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Studies toward the Total Synthesis of Axinellamine and Massadine

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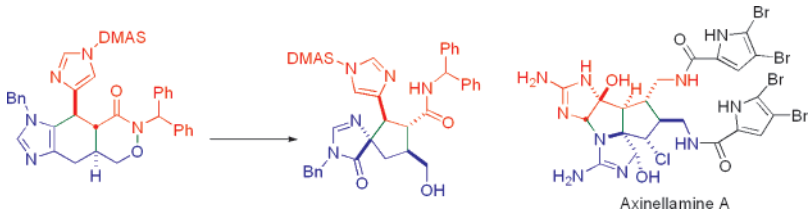
ABSTRACT



Intramolecular Diels–Alder reactions of several N–O linked 4-vinylimidazole dimers provide the expected adduct in moderate to good yield as a single, all *trans* stereoisomer, along with smaller amounts of the inverse electron demand adduct. Oxidative rearrangement of the cycloadducts occurs on treatment with Davis' reagent, providing a single spiro imidazolone in good yield and with excellent levels of stereocontrol albeit epimeric at the spiro center found in axinellamine and massadine.

The dimeric pyrrole-imidazole alkaloids axinellamine A (**1**)[1,2] and massadine (**2**)[3] were recently isolated from the marine sponges *Axinella* sp. and *Stylissa* aff. *massa*, respectively (Figure 1). These marine natural products are members of the oroidin family of sponge metabolites and are formally derived from the dimerization of two molecules of oroidin.[4] In addition to their complex structures, both **1** and **2** display substantial biological activity as an antibacterial agent (against *Helicobacter pylori*) and as a geranylgeranyltransferase inhibitor, respectively. Although these molecules exhibit different constitutions, one key disconnection (**1** → **3**; **2** → **3**, Figure 1) reveals that they are in fact very closely related. The differences of consequence relate to the connectivity of the two imidazole moieties (C−N vs C−O) and the nature of the C13 or C14 substituent (Cl vs OH). In other words, strategically, they might be accessible from a common, and possibly late stage, intermediate **3**. It is also of note that these two alkaloids bear some resemblance to palau'amine, at least around the polysubstituted cyclopentane moiety.[5,6]

Over the past few years, our group has developed an interest in the elaboration of simple imidazoles into more complex derivatives, with the long-term goal of utilizing this chemistry in natural product total synthesis.[7] Among the key transformations that we have developed are the Diels−Alder

(1) Urban, S.; de Almeida Leone, P.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.

(2) For synthetic efforts toward **1**, see: (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793. (b) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535. (c) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679. (d) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Lowe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203. (e) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 765. (f) Tan, X.; Chen, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4345.

(3) Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255.

(4) For a general review of synthetic studies toward the oroidin family of alkaloids, see: Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.

(5) (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. For synthetic studies, see: (c) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551 and ref 4.

(6) Very recently, the stereochemical assignment of palau'amine has been called into question, with three almost simultaneous reports suggesting that palau'amine does in fact share a common stereochemistry with both the axinellamine family and massadine. (a) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127. (b) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320. (c) Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **2007**, *72*, 2309. Therefore, our approach to **1** and **2** may in fact be applicable to palau'amine's revised structure.

(7) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965.

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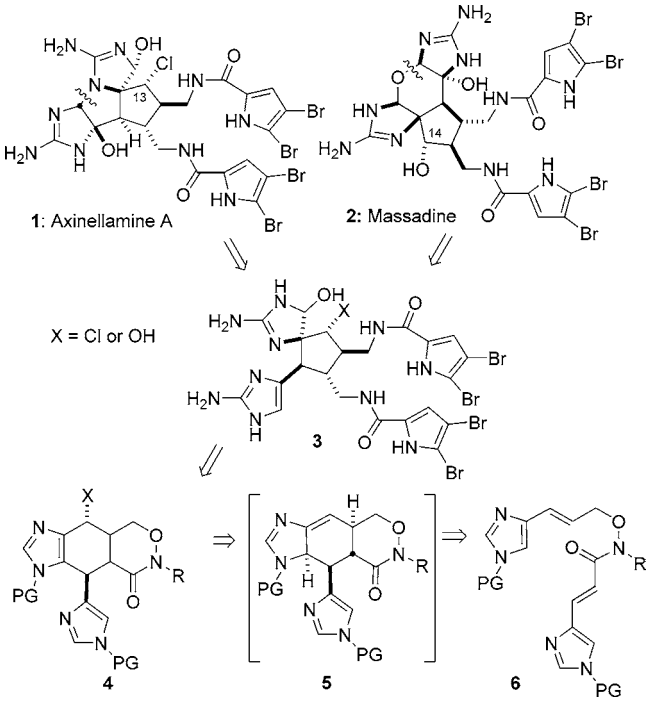


