JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Enantioselective Total Synthesis of (−)-Citrinadin A and Revision of Its Stereochemical Structure

Zhiguo Bian, Christopher C. Marvin,[†] and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: The first enantioselective total synthesis of (−)-citrinadin A has been accomplished in 20 steps from commercially available materials via an approach that minimizes refunctionalization and protection/deprotection operations. The cornerstone of this synthesis features an asymmetric vinylogous Mannich addition of a dienolate to a chiral pyridinium salt to set the initial chiral center. A sequence of substrate-controlled reactions, including a highly stereoselective epoxidation/ring-opening sequence and an oxidative rearrangement of an indole to furnish a spirooxindole, are then used to establish the remaining stereocenters in the pentacyclic core of (−)-citrinadin A. The successful synthesis of citrinadin A led to a revision of the stereochemical structure of the core substructure of the citrinadins.

Citrinadin A (**1**), citrinadin B (**2**), and PF1270A−C (**3**−**5**) are members of a small family of novel spirooxindole alkaloids that exhibit potentially useful biological activities (Figure 1).[1,2] Citrinadins A and B, which were isolated by

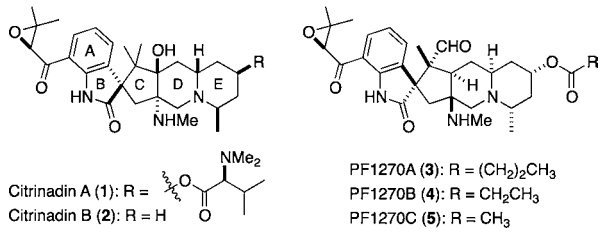


Figure 1. Citrinadin A, B and PF1270A−C.

Kobayashi from a culture broth of *Penicillium citrinum*, are active against murine leukemia L1210 and human epidermoid carcinoma KB cells.[1] The absolute and relative stereochemistry of citrinadin A (**1**) was assigned based upon a combination of 1D and 2D NMR experiments, including ROESY, and CD studies. The related alkaloids PF1270A−C, which were isolated from *Penicillium waksmanii* strain PF1270 by Kushida,[2] show submicromolar affinities for the human H3 histamine receptor, with **3** being the most active (K_i = 0.07 μM, EC_{50} = 0.12 μM). The structure and relative stereochemistry of **3**−**5** were assigned based upon crystallographic analysis of **3**.

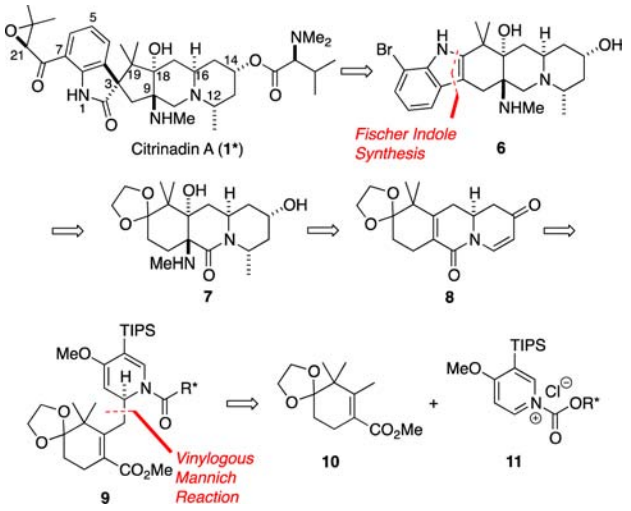
The alkaloids **1**−**5** share a number of structural features, but there are also some significant differences. For example, both citrinadins and the PF1270s possess a pentacyclic core structure comprising a spirooxindole motif with two contiguous stereogenic centers (BC ring), a densely functionalized quinolizidine (DE rings), and an α,β-epoxycarbonyl moiety on the A ring. The most notable difference in the assigned structures of citrinadins A and B and PF1270A−C is the relative stereochemistry of the α,β-epoxy ketone and the pentacyclic core. The complex molecular architecture of these alkaloids coupled with their important biological activities have inspired several synthetic investigations, especially toward the citrinadins, but none of these alkaloids have yet been prepared by total synthesis.[3] In this communication, we report the first enantioselective total synthesis of citrinadin A (**1**), and in the accompanying communication Wood and co-workers report the first total synthesis of citrinadin B (**2**). These investigations have also led to a revision in the structures of **1** and **2**, and the reassignment of the absolute stereochemistry of the pentacyclic core to correspond to that of PF1270A−C. In light of this discovery, the structures in the schemes that follow will depict what we now know to be the correct stereochemical structure of citrinadin A (**1***).[4]

