give **15**[15] along with the monocyclization products **16** in an approximate 1:1 ratio (Table 2, entry 1). No 6-*endo* products and other diastereomers were observed in the ^1H NMR spectra of the crude product. Introduction of an electron-withdrawing nitro group to the cinnamyl ester did not change the product ratio significantly (entry 2). Oxidation of the crotyl ester **20** also gave a mixture of **21** and **22** (entry 3). Remarkably, formation of the monocyclization product can be suppressed with X = CN. Hydantoin **24** was obtained as the only product from the oxidation of **23** in 60% yield (entry 4).

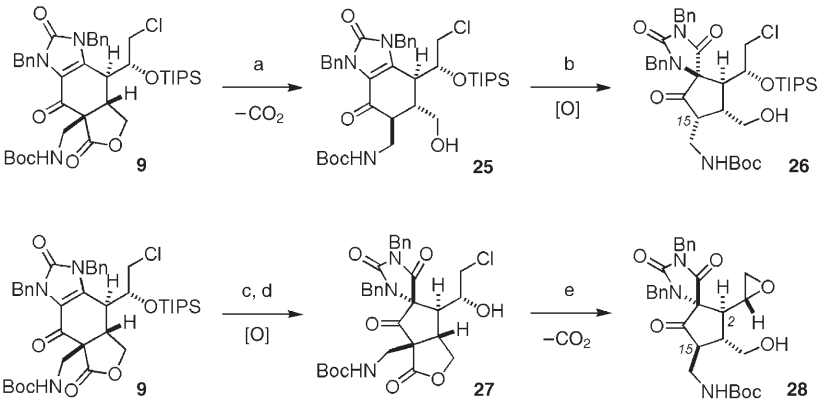
The temporary ester linkage used in the intramolecular reaction with $[Mn(OAc)_3]$ can be removed under decarboxylative conditions (Scheme 3). For example, briefly treating **9** with LiOH revealed the ageliferin core **25**. We also demonstrated that the ageliferin core skeleton **25** could be oxidatively rearranged to the massadine core **26** by mCPBA (namely, **4**→**5**) despite epimerization at C15. Notably, in contrast to the system developed by Dilley and Romo,[10a] ring contraction was achieved directly without competing migration of the olefin.

Lactone **9** can also be oxidized by mCPBA after deprotection of the triisopropylsilyl (TIPS) group (namely, **2**→**3**). In contrast to the oxidation of **9**, the reaction proceeded with opposite facial selectivity to afford hydantoin **27**, which bears the palau'amine spiro configuration. The ester linker of **27** can be removed with concomitant epoxide formation to provide **28**. The modifiable C2 and C15 stereogenic centers of **28** are opposite to those of palau'amine.

Table 2: Mn^{III}-promoted 5-*exo*/5-*exo* radical cyclization reactions.[a]

Entry	Substrate	Product(s)	Yield [%]
1	 **14**	 **15** + **16**	87 (1:1.2)
2	 **17**	 **18** + **19** Ar = 4-NO_2Ph	69 (1:1)
3	 **20**	 **21** + **22**	61 (1:1.4)
4	 **23**	 **24**	60

[a] Reaction conditions: $[Mn(OAc)_3]$ (2.5 equiv), HOAc, 60 °C.



Scheme 3. Reaction conditions: a) LiOH, THF/H_2O, 50 °C, 15 min, 59% yield; b) mCPBA, $CHCl_3$, 23 °C, 16 h, 78% yield; c) NH_4F, HOAc, MeOH, 60 °C, 12 h, 83% yield; d) mCPBA, $CHCl_3$, 60 °C, 16 h, 78% yield; e) LiOH, THF/H_2O, 60 °C, 12 h, 72% yield. Boc = *tert*-butyloxycarbonyl, mCPBA = *m*eta-chloroperoxybenzoic acid.

In summary, we have devised a Mn^{III}-promoted radical cascade cyclization reaction to deliver the core skeletons of two types of oroidin dimers, ageliferin/nagelamide and massadine/palau'amine/axinellamine. Two C–C bonds and three or four contiguous stereogenic centers are established in one step. We have also demonstrated that the ageliferin cores thus obtained can be oxidatively rearranged to the massadine/palau'amine core skeletons with controlled installation of either spiro configurations. Efforts to synthesize selected oroidin dimers are currently in progress.

