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Total Synthesis of Epicoccin G

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Supporting Information

ABSTRACT: An expedient enantioselective total synthesis of epicoccin G and related dithiodiketopiperazines through a strategy featuring direct two-directional sulfenylation, photooxygenation, and Kornblum−DeLaMare rearrangement is described.

Diketopiperazines are an important class of natural products whose molecular structures are as varied as their biological properties.[1] Those that contain sulfur atoms within their structures are particularly interesting because of the synthetic challenge they present and their potent activities against viruses, bacteria, and cancer cells.[2] Combined with the scarcity of these compounds, these properties have inspired studies leading toward their synthesis as a means to develop new chemistry and render them readily available for further biological investigations.[3] Epicoccin G (**1**) [Figure 1; isolated from the endophytic fungus *Epicoccum nigrum*; exhibits anti-HIV activity in C8166 cells (IC_{50} = 13.5 μM)],[4] rostratin B (**2**) [Figure 1; isolated from the marine-derived fungus *Exserohilum rostratum*; exhibits cytotoxicity against human colon carcinoma HTC-116 (IC_{50} = 1.9 μM)],[5] and exserohilone (**3**) (Figure 1; isolated from the endophytic fungus *Exserohilum holmii*; suspected of antibacterial and antifungal activity)[6] are three examples representing this class of compounds, whose structural motifs are situated on a 6−5−6−5−6 diketopiperazine framework (**I**, Figure 1). In this communication, we report a total synthesis of epicoccin G (**1**) and 8,8′-*epi*-*ent*-rostratin B (**4**) featuring a direct and improved procedure for the introduction of the sulfur atoms in diketopiperazines and a novel singlet oxygen/DeLaMare rearrangement cascade sequence for the attachment of the oxygen functionalities of the target molecules.

Figure 2 shows, in retrosynthetic format, the evolution of the synthetic strategy leading to epicoccin G (**1**). The C_2 symmetry of **1** allowed for a general two-directional strategy for all three dithiodiketopiperazine natural products shown in Figure 1 (**1**−**3**), their diastereoisomers (e.g., **4**), and their analogues. In view of the special reactivity of the sulfur moieties, the timing of their introduction was crucial. Thus, while early introduction of sulfur may have thwarted subsequent steps required for pending functionalizations, their late installation was excluded by the higher reactivity of the ketone groups (relative to the diketopiperazine moiety) under the basic conditions needed for the sulfenylation reaction. On balance, we decided to explore the possibility of introducing the sulfur atoms on bisdiene **7** and attempt to navigate the growing molecule through selective endoperoxide formation effected by a photooxygenation reaction, followed by the rarely employed Kornblum−DeLaMare rearrangement[7] and reduction of the remaining olefinic bonds. The requisite bisdiene system **7** was to be formed from *N*-Boc tyrosine (**9**) through intermediate **8** via appropriate functional group manipulations and dimerization.

The construction of the C_2-symmetric bisdiene diketopiperazine **7** from **9** is summarized in Scheme 1. Thus, **9** was converted to bicyclic hydroxy enone **10** through a known two-step procedure.[8] Deoxygenation of the latter was achieved through a three-step sequence involving acetylation, zinc reduction, and base-induced isomerization of the resulting β,γ-unsaturated ketone to afford the desired bicyclic enone **8** in 51% overall yield. Luche reduction[9] of this enone led to hydroxy *N*-Boc methyl ester **11** (92% yield), which was advanced through acid (TFA) and base (LiOH) treatment to intermediates hydroxy amine **12** and hydroxy acid **13**, respectively. The dimerization step was realized through BOP-Cl facilitated coupling of **12** and **13** to afford *N*-Boc methyl ester amide **14** (86% yield). Deprotection of the amine and Et_3N-induced ring closure gave pentacyclic bisallylic system **15** in 77% overall yield for the two steps. The desired bisdiene **7** was generated from **15** through intermediate bistrifluoroacetate **16** by treatment with $(CF_3CO)_2O$ and Et_3N (69% yield) followed by exposure to $Pd(PPh_3)_4$ catalyst (90% yield).[10]