We have been interested in the synthesis of indole and oxindole alkaloids for a number of years,[5] and in 2007, we developed a method for the enantioselective synthesis of the spirooxindole ring system (ABC ring) present in citrinadin A (**1***) via a process in which (−)-8-phenylmenthol was utilized as a chiral auxiliary to promote the diastereoselective, oxidative rearrangement of an indole to generate an oxindole.[3a] However, further investigations exploring the feasibility of elaborating such intermediates toward the citrinadins by introducing the requisite D and E rings were not successful. Consequent to these findings, we formulated a new plan that is outlined in a retrosynthetic format in Scheme 1. We envisioned that the spirocenter in **1*** could be introduced by a late-stage, stereoselective oxidative rearrangement of **6**, which would be assembled via a Fisher indole synthesis of the ketal **7**. Introduction of the trans amino-alcohol moiety in **7** would then be achieved via substrate-controlled epoxidation/ring opening, whereas the methyl and hydroxyl groups in **7** would be accessible from **8** by a diastereoselective Michael addition and reduction of the carbonyl group. The sole stereocenter in **8**, which was destined to control the creation of all of the remaining chirality in the pentacyclic core, would then be established by a diastereoselective, vinylogous Mannich reaction[6] of the dienolate derived from **10** to the chiral pyridinium salt **11** to give **9**.[7]

Received: June 3, 2013
Published: July 9, 2013

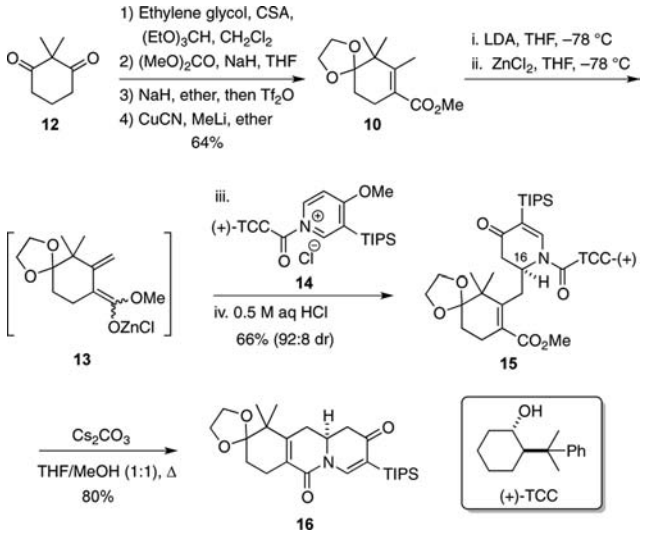
dx.doi.org/10.1021/ja405547f | J. Am. Chem. Soc. 2013, 135, 10886−10889

Scheme 1. Retrosynthetic Analysis of Citrinadin A



The total synthesis of citrinadin A thus commenced with the preparation of **10** from commercially available 2,2-dimethylcyclohexane-1,3-dione (**12**) in 64% overall yield for the four steps (Scheme 2). With **10** in hand, the stage was set for the key,

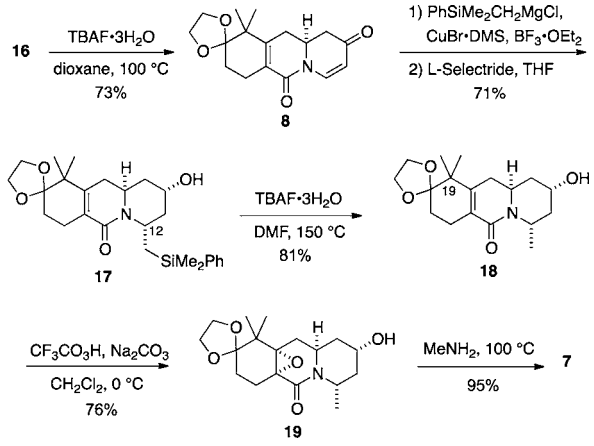
Scheme 2. Vinylogous Mannich Reaction



diastereoselective, vinylogous Mannich reaction involving the chiral pyridinium salt **14** to give **15**. Although we are not aware of any examples of the addition of dienolates to chiral acyl pyridinium salts, we were cognizant of the seminal work of Comins and Sahn, who added the zinc enolate of acetone to **14**.[7b] After evaluating different vinylogous enolates, solvents, and reaction temperatures, we discovered that the addition of the zinc dienolate **13** to the pyridinium salt **14**, which was generated *in situ* by the reaction of 3-TIPS-4-methoxypyridine and the chloroformate derivative of (+)-*trans*-2-(α-cumyl)-cyclohexanol [(+)-TCC], provided the adduct **15** in 66% yield with a dr of 92:8. The absolute stereochemistry at the newly created stereocenter at C(16) was assigned at this point by analogy with the findings of Comins.[7a] Base-induced cleavage of the chiral auxiliary and spontaneous cyclization afforded the tricyclic intermediate **16** in 84% ee, together with about 70% of recovered (+)-TCC. Gratifyingly, the optical purity of **16** was readily improved to 98% ee upon recrystallization.

