ORGANIC LETTERS

2007
Vol. 9, No. 3
385−388

Asymmetric Total Synthesis of Nigerone

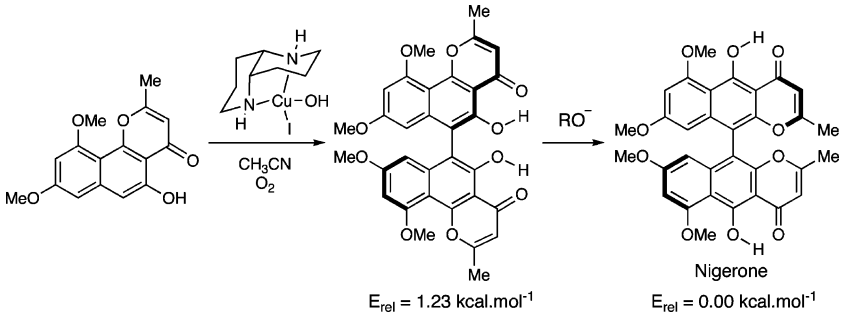
Evan S. DiVirgilio, Elizabeth C. Dugan, Carol A. Mulrooney, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

marisa@sas.upenn.edu

Received October 6, 2006

ABSTRACT



An enantioselective synthesis of the chiral bisnaphthopyrone natural product nigerone is reported. The key step was an eight-step isomerization process to form the final natural product. The isomerization precursor was constructed via asymmetric oxidative biaryl coupling of an advanced intermediate with a 1,5-diaza-*cis*-decalin copper catalyst.

The number of natural products containing axial chirality has grown substantially in recent years.[1] Development of synthetic routes to these architecturally interesting targets, however, remains a challenge.[2] One class of these compounds, the bisnaphthopyrone natural products, includes mold isolates nigerone (**1**) and isonigerone (**2**) (Figure 1),[3] that display antitumor[4] and antibacterial[5] activity. Although these compounds have been characterized, no total synthesis efforts have appeared.

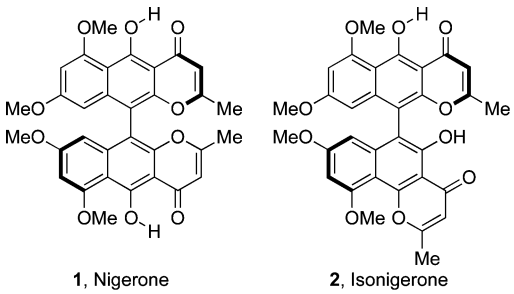


Figure 1. Bisnaphthopyrone natural products.

Nigerone is formally the dimer of a tricyclic oxygen heterocycle. The synthetic approach reported herein hinges upon a rearrangement from "bisisonigerone" **3** (Scheme 1). Bisisonigerone was in turn constructed by oxidative coupling

(1) (a) Baudoin, O.; Gueritte, F. *Stud. Nat. Prod. Chem., Part J* **2003**, *29*, 355−417. (b) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1−293. (c) Weiss, U.; Merlini, L.; Nasini, G. *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1−71.

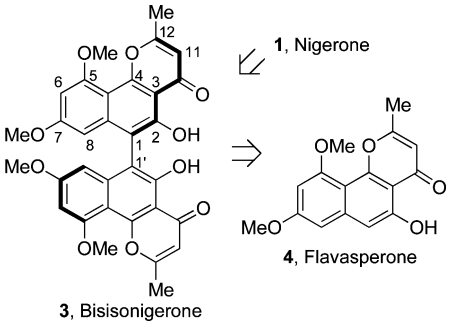
(2) (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427. (b) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223−4229. (c) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett.* **2005**, *7*, 3119−3121. (d) Cepanec, I. *Synthesis of Biaryls*; Elsevier Science: Oxford, 2004. (e) Hayashi, T. *J. Organomet. Chem.* **2002**, *653*, 41−45. (f) Bringmann, G.; Breuning, M.; Pfeifer, R.-M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. *J. Organomet. Chem.* **2003**, *661*, 31−47. (g) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308. (h) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331−343. (i) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938−949.

(3) (a) Gorst-Allman, C. P.; Steyn, P. S.; Rabie, C. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2474−2479. (b) Ehrlich, K. C.; DeLucca, A. J., II; Ciegler, A. *Appl. Environ. Microbiol.* **1984**, *48*, 1−4. (c) Koyama, K.; Natori, S.; Iitaka, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4049−4055.