With diketopiperazine bisdiene **7** in hand, the installation of the sulfur atoms became the next task. Initial attempts to accomplish bis-sulfenylation of **7** by the classical method[11] of treatment of the diketopiperazine substrate with base followed by addition of S_8 failed; at best, only trace amounts of bis-sulfenylated products were obtained. Upon extensive experimentation, we discovered that pretreatment of S_8 with 3 equiv of NaHMDS at ambient temperature followed by sequential addition of **7** and an additional 2 equiv of NaHMDS provided a mixture of oligosulfenylated compounds (**17**; Scheme 2). Bismethylthio derivative **18** [together with its chromatographically separable 2,2′-*epi*-diastereoisomer (2,2′-*epi*-**18**, not shown)][12] was obtained as the major product upon reduction of oligosuflide **17** with $NaBH_4$ and subsequent quenching of the resulting dianion with MeI (58% yield, ∼1.4:1 dr). Oxidation of the dianion resulting from $NaBH_4$ reduction of **17** with KI_3 led to the corresponding epidithiodiketopiperazine **19** as the major product, formed together with its chromatographically separable

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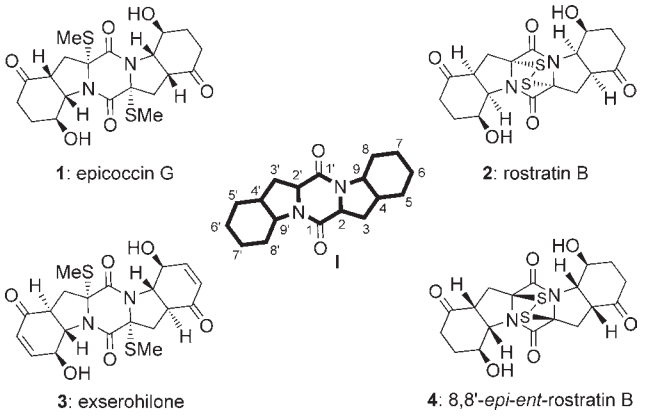


Figure 1. Molecular structures of selected dithiodiketopiperazines: epicoccin G (**1**), rostratin B (**2**), exserohilone (**3**), and 8,8′-*epi*-*ent*-rostratin B (**4**).

