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Concise, Stereoselective Approach to the Spirooxindole Ring System of Citrinadin A

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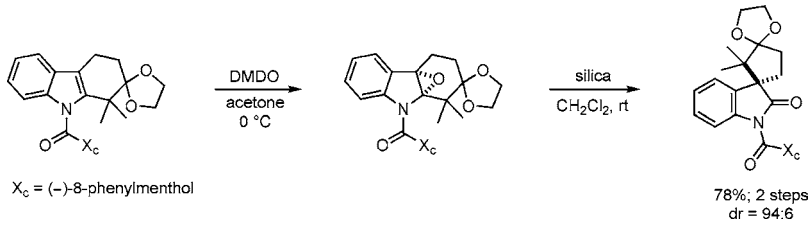
ABSTRACT



The spirooxindole ring system of citrinadin A has been synthesized with excellent control over the absolute stereochemistry at the spirocenter. The key step involves a novel diastereoselective DMDO-mediated oxidative rearrangement employing an 8-phenylmenthol chiral auxiliary on the indole nitrogen.

Marine-derived fungi have emerged as an important source of complex and structurally diverse secondary metabolites, many of which possess important biological activity.[1] Recently, Kobayashi and co-workers reported the isolation of citrinadin A (**1**) from the fermentation broth of *Penicillium citrinum* (strain N-059), which was obtained from the red algae *Actinotrichia fragilis*.[2] This pentacyclic spiroindolinone natural product possesses a complex molecular framework comprising nine stereocenters, an α,β-epoxycarbonyl moiety, and a rare *N*,*N*-dimethylamino valine residue. The central five-membered ring is densely functionalized with all but one of the carbon atoms being fully substituted and possessing two adjacent quaternary centers. Adding to its attractiveness as a target for total synthesis, citrinadin A has been shown to exhibit cytotoxicity against murine leukemia L1210 ($IC_{50} = 6.2\ \mu g/mL$) and human epidermoid carcinoma KB cells ($IC_{50} = 10\ \mu g/mL$).[2]

In the context of a longstanding interest in developing general approaches to indole and oxindole alkaloids,[3,4] we were attracted to **1** because of the intriguing challenges inherent in its structure. The fact that no work toward the synthesis of citrinadin A has been reported increased our enthusiasm, as there would be ample opportunity for the discovery and development of new chemistry. Our approach, which is depicted in Scheme 1, is a convergent one in which the ABC and E subunits of citrinadin A would be indepen-

(1) Bugni, T. S.; Ireland, C. M. *Nat. Prod. Rep.* **2004**, *21*, 143 and references therein.

(2) (a) Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087. (b) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430.

(3) For reviews, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

(4) (a) For some examples see: (a) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. (b) Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557. (c) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161. (d) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236. (e) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (f) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (g) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918. (h) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (i) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867. (j) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541. (k) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547. (l) Miller, K. A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113.

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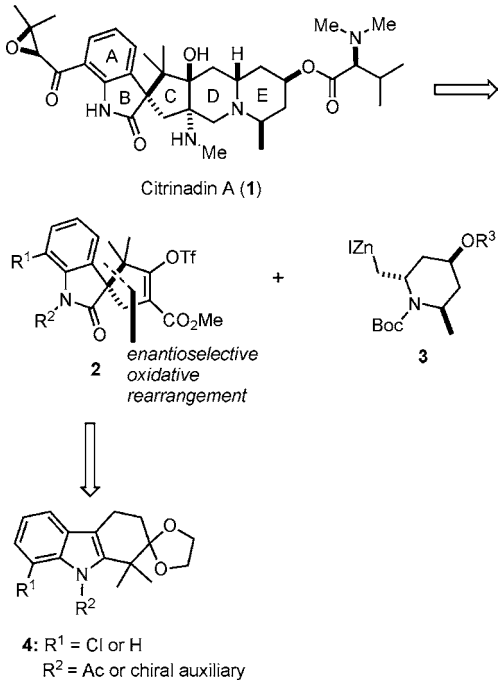
Scheme 1. Synthetic Approach to Citrinadin a (**1**)



dently assembled and then coupled to give an intermediate that would then be elaborated into **1**. More specifically, we envisioned the triflate **2** and the piperidine **3** as being potential key intermediates that would be joined by the Negishi protocol.[5]

