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Total Syntheses of (±)-Preussomerins G and I

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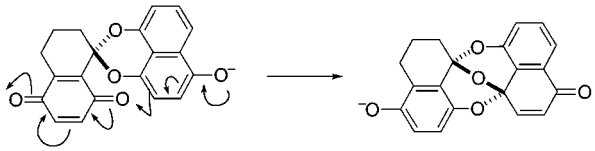
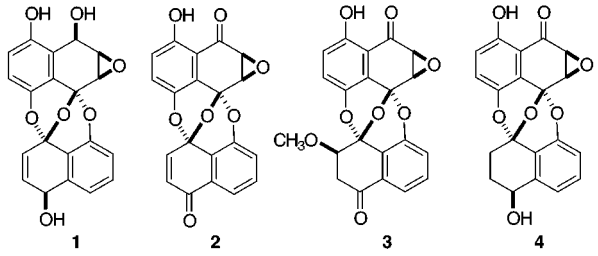
ABSTRACT



Preussomerins G and I (2 and 3) have been synthesized for the first time. The key reaction in the synthesis is a possibly biomimetic tautomerization reaction depicted in Scheme 3 and the foregoing graphic. The driving force for this interesting rearrangement is primarily derived from the increase in resonance energy associated with converting a naphthalene ring into two isolated benzene rings.

The preussomerins are a novel class of fungal metabolites isolated from the coprophilous (dung-colonizing) fungus *Preussia isomera* and the endophytic fungus *Harmonema dematioides*.[1]



1 **2** **3** **4**

Nine members of the preussomerin family have been identified, all of which share an unusually stable bis-acetal ring system. Examples are preussomerin A (**1**), preussomerin G (**2**), preussomerin I (**3**), and preussomerin F (**4**). These metabolites are natural antifungal agents and are thought to play an important biological role as part of the survival mechanism of the fungi.[1c] In addition, they have been identified as novel inhibitors of Ras farnesyl transferase, an enzyme associated with the regulation of tumor growth.[1a]

Biosynthetically, the preussomerins are related to a growing class of natural products that includes the deoxypreussomerins,[1b] palmarumycins,[2] diepoxins,[3] and others,[4] which all have a 1,8-naphthalenediol-derived spiroacetal as a key structural element; for example, deoxypreussomerin B (**5**), CJ-12,371 (**6**), palmarumycin CP_3 (**7**), and diepoxin σ (**8**, also called Sch 49209 or cladospirone bis-epoxide). These compounds show a wide range of biological activity as antifungal,[1b,c] antibacterial,[3] antitumor,[1a,4e−h] and herbicidal agents.[2] The additional spiroacetal linkage present in the preussomerins,

(1) (a) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296−6302. (b) Weber, H. A.; Baenziger, N. C.; Gloer, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 6718−6719. (c) Weber, H. A.; Gloer, J. B. *J. Org. Chem.* **1991**, *56*, 4355−4360.

(2) (a) Krohn, K.; Michel, A.; Florke, U.; Aust, H. J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1099−1108. (b) Krohn, K.; Michel, A.; Florke, U.; Aust, H. J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1093−1097. (c) Krohn, K.; Beckmann, K.; Florke, U.; Aust, H. J.; Draeger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Tetrahedron* **1997**, *53*, 3101−3110.

(3) (a) Schlingmann, G.; West, R. R.; Milne, L.; Pearce, C. J.; Carter, G. T. *Tetrahedron Lett.* **1993**, *34*, 7225−7228. (b) Schlingmann, G.; Matile, S.; Berova, N.; Nakanishi, K.; Carter, G. T. *Tetrahedron* **1996**, *52*, 435−446.

(4) (a) Thiergardt, R.; Hug, P.; Rihs, G.; Peter, H. H. *Tetrahedron Lett.* **1994**, *35*, 1043−1046. (b) Thiergardt, R.; Rihs, G.; Hug, P.; Peter, H. H. *Tetrahedron* **1995**, *51*, 733−742. (c) Sakemi, S.; Inagaki, T.; Kaneda, K.; Hirai, H.; Iwata, E.; Sakakibara, T.; Yamauchi, Y.; Norcia, M.; Wondrack, L. M.; Sutcliffe, J. A.; Kojima, N. *J. Antibiot.* **1995**, *48*, 134−142. (d) Peterson, F.; Moerker, T.; Vanzanella, F.; Peter, H. H. *J. Antibiot.* **1994**, *47*, 1098−1103. (e) Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Puar, M. S.; McPhail, A. T. *J. Org. Chem.* **1994**, *59*, 1222−1223. (f) Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Blood, C.; King, I.; Pai, J. K.; Puar, M. S. *Tetrahedron Lett.* **1994**, *35*, 1343−1346. (g) Chu, M.; Truumees, I.; Patel, M.; Blood, C.; Das, P. R.; Puar, M. S. *J. Antibiot.* **1995**, *48*, 329−331. (h) Chu, M.; Patel, M. G.; Pai, J. K.; Das, P. R.; Puar, M. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 579−584.