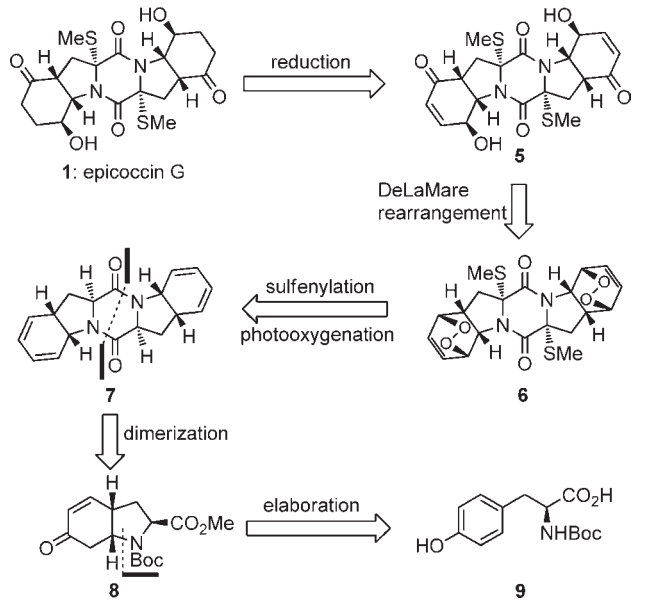
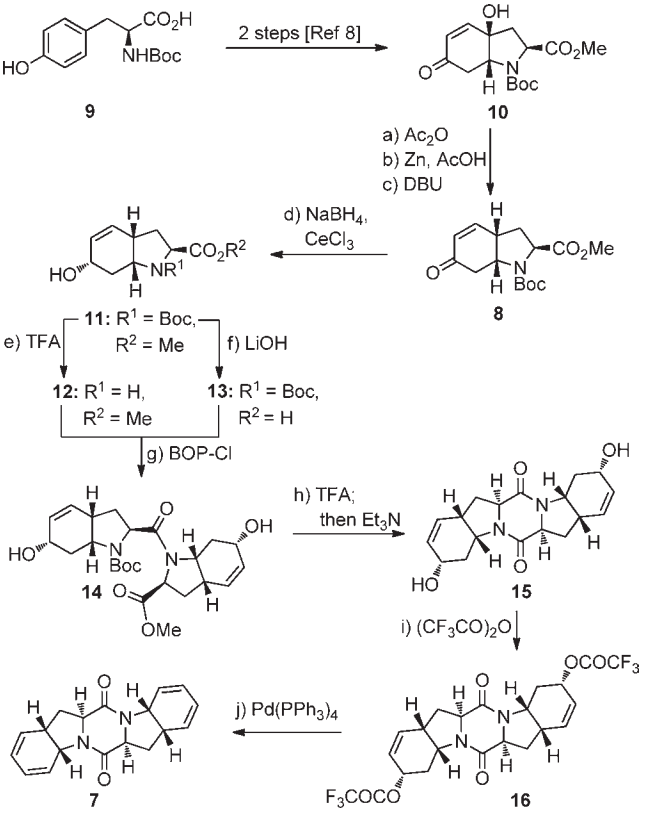


Figure 2. Retrosynthetic analysis of epicoccin G (**1**).

2,2′-*epi* diastereoisomer (2,2′-*epi*-**19**, see scheme 4) in 55% combined yield (~1.4:1 dr). Selective synthesis of **18** could also be achieved starting from **19** by reduction with $NaBH_4$ and quenching with MeI (65% yield). At this stage, the stereochemical configurations of **18** and 2,2′-*epi*-**18** (and by extension **19** and 2,2′-*epi*- **19**) were assigned by NMR studies [see the nuclear Overhauser effect spectroscopy (NOESY) correlations in Figure 3] and later confirmed by the successful conversion of **18** to epicoccin G (**1**) (see below).

With the challenging sulfenylation successfully completed through the newly developed procedure, the next hurdle, involving regio- and stereoselective oxygenation of the diene systems of **18** in the presence of the sulfur atoms, was addressed. Reaction of **18** with singlet oxygen [generated from triplet oxygen and light in the presence of TPP as a sensitizer[13] (CH_2Cl_2, 45 °C, 40 min)] gave bisendoperoxide **6** (Scheme 3). The latter underwent regioselective Kornblum−DeLaMare rearrangement[7] upon in situ treatment with DBU to afford bishydroxy enone **20** in 52% overall yield. Finally, catalytic hydrogenation of the highly

Scheme 1. Synthesis of Diketopiperazine Bisdiene 7[a]