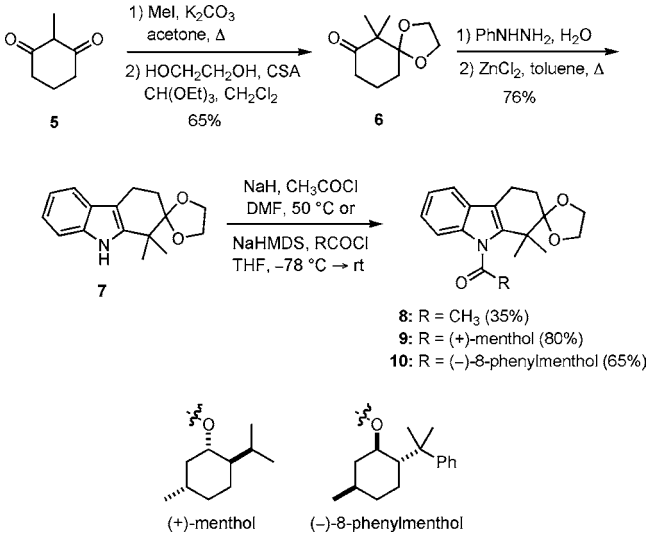
Given this strategy, one challenge we would have to address involved effective control of the absolute stereochemistry at the spirocenter of the oxindole moiety. Toward this end, we envisioned an enantioselective, oxidative rearrangement of an indole derivative of the general type **4**. Examination of the literature quickly revealed that such a tactic was not well precedented. Although there are a number of strategies for the synthesis of spiro[pyrrolidine-3,3′-oxindoles],[6] methods for the construction of spirooxindoles lacking a nitrogen atom in the C-ring are rather limited in scope.[7] Further exacerbating the problem is the notable lack of enantioselective methods for the synthesis of such spirooxindoles.[8,9] Indeed, to our knowledge, the only two approaches to homochiral spirooxindoles are an enantioselective Heck reaction developed by Overman[8a] and a palladium-catalyzed, enantioselective cyclization of silyloxy-1,6-enynes reported by Toste.[8b]

Our previous experience with preparing spirooxindoles by oxidative rearrangements of indoles[4b,c,f,k] coupled with several examples of diastereoselective oxidations of indoles[9,10] led us to query whether we might develop an enantioselective variant of this transformation that might be applied to the preparation of **2** from a precursor related to **4**.[11] Such a process would constitute a useful addition to the reactions comprising the synthome.[12] We considered several possibilities that were explored simultaneously. One of these was inspired by the collective observations of Foote[13] and Adams[14] who have shown that *N*-acylindoles can be efficiently converted to oxindoles using dimethyldioxirane (DMDO). This transformation proceeds via the intermediacy of an indole 2,3-epoxide that readily rearranges to the corresponding oxindole. We thus hypothesized that such an oxidation might proceed enantioselectively on **4** (R^2 = Ac) employing a chiral dioxirane such as those nicely developed Shi.[15] Alternatively, the requisite facial selectivity might be achieved via the agency of appending a chiral auxiliary onto the indole nitrogen atom as in **4** (R^2 = chiral auxiliary). Based upon the precedents of Williams and Snider,[9b,c,10] we also considered the related possibility of using a chiral Davis oxaziridine.[16]

In order to examine the feasibility of these various tactics, compounds **8**−**10** were synthesized by *N*-acylation of the indole **7**, which was prepared from the known ketal **6**[17] via a Fisher indole synthesis (Scheme 2). Although the yield for preparing the *N*-acetyl derivative **8** was modest, yields for forming the carbamates **9** and **10** were good. With **8**−**10** in hand, we began exploring the key oxidative rearrangement. When *N*-acetylindole **8** was subjected to the standard Shi asymmetric epoxidation conditions using D-epoxone, which may be prepared in two steps from D-fructose,[15b] the corresponding oxindole **12** was isolated in <20% yield and with virtually no asymmetric induction (Scheme 3). However, oxidation of **8** with the related *N*-aryloxazolidinone **11**,[18] which was prepared from D-glucose in four steps, followed by hydrolysis of the *N*-acetyl group gave **13** in 77% overall