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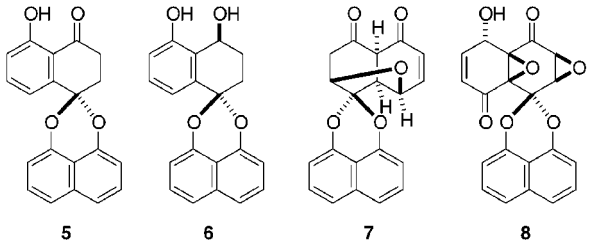
which probably results from further oxidation of the naphthalenediol spiroacetal of the deoxypreussomerins, distinguishes these compounds as the only natural products known to possess this unusual bis-acetal ring system.

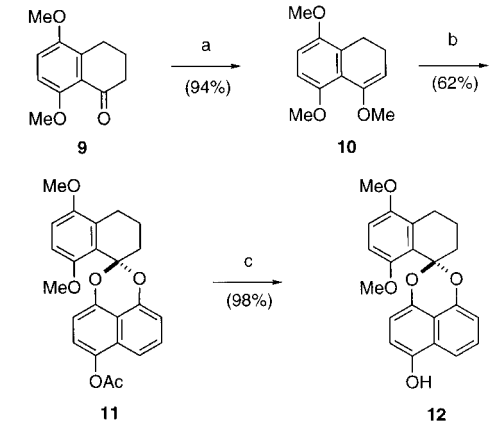


5 **6** **7** **8**

The diverse pharmacological effects of these naphthalenediol based natural products, as well as their unusual highly oxygenated structures have generated significant interest in their laboratory syntheses and there have been several syntheses of the naphthalenediol monoacetal natural products.[5] However, there has not yet been a synthesis of the more elaborate bis-spiroacetal structures typified by the preussomerins. In this Letter we report a simple, possibly biomimetic construction of this unusual bis-acetal ring system and its application to the first total syntheses of preussomerin G (**2**) and preussomerin I (**3**).

Our synthesis of the preussomerins begins with the known 5,8-dimethoxytetralone (**9**),[6] which is converted into the corresponding methyl enol ether **10**, which was allowed to react with 4-acetoxy-1,8-naphthalenediol[7] to obtain the requisite monoacetal **11**. Hydrolysis of **11** with sodium methoxide in methanol yielded hydroxymonoacetal **12** (Scheme 1).

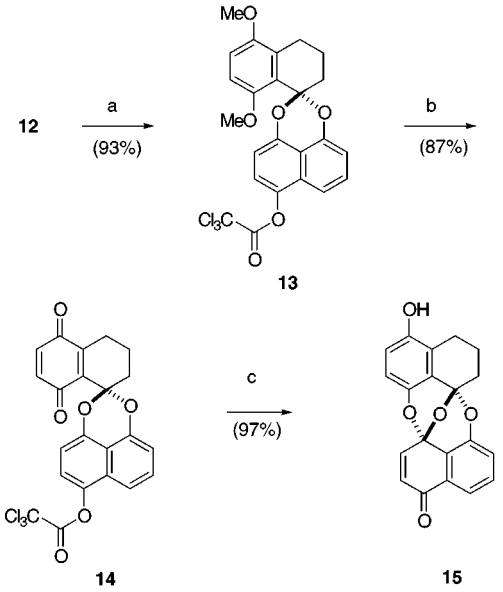
Scheme 1



a. CH_3OH, $(CH_3O)_3CH$, PPTS. b. 4-Acetoxy-1,8-napthalenediol, *p*TsOH, PhH, reflux. c. 4M NaOMe, MeOH.