[a] Reagents and conditions: (a) Ac_2O (2.0 equiv), Et_3N (3.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 → 25 °C, 4 h. (b) Zn (8.0 equiv), AcOH (2.0 equiv), MeOH, 65 °C, 0.5 h. (c) DBU (5.0 equiv), PhMe, 65 °C, 3 h; 51% for the three steps. (d) $NaBH_4$ (1.1 equiv), $CeCl_3 \cdot 7H_2O$ (1.0 equiv), MeOH, −78 → 0 °C, 1 h, 92%. (e) TFA/CH_2Cl_2 (1:1), 0 → 25 °C, 0.5 h, 99%. (f) aq. LiOH (1.0 M)/THF (5:1), 0 → 25 °C, 3 h, 99%. (g) **12** and **13** (1.0 equiv each), BOP-Cl (1.1 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 0 → 25 °C, 15 h, 86%. (h) TFA (27 equiv), CH_2Cl_2, 0 → 25 °C, 1.5 h; then Et_3N (5.0 equiv), CH_2Cl_2, 0 → 25 °C, 15 h; 77% for the two steps. (i) $(CF_3CO)_2O$ (4.0 equiv), Et_3N (6.0 equiv), DMAP (0.3 equiv), MeCN, −40 → 25 °C, 1 h, 69%. (j) $Pd(PPh_3)_4$ (0.1 equiv), K_2CO_3 (2.1 equiv), dioxane, 65 °C, 0.5 h, 90%.

functionalized pentacyclic precursor **20** [H_2, 20% $Pd(OH)_2/C$] furnished epicoccin G (**1**) in 86% yield. The physical properties of synthetic **1** (i.e., ^1H and ^{13}C NMR spectra, mass spectral data, and optical rotation) matched those reported for the natural substance.[4b]

As a demonstration of the power of the developed methodology to construct complex dithiodiketopiperazine systems, we successfully completed the total synthesis of the epidithiodiketopiperazine 8,8′-*epi*-*ent*-rostratin B (**4**) as shown in Scheme 4. Thus, photooxygenation of 2,2′-*epi*-**19** followed by in situ treatment of the so-generated bisendoperoxide **21** with Et_3N regioselectively furnished bishydroxy enone **22** in 55% overall yield. Reduction of the olefinic bonds within **22** was achieved through the use of Stryker's reagent,[14] and subsequent treatment with KI_3 furnished **4** in 82% yield.

Described herein is an improved direct procedure for sulfenylation of diketopiperazines and its application to the synthesis of the bismethylthio- and epidithiodiketopiperazine structural motifs, as exemplified by the total synthesis of epicoccin G (**1**)

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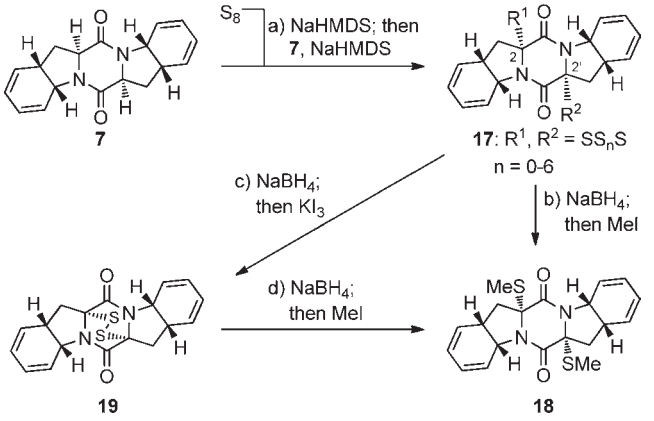
Scheme 2. Synthesis of Dithiodiketopiperazines 18 and 19[a]



[a] Reagents and conditions: (a) NaHMDS (0.6 M in PhMe, 3.0 equiv), S_8 (1.0 equiv), THF, 25 °C, 1 min; then **7** (1 M in THF, 1.0 equiv) 1 min; then NaHMDS (0.6 M in PhMe, 2.0 equiv), 25 °C, 0.5 h. (b) $NaBH_4$ (25 equiv), THF/MeOH (1:1), 0 → 25 °C, 0.75 h; then MeI (50 equiv), 25 °C, 15 h; 58% over three steps from **7** (**18**:2,2′-*epi*-**18**, ~1.4:1 *dr*). (c) $NaBH_4$ (25 equiv), THF/MeOH (1:1), 0 → 25 °C, 0.75 h; then aq. KI_3 (1.4 M), 25 °C, 10 min; 55% over three steps from **7** (**19**:2,2′-*epi*-**19**, ~1.4:1 *dr*). (d) $NaBH_4$ (25 equiv), THF/MeOH (1:1), 0 → 25 °C, 0.75 h; then MeI (50 equiv), 25 °C, 15 h; 65% from **19**.