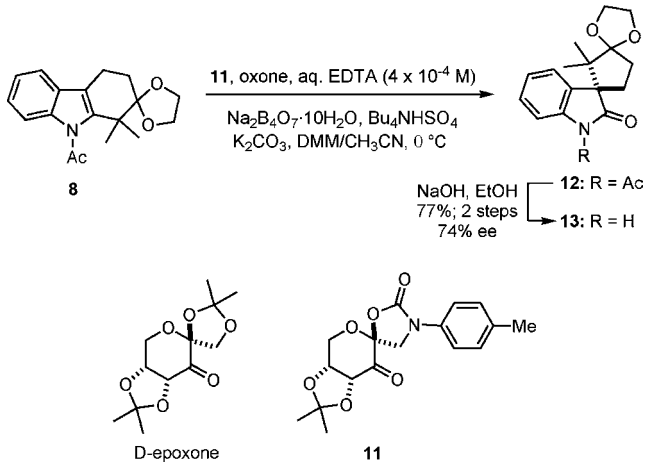
(5) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340.
(6) For a recent review, see: Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *12*, 2209 and references therein.
(7) For some examples, see: (a) Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226. (b) Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073. (c) Mao, Z.; Baldwin, S. W. *Org. Lett.* **2004**, *6*, 2425. (d) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448. (e) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, *129*, 3086.
(8) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764. (c) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137.
(9) (a) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323. (b) Artman, G. D., III; Grubbs, A. W.; Williams, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 6336. (c) Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2262.
(10) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545−563.
(11) Some of these results were presented at the 232nd ACS National Meeting. See: Pettersson, M.; Martin, S. F. *Abstracts of Papers*, 232nd ACS National Meeting, San Francisco, CA, Sep 10−14, 2006; American Chemical Society: Washington, DC, 2006; ORGN-854.
(12) In analogy with the "ome" nomencalture in the biological arena, the synthome is the complete set of reactions available to the chemist for the synthesis of molecules of interest.
(13) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867.
(14) Adam, W.; Ahrweiler, M.; Peters, K.; Schmiedeskamp, B. *J. Org. Chem.* **1994**, *59*, 2733.
(15) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. J. *Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. For a review on organocatalytic asymmetric epoxidations, see: (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
(16) (a) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
(17) (a) Törmäkangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskinen, A. M. P. *Tetrahedron* **2002**, *58*, 2175. (b) Shibuya, S.; Isobe, M. *Tetrahedron* **1998**, *54*, 6677.
(18) (a) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093. (b) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715. (c) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. Org. Lett. **2003**, *5*, 293. *N*-Aryl-substituted ketone **11** prepared according to: (d) Zhao, M.-X.; Goeddel, D.; Li, K.; Shi, Y. *Tetrahedron* **2006**, *62*, 8064.

Scheme 2. Preparation of Substrates for Oxidation



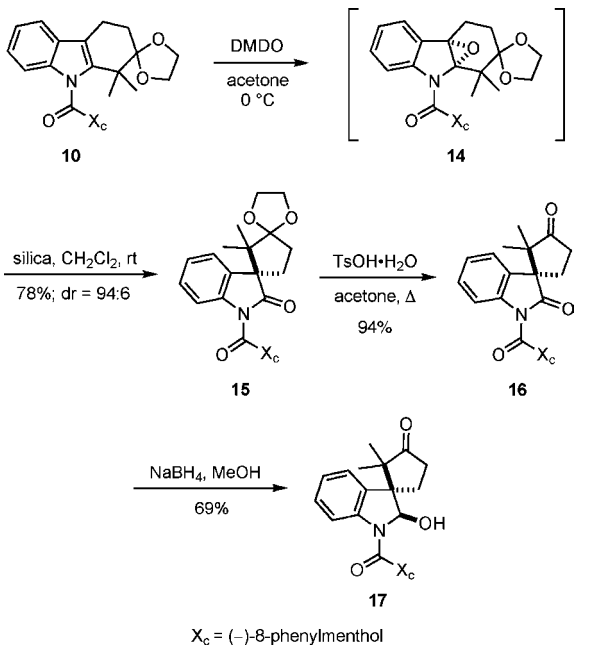
yield and 74% ee.[19] To our knowledge, this represents the first example of an enantioselective oxidation of an indole to an oxindole. More importantly for the task before us, this transformation provides compelling proof of principle for the proposed asymmetric oxidative rearrangement depicted in Scheme 1. Efforts are currently underway to improve the enantioselectivity and to explore the scope of this route to homochiral spirooxindoles. In preliminary experiments, we found that neither **7** nor **8** react with oxaziridines.