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[1] For a review of the pyrrole–imidazole family of natural products, see: H. Hoffmann, T. Lindel, *Synthesis* **2003**, 1753 – 1783.

[2] For concise syntheses of sceptrin, see: a) P. S. Baran, A. L. Zografos, D. P. O'Malley, *J. Am. Chem. Soc.* **2004**, *126*, 3726 – 3727; b) V. B. Birman, X.-T. Jiang, *Org. Lett.* **2004**, *6*, 2369 – 2371; for an elegant synthesis of ageliferin, see: c) P. S. Baran, K. Li, D. P. O'Malley, C. Mitsos, *Angew. Chem.* **2006**, *118*, 255 – 258; *Angew. Chem. Int. Ed.* **2006**, *45*, 249 – 252; d) P. S. Baran, D. P. O'Malley, A. L. Zografos, *Angew. Chem.* **2004**, *116*, 2728 – 2731; *Angew. Chem. Int. Ed.* **2004**, *43*, 2674 – 2677; for synthetic approaches to palau'amine, see: e) H. Garrido-Hernandez, M. Nakadai, M. Vimolratana, Q. Li, T. Doundoulakis, P. G. Harran, *Angew. Chem.* **2005**, *117*, 775 – 779; *Angew. Chem. Int. Ed.* **2005**, *44*, 765 – 769, and references therein; for a synthetic approach to axinellamine, see: f) J. T. Starr, G. Koch, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 8793 – 8794.

[3] For a review of radical cascade cyclizations, see: a) A. J. McCarroll, J. C. Walton, *Angew. Chem.* **2001**, *113*, 2282 – 2307; *Angew. Chem. Int. Ed.* **2001**, *40*, 2224 – 2248; for reviews of cascade reactions, see: b) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551 – 564; c) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195 – 206.

[4] a) E. I. Heiba, R. M. Dessau, W. J. Koehl, Jr., *J. Am. Chem. Soc.* **1968**, *90*, 5905 – 5906; b) J. B. Bush, Jr., H. Finkbeiner, *J. Am. Chem. Soc.* **1968**, *90*, 5903 – 5905.

[5] E. J. Corey, M.-c. Kang, *J. Am. Chem. Soc.* **1984**, *106*, 5384 – 5385.

[6] For an example of an application of this reaction to complex natural-product synthesis, see: D. Yang, X.-Y. Ye, M. Xu, K.-W. Pang, K.-K. Cheung, *J. Am. Chem. Soc.* **2000**, *122*, 1658 – 1663.

[7] For reviews, see: a) G. G. Melikyan, *Org. React.* **1997**, *49*, 427 – 675; b) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339 – 363.

[8] a) C.-P. Chuang, S.-F. Wang, *Tetrahedron Lett.* **1994**, *35*, 1283 – 1284; b) C.-P. Chuang, S.-F. Wang, *Synth. Commun.* **1994**, *24*, 1493 – 1505; c) A. Citterio, R. Sebastiano, M. C. Carvayal, *J. Org. Chem.* **1991**, *56*, 5335 – 5341.

[9] There is only one report of the oxidation of allylic β-ketoesters with Mn^{III}, wherein the thermodynamic *trans*-5-*exo* cyclization products were obtained: K. Sung, Y. Y. Wang, *J. Org. Chem.* **2003**, *68*, 2771 – 2778; the Mn^{III}-promoted cyclization of allylic β-dicarboxylate is more common, for example, Ref. [5].

[10] For a two-step oxidation of imidazolinone with dimethyldioxirane (DMDO)/*N*-chlorosuccinimide (NCS) to construct the palau'amine core skeleton, see: a) A. S. Dilley, D. Romo, *Org. Lett.* **2001**, *3*, 1535–1538; for a similar DMDO-promoted oxidation of imidazole, see: b) C. J. Lovely, H. Du, Y. He, H. V. R. Dias, *Org. Lett.* **2004**, *6*, 735–738.

[11] The ^{1}H NMR spectra of the crude product indicated a clean transformation; however, the cyclization products were not stable to column chromatography on silica gel (among all the isolation conditions examined, Davisil 633 silica gel provided the best yields of the isolated products).

[12] For a review of $A^{1,3}$ strain, see: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860.

[13] For a similar stereospecificity issue, see: Ref. [6].

[14] A slightly higher temperature (80 °C) was required to suppress the formation of the monocyclization product; however, the diastereoselectivity was compromised.

[15] CCDC-290044 (**15**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

