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Total Synthesis of Epicoccin G

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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 due to the challenge they present to synthesis and their potent activities against viruses, bacteria and cancer cells.[2] Combined with their scarcity, these properties inspire studies 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 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 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 toward epicoccin G (**1**). The C_2-symmetry of **1** allowed for a general two-directional strategy for all three epidithiodiketopiperazine natural products shown in Figure 1 (**1**–**3**), their diastereoisomers (e.g. **4**) and their analogues. Given 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 (as compared to the diketopiperazine moiety) under the basic conditions needed for the sulfenylation reaction. On balance, it was decided to explore the possibility of introducing the sulfur atoms at the *bis*-diene **7** stage 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

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

bonds. The requisite *bis*-diene 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 *bis*-diene diketopiperazine **7** from *N*-Boc tyrosine **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 ß,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 *bis*-allylic system **15** in 77% overall yield for the two steps. The desired *bis*-diene **7** was generated from **15**, through intermediate *bis*-trifluoroacetate **16**, by treatment with $(CF_3CO)_2O$ and Et_3N (69% yield), followed by exposure to $Pd(PPh_3)_4$ (cat.) (90% yield).[10]

With diketopiperazine *bis*-diene **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 pre-treatment of S_8 with three equiv of NaHMDS at ambient temperature, followed by sequential addition of the diketopiperazine substrate **7** and further two equiv of NaHMDS, provided a mixture of oligosulfenylated compounds (**17**, Scheme 2). *bis*-Methylthio 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, ca. 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 2,2′-*epi*-diastereoisomer (2,2′-*epi*-**19**, not shown) in 55% combined yield (ca. 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 NOESY correlations, Figure 3) and confirmed later 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, that of 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, 0 °C, 15 min), gave *bis*-endoperoxide **6** (Scheme 3). The latter underwent regioselective Kornblum–DeLaMare rearrangement[7] upon in situ treatment with DBU to afford *bis*-hydroxy enone **20** in 52% overall yield. Finally, catalytic hydrogenation of the highly functionalized pentacyclic precursor **20** (H_2, 20% $Pd(OH)_2$/C) furnished epicoccin G (**1**, 86% yield). The physical properties of synthetic **1** (i.e. ^1H and ^{13}C NMR, mass spec 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 epidithiodiketopiperazine 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 *bis*-endoperoxide (**21**) with Et_3N furnished, regioselectively, *bis*-hydroxy enone **22** in 55%

overall yield. Reduction of the olefinic bonds within **22** was achieved through the use of Stryker's reagent,[14] followed by treatment with KI_3, furnished 8,8′-*epi*-*ent*-rostratin B (**4**) in 82% yield.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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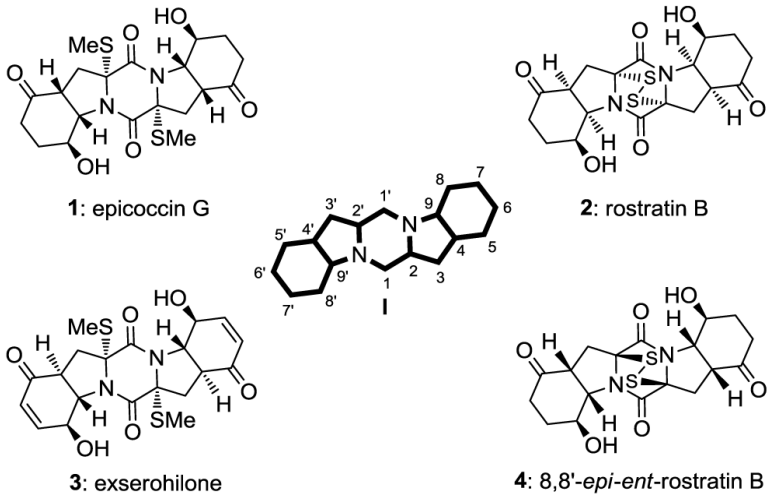


Figure 1.
Molecular structures of selected epidithiodiketopiperazines: epicoccin G (**1**), rostratin B (**2**), exserohilone (**3**) and 8,8′-*epi*-*ent*-rostratin B (**4**).

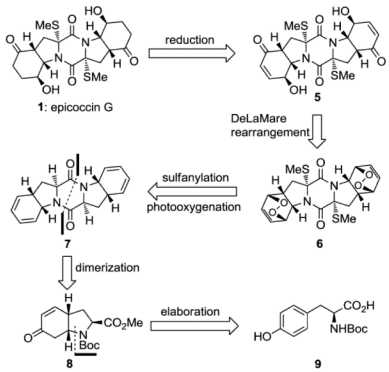


Figure 2.
Retrosynthetic analysis of epicoccin G (**1**).