To deactivate the naphthalene ring toward oxidation conditions, hydroxymonoacetal **12** was protected as its trichloroacetate ester **13**, which was oxidized with ceric ammonium nitrate[8] to obtain quinone **14** in excellent yield (Scheme 2). Hydrolysis of trichloroacetate ester **14** provided bis-acetal **15** as the only observable product in a remarkable 97% yield.

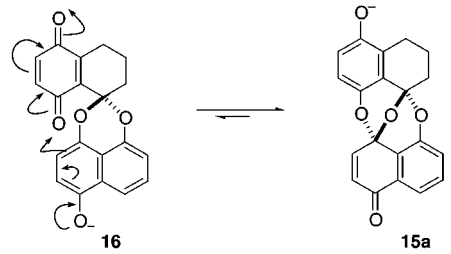
Scheme 2



a. $(Cl_3CO)_2O$, TEA. b. $Ce(NH_4)_2(NO_3)_6$, 70% aq. CH_3CN, CH_2Cl_2. c. LiOH, THF-H_2O.

This unusual reaction may be viewed as a "ring-chain tautomerization" or as a nucleophilic 1,6-addition of a phenoxide to the oxygen end of the quinone carbonyl group. The resonance energy gained from the formation of two isolated benzene rings in **15a** provides a strong driving force for this transformation. Thermodynamic analysis using bond strength energies[9] qualitatively suggests that the rearrangement of **16** to **15a** is exothermic by approximately 5 kcal/mol (Scheme 3). Ab initio (HF 6-31G*) calculations indicate this energy difference to be about 7.9 kcal/mol in favor of **15a**.

Scheme 3

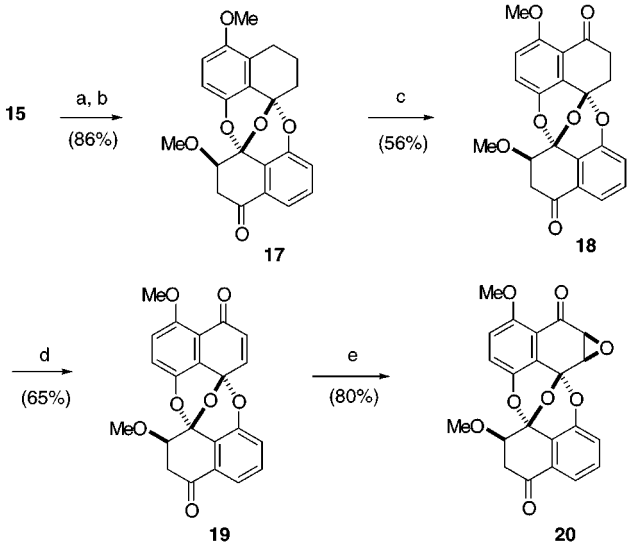


16	**15a**
2 C=O @ 179	1 C=O @179
5 C–O @ 86	7 C–O @ 86
naphthalene resonance energy @ 60	2 benzene resonance energy @ 36
848 kcal/mol	853 kcal/mol

With a viable route to the bis-acetal nucleus established, it remained to functionalize the tetralin ring to demonstrate the utility of this strategy in the synthesis of the preussomerins. We first chose to convert enone **15** to its β-methoxy adduct for several reasons. Not only was the β-methoxy

ketone a functionality present in preussomerin I (**3**), it also served to protect the C2′−C3′ enone from the epoxidation conditions used later in the synthesis. Axial attack of lithium methoxide from the less hindered face of enone **15** followed by protection of the phenolic oxygen as its methyl ether provided methoxide adduct **17** in 86% yield for the two steps. Although introduction of the benzylic ketone could be accomplished from a direct benylic oxidation reaction using chromium reagents,[10] the highest overall yield of ketone **18** was consistently achieved using a benzylic bromination/solvolysis/oxidation protocol which required only a single purification step (Scheme 4). The C2−C3 olefin was