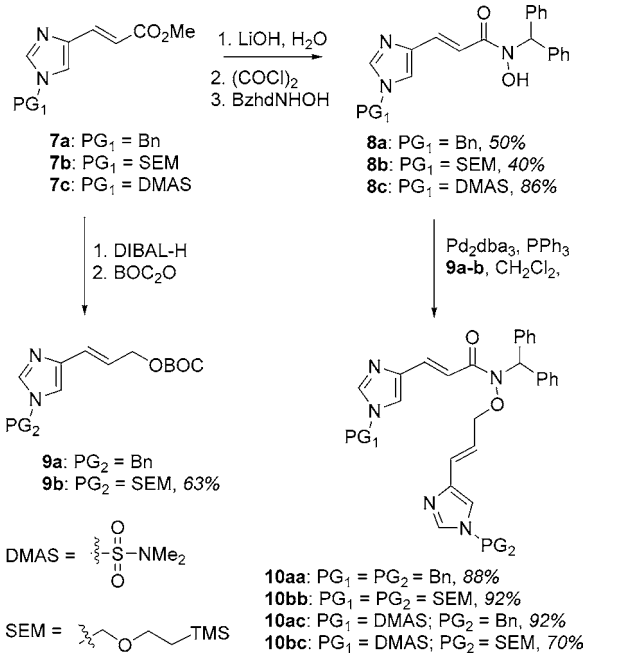
Figure 1. Retrosynthetic analysis of axinellamine A and massadine.

(DA) reactions of vinylimidazoles[8] and the oxidative rearrangement of tetrahydrobenzimidazoles.[9] As a result of these studies, we were able to propose an approach to **1** and **2** depicted retrosynthetically in Figure 1, which involves an intramolecular DA reaction of a bisvinylimidazole **6** → **4** and its subsequent rearrangement and elaboration of the tether **4** → **3**. In this communication, we describe the investigation and execution of the initial phases of this strategy.

Earlier studies from our lab with amide-linked dimers related to **6** indicated that these were viable substrates in the intramolecular DA reaction,[8d] leading stereoselectively to the required all-*trans* substituted cycloadducts, but these were not ideal due to selectivity issues relating to normal vs inverse electron demand cyclization pathways (cf. **11** and **12** in Scheme 2).[3,10] This was further exacerbated by the difficulty in elaborating the amide tether under sufficiently mild conditions that did not lead to concomitant imidazole nitrogen deprotection. To circumvent this deficiency, we explored the use of hydroxamates which provide tethers that can be cleaved relatively easily.[2d,11] We have used this strategy to effect, in our approach to the oroidin dimer, ageliferin.[10,12,13] However, in this latter study, the dimethylaminosulfonyl (Me_2NSO_2 = DMAS) group was used to protect the imidazole, and it has been found that the electron-withdrawing nature of this substituent is not conducive to our oxidative rearrangement chemistry.[9] Therefore, the preparation of more electron-rich derivatives was necessary.

Although we had wanted to investigate this chemistry for some time, the preparation of the requisite substrates proved to be rather problematic due to competitive allylic rearrangement in simple nucleophilic substitution reactions until we discovered that Pd-catalyzed π-allyl substitution reactions provided an expedient solution to this problem.[14,15] Application of this chemistry allowed efficient access to several homodimers[16] (PG_1 = PG_2 = Bn or SEM, **10aa** and **10bb**) and heterodimers (PG_1 = DMAS; PG_2 = Bn or SEM, **10ac** and **10bc**, Scheme 1). The precursor hydroxamic acids **8a**−**c**