Having established a reliable procedure to access **16** with high enantioselectivity, we turned our attention to the preparation of aminoalcohol **7** (Scheme 3). Protiodesilylation

Scheme 3. Preparation of Tricyclic Aminoalcohol 7

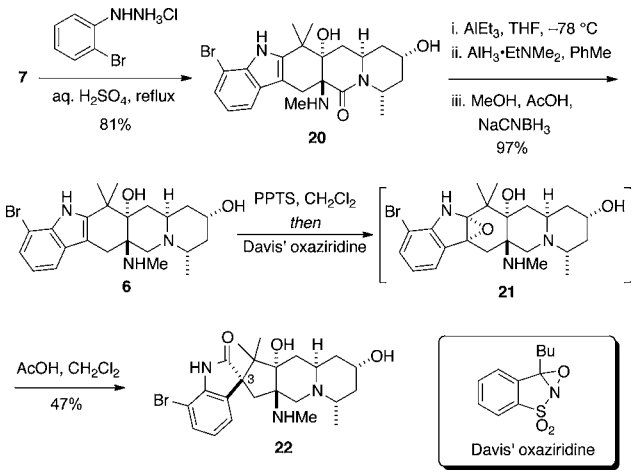


of **16** employing excess TBAF and microwave heating afforded enone **8**. The stereoselective 1,4-addition of a methyl group to **8** proved to be problematic, presumably owing to the relatively planar nature of the tricyclic ring system of **8**. Indeed, conjugate additions of different methyl nucleophiles under a variety of conditions were examined, and we eventually discovered that the copper-mediated addition of (dimethylphenylsilyl)-methylmagnesium chloride[8] provided a mixture of 1,4-addition products. This mixture was directly reduced with high stereoselectivity using L-Selectride to give the desired isomer **17** in 71% yield over the two steps; 19% of the C(12) epimer of **17** was also isolated. Heating **17** with TBAF in a microwave oven furnished the unsaturated lactam **18**.[9] Epoxidation of **18** with peroxytrifluoroacetic acid in the presence of sodium carbonate gave a single epoxide **19**.[10] Although the epoxidation could be performed in unbuffered media, the ketal moiety was cleaved. The diastereoselectivity of this epoxidation was apparently directed by steric effects associated with the adjacent quaternary center at C(19) in which the axial methyl group blocked the top face of the alkene. Treatment of **19** with aqueous methylamine in a sealed tube furnished the amino-alcohol **7**.[11,12]

The next stage of the synthesis involved creation of the pentacyclic core of citrinadin A (Scheme 4). In the event, when **7** was heated with *o*-bromophenyl hydrazine hydrochloride in aqueous acid,[13] the desired indole **20** was obtained. Although reduction of the lactam moiety using only alane provided the desired product **6**, the procedure with alane followed by $NaCNBH_3$ gave superior yields of **6**.[14] The moment was now at hand to test the feasibility of creating the critical spirocenter at C(3) by the substrate-controlled oxidative rearrangement of **6**. Although oxidative rearrangements of indoles to give spirooxindoles have been well documented,[15] inducing such a transformation on **6** proved to be more challenging than anticipated. Indeed, all attempts utilizing a variety of standard oxidants including *tert*-BuOCl, OsO_4, and NBS failed to give **22**. We eventually discovered that Davis' oxaziridine, which had been used by Williams to prepare spirooxindole alkaloids,[16] was effective. The indole **6** was first treated with pyridinium *p*-