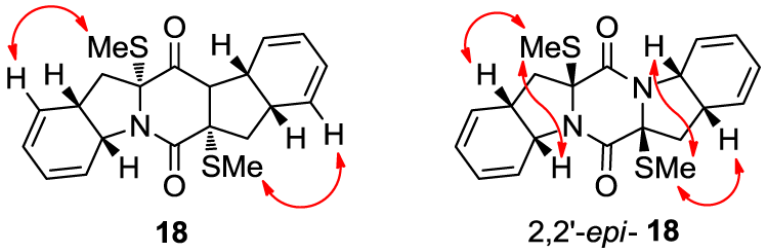
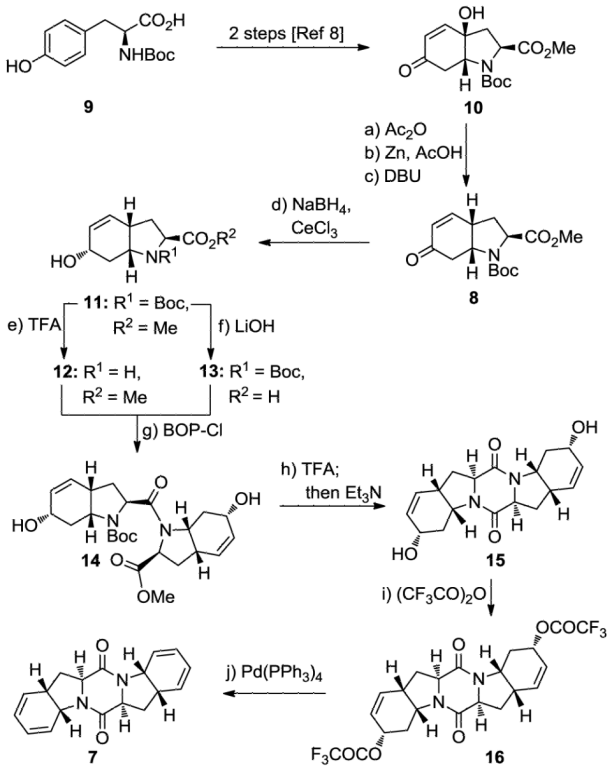
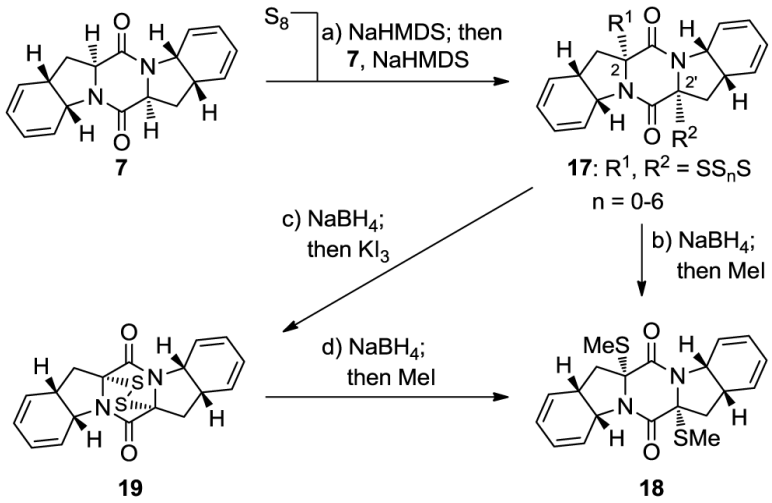


Figure 3.
Stereochemical assignments of **18** and 2,2′-*epi*-**18** by NOESY studies. Arrows designate NOESY correlations.



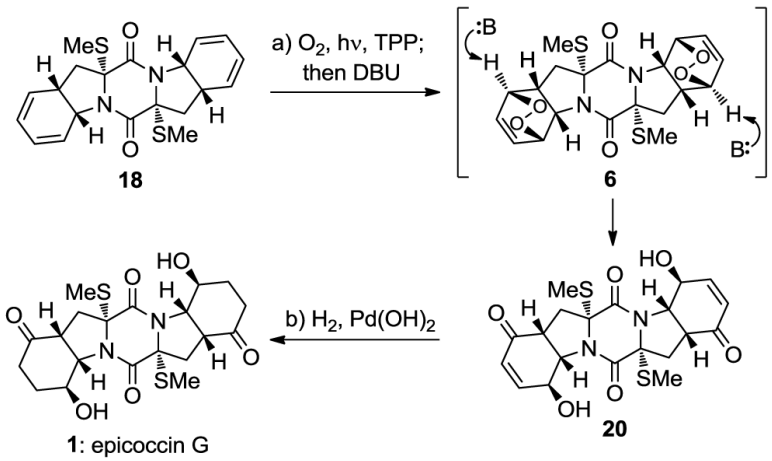
Scheme 1. Synthesis of Diketopiperazine *bis*-Diene 7[a]

[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 (4:1), 0→25 °C, 3 h, 99%; g) **12**, **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 (32 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%.



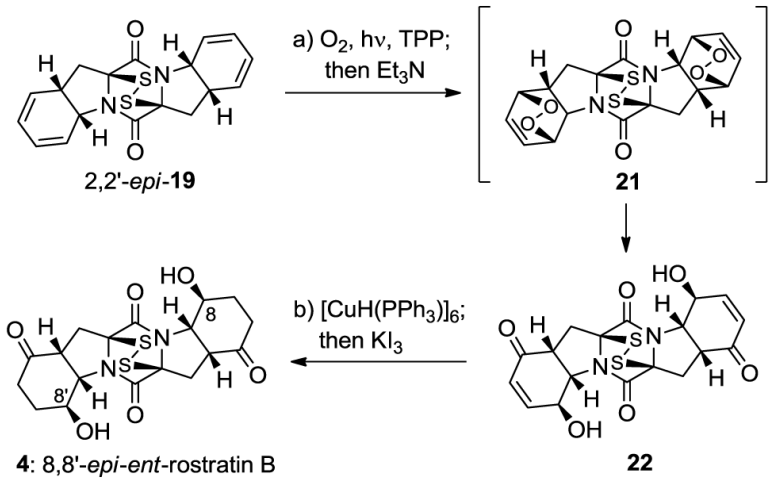
Scheme 2. Synthesis of Dithiodiketopiperazines 18 and 19[a]

[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**, ca. 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**, ca. 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**.



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, 400W Philips-MH400/U sunlamp, −45 °C, 0.7 h; 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%.



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, 400W Philips-MH400/U sunlamp, 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), 82%.