Scheme 1. Construction of the Cycloaddition Precursors



can be easily obtained from the corresponding urocanic acid derivatives **7a**−**c**[17] by ester hydrolysis, conversion to the acid chloride, and coupling with benzhydryl hydroxylamine (Scheme 1).[18,19] The allylic carbonates **9a**,**b**[13] were prepared by DIBAL reduction of the same esters **7a**,**b** and then converted to the corresponding carbonates. Reaction of **8a**−**c** and **9a**,**b** in the presence of Pd_2dba_3 provided the required dimers **10aa**−**bb**, **10ac**, and **10bc** in generally good yield

(8) Intermolecular variants: (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319. (b) Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *60*, 1. (c) Du, H.; Sivappa, R.; Bhandari, M. K.; He, Y.; Dias, H. V. R.; Lovely, C. J. *J. Org. Chem.* **2007**, *72*, 3741. Intramolecular variants: (d) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623.

(9) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.* **2004**, *6*, 735.

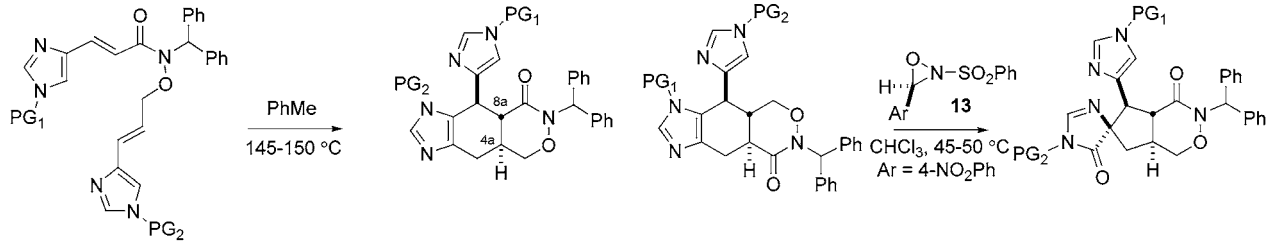
(10) Simple unsaturated esters were poor substrates in the intramolecular Diels−Alder reaction. He, Y. Ph.D. Dissertation, The University of Texas at Arlington, 2005.

(11) Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S.; Kobayashi *J. Am. Chem. Soc.* **2001**, *123*, 4607. See also ref 2d.

(12) For isolation see: (a) Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579. (b) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965. (c) Williams, D. H.; Faulkner, D. J. *Tetrahedron* **1996**, *52*, 5381. For total synthesis, see: (d) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762.

(13) Sivappa, R.; He, Y.; Krishnamoorthy, P.; Lovely, C. J. unpublished results.

Scheme 2. Cycloaddition and Oxidative Rearrangement



10aa: $PG_1 = PG_2$ = Bn
10bb: $PG_1 = PG_2$ = SEM
10ac: PG_1 = DMAS; PG_2 = Bn
10bc: PG_1 = DMAS; PG_2 = SEM

11aa: $PG_1 = PG_2$ = Bn
11bb: $PG_1 = PG_2$ = SEM
11ac: PG_1 = DMAS; PG_2 = Bn
11bc: PG_1 = DMAS; PG_2 = SEM

12aa: $PG_1 = PG_2$ = Bn
12bb: $PG_1 = PG_2$ = SEM
12ac: PG_1 = DMAS; PG_2 = Bn
12bc: PG_1 = DMAS; PG_2 = SEM

14aa: $PG_1 = PG_2$ = Bn
14bb: $PG_1 = PG_2$ = SEM
14ac: PG_1 = DMAS; PG_2 = Bn
14bc: PG_1 = DMAS; PG_2 = SEM

(Scheme 1). Subjection of each dimer to DA reaction in toluene at 150 °C (sealed tube) led to a smooth cycloaddition providing a mixture of the normal **11** and inverse electron demand product **12**, favoring the normal addition product (7−3:1, Table 1). Under the reaction conditions employed,

Table 1. Cycloaddition (**10** → **11** + **12**) and Rearrangement Yields (**11** → **14**)

substrate	product	yield/% (N:I)[a]	product	yield/%
10aa	**11aa/12aa**	68/21 (3.9:1)	**14aa**	81
10bb	**11bb/12bb**	62/20 (3:1)	**14bb**	47
10ac	**11ac/12ac**	84/10 (7:1)	**14ac**	71
10bc	**11bc/12bc**	68/7 (6:1)	**14bc**	61

[a] N:I = normal:inverse electron demand Diels−Alder products. The ratio was determined by integration values in the ^{1}H NMR spectra of the crude reaction mixtures.