dx.doi.org/10.1021/ja405547f | J. Am. Chem. Soc. 2013, 135, 10886–10889

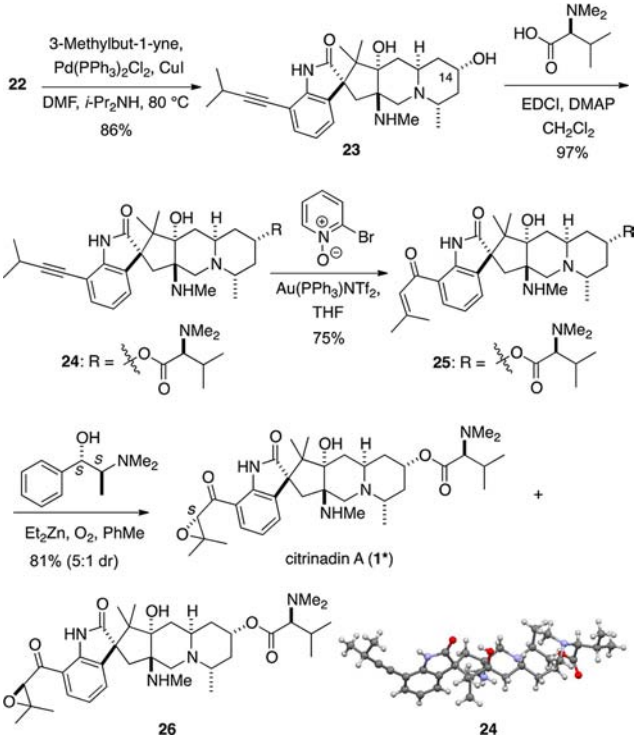
Scheme 4. Preparation of Pentacyclic Core 22 of Citrinadin A



toluenesulfonate (PPTS) to protect the amino groups from oxidation, and an excess of Davis' oxaziridine was added to afford a moderately stable epoxide, which was tentatively assigned the structure **21**.[16b] When **21** was treated with acetic acid, the anticipated semipinacol rearrangement ensued to provide the spirooxindole **22**.

At this juncture, it remained to install the requisite side chains on the A and E rings (Scheme 5). In initial experiments,

Scheme 5. Endgame: Completing the Total Synthesis of 1*



we examined the possibility of directly converting the aryl bromide moiety into an α,β-unsaturated ketone by a carbonylative cross-coupling reaction in analogy with prior work in our laboratories.[17] However, these efforts were to no avail, and we resorted to a stepwise process that commenced with the Sonogashira coupling between **22** and 3-methylbut-1-yne to furnish the alkyne **23**.[18] *O*-Acylation of the hydroxyl group at C(14) with *N*,*N*-dimethyl-L-valine in the presence of EDCI and DMAP provided **24**,[19] the absolute and relative stereochemistry of which were unambiguously proven by X-ray crystallography. The gold-promoted oxidation of **24** using 2-bromopyridine *N*-oxide according to a method reported by Zhang gave the enone **25**.[20] Finally, the diastereoselective epoxidation of the enone moiety using a method reported by Enders for the enantioselective synthesis of (*S*)-epoxides from α,β-unsaturated ketones delivered a separable mixture (5:1) of **1*** and **26** in 81% yield.[21] The CD spectrum of the synthetic **1*** thus obtained as the free base is identical with that reported for (−)-citrinadin A,[1a] whereas the CD spectrum for **26** is different (see Supporting Information).[22] The ^{1}H and ^{13}C NMR data of the free base forms of **1*** and **26** are wholly consistent with their assigned structures, and the ^{1}H and ^{13}C NMR data of **1*** as its putative bis-hydrochloride salt, which was formed upon standing in $CDCl_3$, are in good agreement with those reported for a bis-salt of (−)-citrinadin A (see Supporting Information). Because we were unable to obtain an authentic sample of (−)-citrinadin A or its bis-salt, a direct comparison with the synthetic sample was not possible. Nevertheless, the CD spectra of synthetic **1*** coupled with the crystallographic data for **24** strongly suggest that the correct stereochemical structure of (−)-citrinadin A is represented by **1***, not **1** as originally assigned by Kobayashi.[1] This revised structure, in which the stereocenters in the pentacyclic core are opposite those depicted in **1**, is in agreement with the findings of Wood and co-workers, who completed the first total synthesis of (+)-citrinadin B.[23]