Scheme 3. Enantioselective Oxidation of **8**



Concurrent with the aforementioned studies, a chiral auxiliary approach was being explored using DMDO as the epoxidizing agent and **9** and **10** as substrates. When the menthol-derived substrate **9** was treated with DMDO and the intermediate epoxide allowed to rearrange in the presence of silica gel, the expected oxindole was obtained with a dr of only 65:35. On the other hand, reaction of indole **10** with DMDO at 0 °C for 1 h, followed by stirring the epoxide thus formed with silica gel, gave the desired spirooxindole **15** in 78% overall yield and with excellent diastereoselectivity (dr = 94:6) (Scheme 4). It is noteworthy that contrary

Scheme 4. Diastereoselective Oxidation of **10**



to the majority of examples reported by Foote,[13] the intermediate epoxide **14** was remarkably stable. No trace of oxindole **15** could be detected by ^1H NMR after the epoxidation step, even when the sample was allowed to warm to room temperature. Partial rearrangement (30−40%) of the epoxide was first observed to occur upon purifying **14** by chromatography on silica gel, a fact that led us to intentionally promote the rearrangement by stirring a solution of **14** over silica gel. Interestingly, a large solvent effect was observed, and best results were obtained using nonpolar solvents such as hexanes, toluene, or CH_2Cl_2, with the later being the optimal solvent. Only trace amounts of **15** were observed using polar solvents such as THF and EtOAc.

It was essential to determine the absolute stereochemistry at the spirocenter in **15**. Toward that end, we set to the task of preparing solid derivatives that would be suitable for structural elucidation by X-ray crystallography. Gratifyingly, when **16**, which was obtained in high yield by hydrolysis of the ketal moiety in **15** (Scheme 4), was treated with $NaBH_4$ in MeOH, the crystalline hemiaminal **17** was isolated, the structure of which was determined to be that shown in Figure 1. Moreover, the stereochemistry at the spirocenter of **17** thus corresponds to that found in citrinadin A (**1**).

Having established an efficient strategy to construct the two adjacent quaternary centers of citrinadin A (**1**) with excellent stereocontrol, we turned to the task of converting

(19) The absolute stereochemistry was established by comparing the HPLC trace of **13** derived from **12** to that of ***ent*-13** by removal of the chiral auxiliary from **15**, the stereochemistry of which was established by X-ray crystallography of **17**.

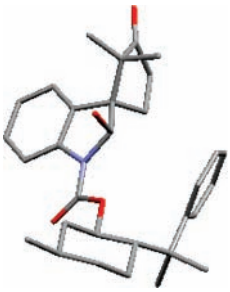
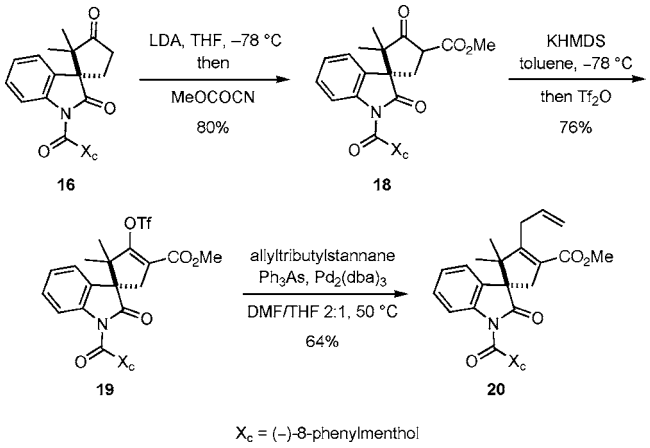


Figure 1. X-ray structure of **17**.

16, which may be easily prepared from **10** on a gram scale, into the triflate **19** in order to explore the coupling of this or related compounds with organometallic reagents. In the event, acylation of the lithium enolate of **16** with Mander's reagent afforded β-keto ester **18** in 80% yield (Scheme 5). Subsequent deprotonation of **18** with KHMDS in toluene followed by the addition of triflic anhydride delivered the target triflate **19** in 76% yield, thereby completing an enantioselective synthesis of the ABC-tricyclic fragment of citrinadin A (**1**) in only 10 steps. Finally, the ability of the sterically hindred triflate **19** to undergo a palladium-catalyzed cross-coupling was established in a model reaction, in which **19** underwent a Stille coupling with allytributylstannane to give **20** in 64% yield.

Scheme 5. Preparation and Cross-Coupling of Triflate **19**



In summary, we have developed a concise approach to the spirocyclic ring system of citrinadin A (**1**). The key step involves a DMDO-mediated oxidative rearrangement of an indole to an oxindole that proceeds in 78% yield and 94:6 dr. This transformation effectively addresses the challenge of establishing the two adjacent quaternary centers of **1** with excellent control over the absolute stereochemistry at the spirocenter. We have also achieved the first enantioselective oxidative rearrangement of an indole to a spirooxindole as exemplified by the conversion of **8** into **13**. The completion of the total synthesis of citrinadin A and further development and application of our dioxirane-mediated oxidative rearrangements to provide homochiral spirooxindoles are currently being pursued in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds and a CIF file for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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