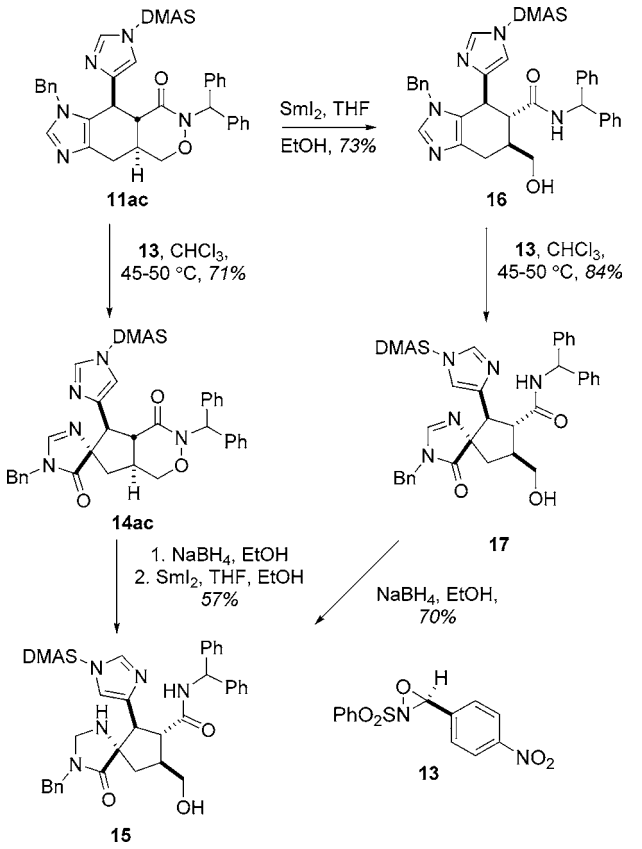
the initial cycloadduct (cf. **5**, Figure 1) was not obtained.[20] The major cycloadduct could be separated in reasonable efficiencies by chromatography, and analysis of the magnitudes of the coupling constants for the bridgehead proton H_{8a} with H_{4a} ($J \sim 10$ Hz) and H_9 ($J \sim 11-12$ Hz) in the ^{1}H NMR spectra clearly indicated that these cycloadducts possessed all *trans* stereochemistry.[21] These coupling constants were consistent with those found in the analogous DMAS-protected system for which an X-ray structure was obtained.[10] Interestingly, it was observed that the homodimers **10aa** and **10bb** afforded poorer chemoselectivity than the heterodimers **10ac** and **10bc** in the cycloaddition chemistry. This observation is consistent with other types of dimeric imidazole systems that we have evaluated. In the case of the heterodimers, the dienophilic component is more electron deficient than the diene, and so presumably this leads to a more pronounced HOMO−LUMO gap between the two possible cycloaddition modes.

As indicated above in Figure 1, the next step in our strategy required the oxidative rearrangement of the tetrahydrobenzimidazoles derived from the DA reaction. Recent studies in our lab have demonstrated that Davis' reagents (*N*-sulfonyloxaziridines) are excellent reagents to effect this transformation.[22,23] We were delighted to discover that all four major cycloadducts underwent smooth rearrangement to a single spiro-fused 5-imidazolone in moderate to excellent yield on treatment with **13** in $CHCl_3$ at 45−50 °C (Scheme 2, Table 1). This transformation exhibited high levels of chemoselectivity with only the imidazole within the tetrahydrobenzimidazole framework undergoing oxidation and high levels of stereoselectivity, although at this point we were unable to establish the stereochemistry of the spiro fusion (vide infra).