In summary, we completed the first total synthesis of (−)-citrinadin A and revised its stereochemical structure to be that depicted in **1***. The synthesis, which requires only 20 steps from commercially available starting material, features a highly diastereoselective vinylogous Mannich reaction of a dienolate with a chiral pyridinium salt to establish the first stereogenic center. The chirality at this critical center was then used to control the introduction of the remaining stereocenters in the pentacyclic core by substrate control. Further applications of this strategy to the syntheses of citrinadin B (**2**) and the related alkaloids PF1270A–C (**3**–**5**) are in progress, and the results of these investigations will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, full characterization of new compounds, X-ray crystallographic data for **24**, comparison of CD spectra of **1***and **26** with those published for (−)-citrinadin A, and a comparison of ^{1}H and ^{13}C NMR data for **1***, both as its free base and bis-salt forms, with those published for a bis-salt of (−)-citrinadin A. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

sfmartin@mail.utexas.edu

Present Address

†Department of Chemistry, Hendrix College, 1600 Washington Ave., Conway, AR 72032.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM 25439) and the Robert A. Welch Foundation (F-0652) for generous support of this research. We are also grateful to Dr. Vincent Lynch (The University of Texas, Austin) for X-ray crystallography and Dr. John Wood (Colorado State University) for helpful discussions regarding the structure of the citrinadins and suggestions for introducing the epoxy ketone moiety. We also thank Dr. James Sahn (The University of Texas, Austin) for helpful suggestions and Professor Daniel Comins (North Carolina State University) for a generous gift of (−)-TCC that was used in initial synthetic studies. We also thank Dr. Eun Jeong Cho (The University of Texas, Austin) for assistance with obtaining the CD spectra.

■ REFERENCES

(1) (a) Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087−3089. (b) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430−9435.

(2) Kushida, N.; Watanabe, N.; Okuda, T.; Yokoyama, F.; Gyobu, Y.; Yaguchi, T. *J. Antibiot.* **2007**, *60*, 667−673.

(3) (a) Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623−4626. (b) McIver, A. L.; Deiters, A. *Org. Lett.* **2010**, *12*, 1288−1291. (c) Chandler, B. D.; Roland, J. T.; Li, Y.; Sorensen, E. J. *Org. Lett.* **2010**, *12*, 2746−2749. (d) Guerrero, C. A.; Sorensen, E. J. *Org. Lett.* **2011**, *13*, 5164−5167.

(4) The originally proposed structures of citrinadins A and B are those given by **1** and **2**, respectively, whereas the corresponding revised structure for citrinadin A is given by **1***.

(5) For some examples, see: (a) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124−6131. (b) Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557−4560. (c) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161−6171. (d) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236−3242. (e) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866−867. (f) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003−8010. (g) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918−5924. (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*, 8584−8592. (i) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867−8878. (j) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541−4550. (k) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547−6561. (l) Miller, K. A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113−1116. (m) Cheng, B.; Sunderhaus, J. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 3622−3625. (n) Fu, T.-H.; McElroy, W. T.; Shamszad, M.; Martin, S. F. *Org. Lett.* **2012**, *14*, 3834−3837.

(6) For reviews of the vinylogous Mannich reaction, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904. (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076−3154.

(7) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719−4728. (b) Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005**, *7*, 5227−5228.

(8) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1995**, *60*, 711−716.

(9) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405−2408.

(10) Fehr, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2407−2409.

(11) Sarabia, F.; Chammaa, S.; Garcia-Castro, M.; Martin-Galvez, F. *Chem. Commun.* **2009**, 5763−5765.

(12) The relative and absolute stereochemistry shown in **7** was later confirmed by X-ray crystallographic analysis of **24**.

(13) For some examples, see: (a) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M. *J. Am. Chem. Soc.* **1985**, *107*, 2474−2484. (b) Chen, C.-Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738−3741. (c) Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L.; Nichols, D. E. *J. Med. Chem.* **2000**, *43*, 4701−4710. (d) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342−11348.

(14) (a) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161−6171. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579.

(15) For a review, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209−2219. See also: (b) Peterson, A. C.; Cook, J. M. *J. Org. Chem.* **1995**, *60*, 120−129. (c) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579. (d) Wearing, X. Z.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4237−4240.

(16) (a) Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2262−2265. (b) Greshock, T. J.; Grubbs, A. W.; Williams, R. M. *Tetrahedron* **2007**, *63*, 6124−6130. (c) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573−3577.

(17) (a) O'Keefe, B. M.; Simmons, N.; Martin, S. F. *Org. Lett.* **2008**, *10*, 5301−5304. (b) O'Keefe, B. M.; Simmons, N.; Martin, S. F. *Tetrahedron* **2011**, *67*, 4344−4351.

(18) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. (b) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 521−549.

(19) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17*, 522−524.

(20) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070−14072.

(21) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 1725−1728.

(22) We have also prepared the enantiomers of **1*** and **26**, but their CD spectra are not consistent with the CD spectrum reported by Kobayashi for (−)-citrinadin A in ref 1a.

(23) See accompanying manuscript in this issue.