Scheme 4

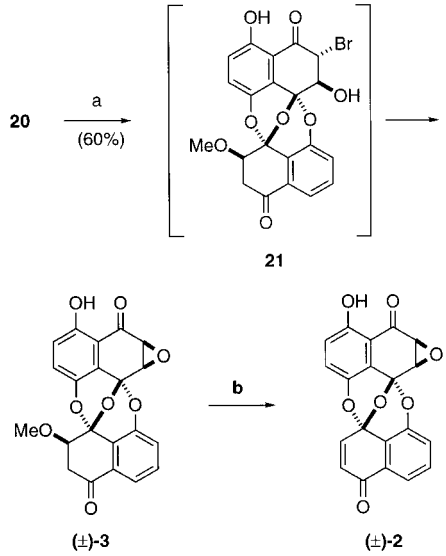


a. $LiOCH_3$, CH_3OH. b. CH_2N_2, Et_2O, CH_3OH. c. i. NBS, AIBN, CCl_4, reflux, ii. THF-H_2O, iii. Dess-Martin periodinane. d. i. TMSOTf, TEA, CH_2Cl_2, -12°C, ii. $Pd(OAc)_2$, CH_3CN. e. 30% aq. H_2O_2, $NaHCO_3$, CH_3OH, 0°C, 5h.

introduced by selective silyation of the C-1 carbonyl of diketone **18** and oxidation of the silyl enol ether with $Pd(OAc)_2$ using Saegusa conditions.[11] Enone **19** was then epoxidized under basic conditions using 30% H_2O_2 and $NaHCO_3$ to yield epoxide **20** in good yield.

Deprotection of methyl ether **20** with boron tribromide proved not to be troublesome, providing the demethylated product **21**, in which bromide addition to the epoxide had occurred (Scheme 5). The regiochemistry of epoxide opening

Scheme 5



a. i. BBr_3, CH_2Cl_2, -78°C. ii. $LiOCH_3$, CH_3OH. b. TMSOTf 2 eq., TEA 2eq., CH_2Cl_2, rt.

was assigned on the basis of the coupling constant of the C-2 and C-3 protons (J = 2 Hz) and from literature precedent[12] which predict that the bromide and the alcohol are trans-diaxial. The epoxide was easily reformed under basic conditions to complete the first synthesis of (±)-preussomerin I (**3**). Elimination of methanol from **3** under Lewis acidic conditions yielded (±)-preussomerin G (**2**).

In summary, we have presented the first syntheses of members of the bis-spiroacetal family of fungal metabolites, (±)-preussomerin G (**2**) and (±)-preussomerin I (**3**). With the discovery of the rearrangement of quinone monoacetal **15** to bis-acetal **14a**, we believe we may have found the transformation that leads to this unique bis-acetal ring system in Nature. Future efforts in our laboratory will be directed at the development of an asymmetric approach to the preussomerins.

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Supporting Information Available: Experimental procedures and full characterization for compounds **10**−**18**, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **3**, **19**, and **20**, and ^{1}H NMR spectrum of compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) Krohn, K.; Beckmann, K.; Aust, H. J.; Draeger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Liebigs Ann.-Recl.* **1997**, 2531−2534. (b) Wipf, P.; Jung, J. K. *J. Org. Chem.* **1998**, *63*, 3530−3531. (c) Wipf, P.; Jung, J. K. *J. Org. Chem.* **1999**, *64*, 1092−1093. (d) Ragot, J. P.; Alcaraz, M. L.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 4921−4924. (e) Barrett, A. G. M.; Hamprecht, D.; Meyer, T. *Chem. Commun.* **1998**, 809−810.

(6) (a) Lurie, A. P.; Brown, G. H.; Thirtle, J. R.; Weissberger, A. *J. Am. Chem. Soc.* **1961**, *83*, 5015−5019. (b) Moore, J. A.; Rahn, M. *J. Org. Chem.* **1961**, *26*, 1109−1111.

(7) (a) Laatsch, H. *Liebigs Ann. Chem.* **1980**, 1321−1347. (b) Laatsch, H. *Liebigs Ann. Chem.* **1986**, 1655−1668.

(8) Castagnoli, N., Jr.; Shulgin, A. T.; Callery, P. S.; Jacob, P., III. *J. Org. Chem.* **1976**, *41*, 3627−3629.

(9) Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*; Macmillian Publishing Company: New York, 1992.

(10) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 2131−2132.

(11) Saegusa, T.; Hirao, T.; Ito, Y. *J. Org. Chem.* **1978**, *43*, 1101−1113.

(12) (a) Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401−13408. (b) Corey, E.; Lee, D. H.; Choi, S. *Tetrahedron Lett.* **1992**, *51*, 6735−6738. (c) Matoba, K.; Karibe, N.; Yamazaki, T. *Chem. Pharm. Bull.* **1983**, *32*, 2639−2645.