(4) Koyama, K.; Ominato, K.; Natori, S.; Tashiro, T.; Tsuruo, T. *J. Pharmacobio. Dynamics* **1988**, *11*, 630−635.

10.1021/ol062468y CCC: $37.00
Published on Web 01/03/2007

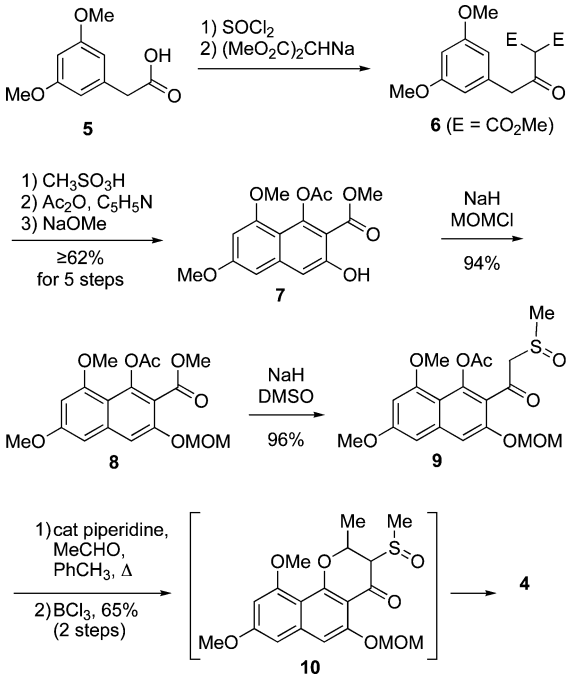
Scheme 1. Synthesis Analysis of Nigerone



of flavasperone **4**[6] to form the C1,C1′-bond using our 1,5-diaza-*cis*-decalin copper catalysts.[7]

The required substrate **4** was efficiently prepared via the process outlined in Scheme 2. Naphthol **7** was constructed

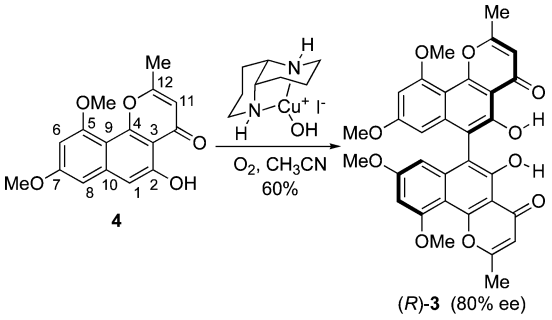
Scheme 2. Synthesis of the Biaryl Coupling Precursor



via an approach that we found to be highly efficient for the structural type.[7d] Preparation of the pyrone ring in **4** was the most difficult aspect of the synthesis. The obvious disconnection involving addition of acetone to the methyl ester of **8** to introduce the carbons of the pyrone ring failed. On the other hand, addition of the dimsyl anion to **8** provided **9** readily and in high yield. The stabilized anion from **9** was then condensed with acetaldehyde. In the same pot, deacylation, cyclization, and then sulfinic acid elimination from intermediate **10** proceeded to supply the requisite pyrone. Subsequent MOM group cleavage provided flavasperone **4**.

Our attention then turned to formation of the chiral biaryl. From the standpoint of an asymmetric coupling with the 1,5-diaza-*cis*-decalin copper catalyst, substrate **4** appears ideal. The heterocyclic ring constrains the C3 carbonyl to align with the C2 hydroxyl for optimal chelation to copper.[7e] In addition, the C4 group is withdrawing via conjugation to the C3 carbonyl; electron-withdrawing groups at C4 suppress racemization of the binaphthyl during the oxidative coupling.[7d] Thus, we were quite surprised to discover that the reaction of **4** with the chiral copper catalyst was sluggish. After one week at 40−45 °C with 10 mol % of catalyst, only 36% of the product (**3**) was isolated but the selectivity was good (~80% ee). Reasoning that the optimized chelation with **4** inhibits turnover, greater amounts of the diaza-*cis*-decalin copper oxidant were employed. The yield of **3** could be improved to 60% with stoichiometric catalyst while maintaining the selectivity (80% ee, Scheme 3).