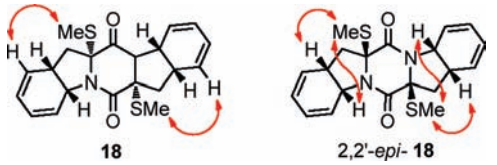
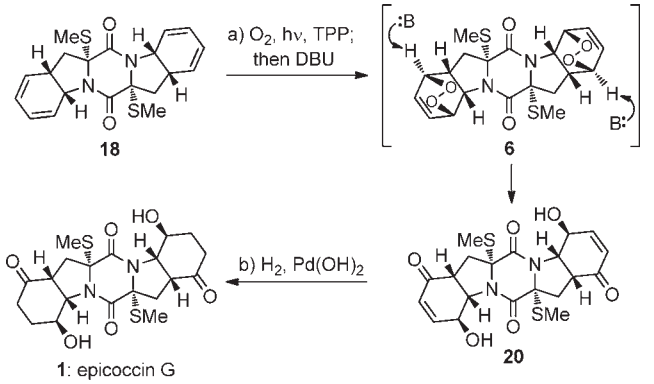


Figure 3. Stereochemical assignments of **18** and 2,2′-*epi*-**18** by NOESY studies. Arrows designate NOESY correlations.

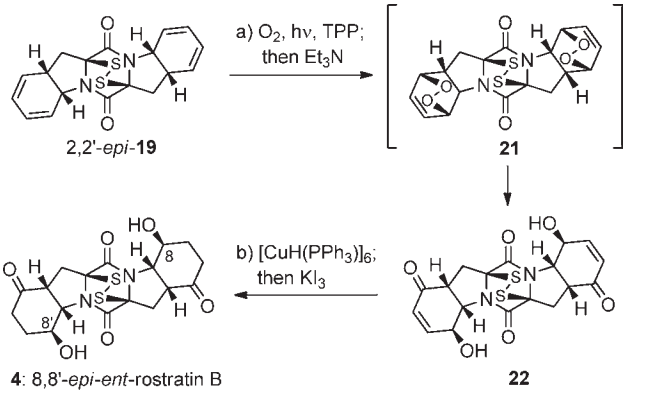
Scheme 3. Completion of the Total Synthesis of Epicoccin G (1)[a]



[a] Reagents and conditions: (a) O_2, TPP (0.02 equiv), CH_2Cl_2, 400 W Philips-MH400/U sun lamp, −45 °C, 40 min; then DBU (10.0 equiv), −45 → 0 °C, 1 h; 52% from **18**. (b) H_2, $Pd(OH)_2/C$ [20% (w/w), 0.4 equiv], MeOH, 25 °C, 1 h, 86%.

and 8,8′-*epi*-*ent*-rostratin B (**4**). Employing endoperoxide intermediates, the described chemistry also demonstrates the applicability of the Kornblum−DeLaMare rearrangement in total synthesis and should facilitate the construction of other members of the dithiodiketopiperazine class of compounds, natural or designed, for biological investigations.

Scheme 4. Completion of the Total Synthesis of 8,8′-*epi*-*ent*-Rostratin B (4)[a]



[a] Reagents and conditions: (a) O_2, TPP (0.02 equiv), CH_2Cl_2, 400 W Philips-MH400/U sun lamp, 0 °C, 2 h; then Et_3N (5.0 equiv), 0 → 25 °C, 3 h; 55% for the two steps. (b) $[CuH(PPh_3)]_6$ (10.0 equiv), benzene, 25 °C, 0.5 h; then aq. KI_3 (1.4 M), 25°C, 10 min 82%.

■ ASSOCIATED CONTENT

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

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