With the spiro-fused systems in hand, we investigated elaboration of the hydroxamate tether in **14ac** through reductive cleavage with SmI_2, which in addition to reducing the N−O bond led to reduction of the C=N bond of the imidazolone in moderate overall yield (**15**, Scheme 3).[24] It was found that this reaction was somewhat capricious providing variable yields and product distributions. Therefore, we subjected **14ac** to reduction with $NaBH_4$, which only

(14) Krishnamoorthy, P.; Sivappa, R.; Du, H.; Lovely, C. J. *Tetrahedron* **2006**, *62*, 10555.
(15) (a) Miyabe, H.; Yoshida, K.; Matsumura, A.; Yamauchi, M.; Takemoto, Y. *Synlett* **2003**, 567. (b) Miyabe, H.; Matsumura, A.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *Synlett* **2004**, 2123. (c) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630.
(16) Although strictly these compounds are not homodimers, we use this term to refer to compounds in which the two imidazole nitrogen-protecting groups are identical. Where these groups are different, we refer to them as heterodimers.
(17) He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529.
(18) Early experiments with benzyl hydroxamates indicated that these were poorer substrates in the Diels−Alder reaction, and so the bulkier and ultimately superior benzhydryl group was employed. See ref 10.
(19) Adam, W.; Beck, A. K.; Pichota, A.; Saha-Moller, C. R.; Seebach, D.; Vogl, N.; Zhang, R. *Tetrahedron: Asymmetry* **2003**, *14*, 1355.
(20) We have found that when these reactions are carried out under microwave irradiation and high dilutions the initial adduct can be obtained. See ref 10.
(21) This was supported by X-ray analysis of a derivative from **11ac** (see Supporting Information).
(22) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(23) Sivappa, R.; Koswatta, P.; Lovely, C. J. *Tetrahedron Lett.* **2007**, *48*, 5771.
(24) Similar results have been obtained with **14aa**. Hernandez, N. M., unpublished results.

Scheme 3. Elaboration of the Cycloadduct



reduced the C═N moiety, followed by treatment with SmI_2, which provided **15** cleanly in moderate yield (Scheme 3).[25]

To obviate the two-step reduction sequence described above, we also investigated elaboration of the cycloadducts prior to oxidative rearrangement. It was found that the N−O bond in **11ac** can be cleaved using SmI_2, providing the corresponding hydroxyamide **16** in good yield. This substrate also undergoes the oxidative rearrangement reaction with the Davis reagent, affording the spiro-fused imidazolone as a single diastereomer **17**. After conversion of the hydroxyl moiety into the *p*-nitrobenzoate, the resulting compound provided crystals suitable for X-ray crystallography which confirmed the all-*trans* relative stereochemistry, derived from the DA reaction, of the hydroxymethyl, amide, and imidazole substituents as required in **1** and **2**. Unfortunately however, the X-ray structure also revealed that the spiro center is epimeric to that found in axinellamine and massadine.[26] We briefly examined other oxidants for initiating the rearrangement but found that either they gave the same product (DMDO, 56%)[9] or no reaction occurred (MCPBA).[2f] As we had found that the C═N of the imidazolone could be reduced with $NaBH_4$, this provided an opportunity to correlate the stereochemistry of the rearrangement products obtained via both routes. Accordingly, **17** was treated with $NaBH_4$, and this provided the same imidazolinone **15** as the first route (**11ac** → **14ac** → **15**) and served to confirm the relative stereochemistry of this rearrangement project. By extrapolation, we have assigned the stereochemistry of the rearrangement products (**14aa**, **bb**, **bc**) obtained from the major Diels−Alder cycloadducts.

In summary, we have described a concise approach to a tetrasubstituted spiro cyclopentyl imidazolone fragment related to the one found in axinellamine A and massadine through an intramolecular Diels−Alder/oxidative rearrangement strategy. The hydroxamate substrates provide a convenient method for tethering the two imidazole fragments, which can be cleaved readily by reduction with SmI_2. Although oxidative rearrangement leads to a single stereoisomer, the spiro ring fusion is epimeric to that found in these natural products. Current efforts are focused on solving this stereochemical flaw, on incorporation of the additional heteroatom, and on end game strategies.

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Supporting Information Available: Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. The X-ray structure of **17**-PNB ester and associated CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) We attempted to obtain a crystal structure of this compound (after treatment with *p*-nitrobenzoyl chloride, which led to benzoylation at both nitrogen and oxygen). This revealed that the molecule had the indicated stereochemistry, but the quality of the data was poor.

(26) Baran and co-workers have made a similar stereochemical observation in their attempts to rearrange ageliferin (via dihydroxylation and base-induced rearrangement) to the axinellamine skeleton. See ref 12d.