Scheme 3. Formation of Bisisonigerone



With (*R*)-**3** in hand, the intriguing isomerization directly to **1** was investigated (Scheme 4) upon the basis of precedent from much simpler systems.[8] The key question was whether such an isomerization would be thermodynamically favorable and whether side reactions would interfere. In particular, elimination of acetone enolate from the 1,3-dicarbonyl tautomer **12** of **11** to form **14** was a concern (Scheme 5). An analysis of the structures of of **3**, **2**, and **1** was promising. Nigerone (**1**) appears to be the most stable of the three as the C2 position of the binaphthyl is less hindered compared to C4 (the C5 group is coplanar to C4, and the C1 biaryl is 70° out-of-plane) and should better accommodate the heterocyclic portion (hydrogen bonding is equivalent in the two

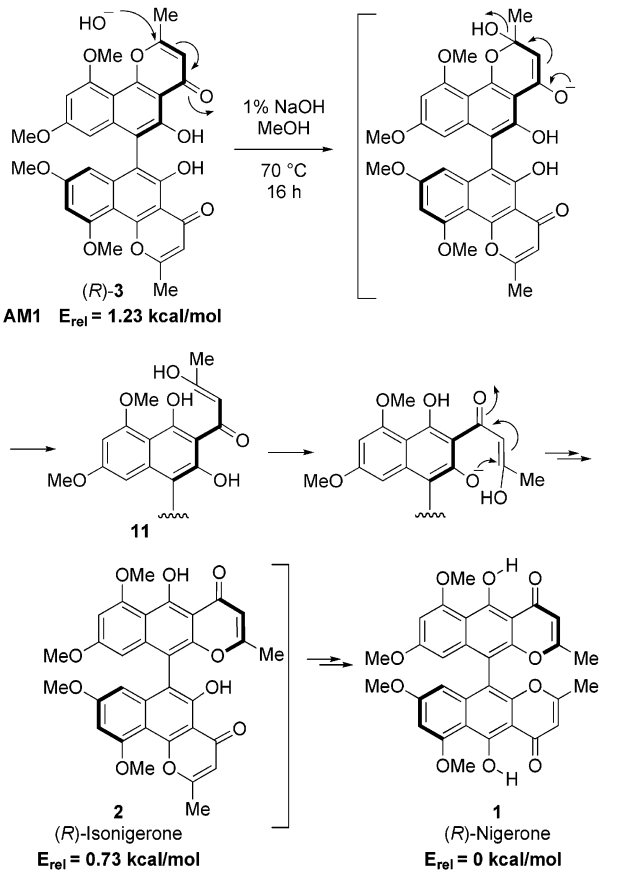
(5) (a) Boutibonnes, P.; Malherbe, C.; Kogbo, W.; Marais, C. *Microbiol., Aliments, Nutr.* **1983**, *1*, 259−264. (b) Boutibonnes, P.; Malherbe, C.; Auffray, Y.; Kogbo, W.; Marais, C. *IRCS Med. Sci.: Libr. Compend.* **1983**, *11*, 430−431. (c) Boutibonnes, P.; Auffray, Y.; Malherbe, C.; Kogbo, W.; Marais, C. *Mycopathologia* **1984**, *87*, 43−49. (d) Auffray, Y.; Boutibonnes, P. *Mutat. Res.* **1986**, *171*, 79−82.

(6) Flavasperone (**13**) has been synthesized previously by a different route entailing 10 steps: Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc.* **1963**, 4868−4872.

(7) (a) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137−1140. (b) Kozlowski, M. C.; Li, X.; Carroll, P. J.; Xu, Z. *Organometallics* **2002**, *21*, 4513−4522. (c) Xie, X.; Phuan, P.-W.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2168−2170. (d) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856−6857. (e) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500−5511.

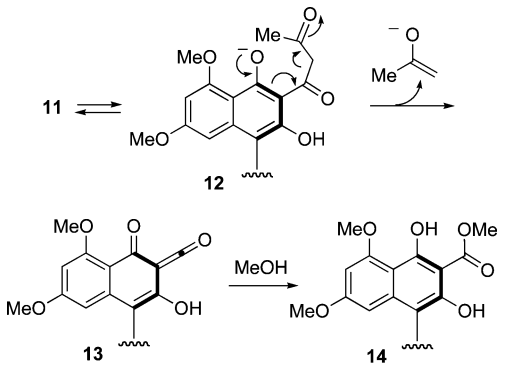
(8) For a precedent for this type of isomerization in a nonbiaryl system, see: Kanai, Y.; Ishiyama, D.; Senda, H.; Iwatani, W.; Takahashi, H.; Konno, H.; Tokumasu, S.; Kanazawa, S. *J. Antibiot.* **2000**, *53*, 863−872.

Scheme 4. Eight-Step Isomerization of Bisisonigerone to Nigerone



structures). Energy calculations (AM1) of the low-energy conformational isomers of the three possible nigerone isomers supported this hypothesis (Scheme 4): **3**, $E_{rel} = 1.23$ kcal mol^{-1}; isonigerone **2** (half-isomerized), $E_{rel} = 0.73$ kcal mol^{-1}; nigerone **1**, $E_{rel} = 0.00$ kcal mol^{-1}. Implementation of this plan using a base-catalyzed isomerization in methanol at 70 °C overnight succeeded in the formation of (*R*)-nigerone in 50% yield. No starting material and only a small amount of isonigerone were seen from this process. The remaining material appears to be intercepted by methoxide to produce the C3-substituted methyl ester **14** as outlined in Scheme 5.[9] Investigation of alternate bases and nucleophiles to optimize this process is underway. The enantioselectivity decreased only slightly during this process (<3% ee). Pleasingly, the resultant nigerone can be triturated to ≥90% ee with 50% ethyl acetate/hexanes.

Scheme 5. Undesired Pathway in the Isomerization of Bisisonigerone to Nigerone



The NMR data for the synthesized material were in complete accord with those of isolated nigerone (Table 1 and Table 2).[3a] In addition, the data for the bisisonigerone (**3**) differed markedly from those of nigerone (**1**) confirming the identity of the natural product. Measurement of the optical rotation also confirmed that the synthesized material corresponded to the natural product, thereby confirming the (*R*)-configuration as revised in later reports.[3a,c]

Table 1. ^{1}H NMR Shifts for Isolated Nigerone vs Synthetic Nigerone and Bisisonigerone **3**

	δ (ppm)						
compd	OH	H6	H8	H11	OMe	OMe	Me
1[a]	15.32	6.06[c]	6.42[c]	6.00	4.05	3.49	2.03
3	13.19	6.32	6.44	6.21	4.01	3.54	2.54
1[b]	15.31	6.05	6.42	6.00	4.05	3.48	2.03

[a] Isolated natural product (see ref 3a). [b]Synthetic material. [c]Different assignments given relative to ref 3a.

Table 2. ^{13}C NMR Shifts for Isolated Nigerone vs Synthetic Nigerone and Bisisonigerone **3**

	δ (ppm)							
compd	C=O	C1	C2	C3	C4	C5	C6	C7
1[a]	184.6	108.8[c]	161.3[c]	104.4	161.9[c]	151.4[c]	97.3	163.2[c]
3	182.9	110.5	159.7	104.3	154.6	156.1	96.9	161.7
1[b]	184.5	108.8	161.2	104.3	161.9	151.3	97.2	163.1

	δ (ppm)							
compd	C8	C10	C9	C11	C12	OMe	OMe	Me
1[a]	96.5	140.8	105.5[c]	107.3	167.6	56.2	55.2	20.5
3	96.7	140.5	108.6	110.3	166.4	56.0	55.2	20.5
1[b]	96.5	140.7	105.5	107.3	167.6	56.2	55.2	20.6

[a] Isolated natural product (see ref 3a). [b]Synthetic material. [c]Different assignments given relative to ref 3a.

In summary, the first total synthesis of the bisnaphthopyrone natural product nigerone has been achieved. A complex 2-naphthol substrate successfully underwent asymmetric oxidative biaryl coupling to produce a highly functionalized chiral 1,1′-binaphthol. From the biaryl coupling product, the key isomerization via a sequence of eight conjugate addition/elimination reactions was found to give rise to nigerone in

(9) We thank a reviewer for the suggestion of a ketene intermediate to account for **14**.

line with the calculated energies. With this asymmetric synthesis, the identity of the natural product has been confirmed.

Acknowledgment. Financial support was provided by the National Science Foundation (CHE-0616885), the National Institutes of Health (CA-109164), and the GAANN program (ESD). We are grateful to Prof. Gerhard Bringmann (Institut für Organische Chemie, Universität Würzburg) for helpful discussions. We thank Magaly Ramirez (NSF-REU) and Kusha Tavakoli for synthesis of precursors.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062468Y