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Synthesis and Biological Evaluation of Epidithio-, Epitetrahydro- and bis-(Methylthio)diketopiperazines. Synthetic Methodology, Enantiomeric Total Synthesis of Epicoccin G, 8,8-epi-ent-Rostratin B, Gliotoxin, Gliotoxin G, Emethallicin E and Haematocin, and Discovery of New Antiviral and Antimalarial Agents

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Synthesis and Biological Evaluation of Epidithio-, Epitetrathio- and *bis*-(Methylthio)diketopiperazines. Synthetic Methodology, Enantioselective Total Synthesis of Epicoccin G, 8,8'-*epi-ent*-Rostratin B, Gliotoxin, Gliotoxin G, Emethallicin E and Haematocin, and Discovery of New Antiviral and Antimalarial Agents

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Natural Products, Total Synthesis, Anti Poliovirus Agents, Antimalarial Agents, Epidithiodiketopiperazines, bis-(Methylthio)diketopiperazines

Supporting Information Placeholder

ABSTRACT: An improved sulfonylation method for the preparation of epidithio-, epitetrathio- and *bis*-(methylthio)diketopiperazines from diketopiperazines has been developed. Employing NaHMDS and related bases and elemental sulfur or *bis*[*bis*(trimethylsilyl)amino]trisulfide (**23**) in THF, the developed method was applied to the synthesis of a series of natural and designed molecules, including epicoccin G (**1**), 8,8'-*epi-ent*-rostratin B (**2**), gliotoxin (**3**), gliotoxin G (**4**), emethallicin E (**5**) and haematocin (**6**). Biological screening of selected synthesized compounds led to the discovery of a number of nanomolar anti poliovirus agents (i.e. **46**, 2,2'-*epi*-**46** and **61**, Table 5) and several low micromolar anti *Plasmodium falciparum* lead compounds (i.e. **46**, 2,2'-*epi*-**46**, **58**, **61** and **1**, Table 5).

INTRODUCTION

2,5-Diketopiperazines are a ubiquitous class of compounds of diverse molecular architectures and biological activities.¹ Numerous have been discovered from natural sources while many more have been synthesized in the laboratory for biological investigations and drug discovery purposes.¹ The 2,5-diketopiperazine structural motif constitutes a unique scaffold upon which three dimensional molecules, including chiral ones, may be constructed,^{1,2} thereby providing a useful alternative to the planar structural motifs commonly found in drugs and drug candidates, the latter being often far from ideal in terms of pharmacological properties.³

Of particular interest are the naturally occurring epidithio-diketopiperazines and *bis*-(methylthio)diketopiperazines, whose biological activities include antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties.^{1,4} Despite their promising biological profiles, however, these compounds remain largely unexplored, primarily due to their natural scarcity and the synthetic laboratory challenge they pose.^{5,6}

In order to alleviate some of these deficiencies and facilitate biological investigations in this area, we recently initiated a research program directed toward the development of improved methods of sulfonylation of 2,5-diketopiperazines and applied them to the total synthesis of natural and designed epidithio-, epitetrathio- and *bis*-(methylthio)diketopiperazines. In preliminary communications we already reported an improved method for the sulfonylation of 2,5-diketopiperazines⁷ and the total synthesis⁸ of epicoccin G⁹ (**1**, Figure 1) and 8,8'-*epi-ent*-rostratin B¹⁰ (**2**, Figure 1). In this article we describe further studies in this area that include enantioselective total syntheses of gliotoxin¹¹ (**3**, Figure 1), gliotoxin G¹² (**4**, Figure 1), emethallicin E¹³ (**5**, Figure 1) and haematocin¹⁴ (**6**, Figure 1), as well as the monomeric unit (**7**, Figure 1) of aranotin^{15,16} (**8**, Figure 1). We also report our biological evaluation of a number of selected synthesized compounds that led to the discovery of potent anti poliovirus and anti *Plasmodium falciparum* agents.

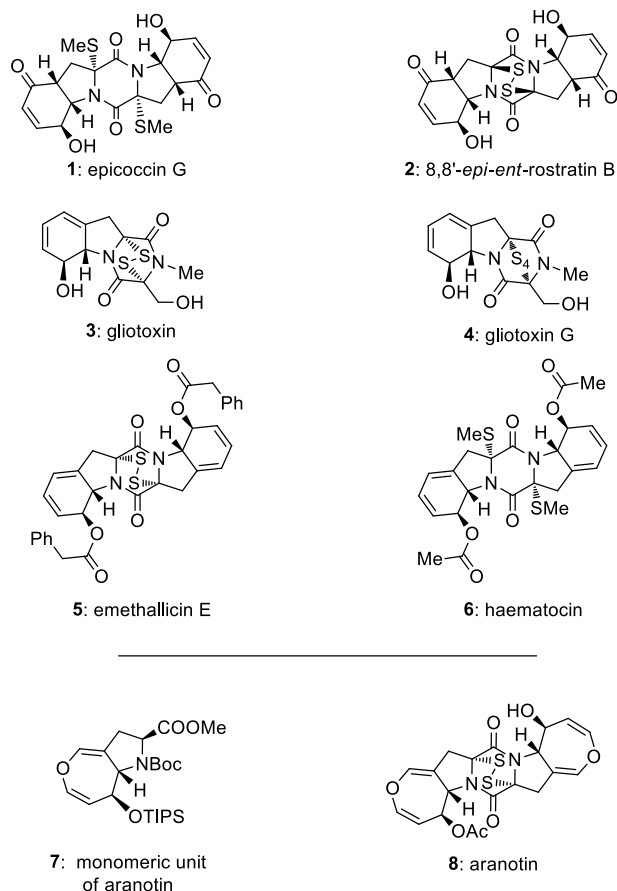


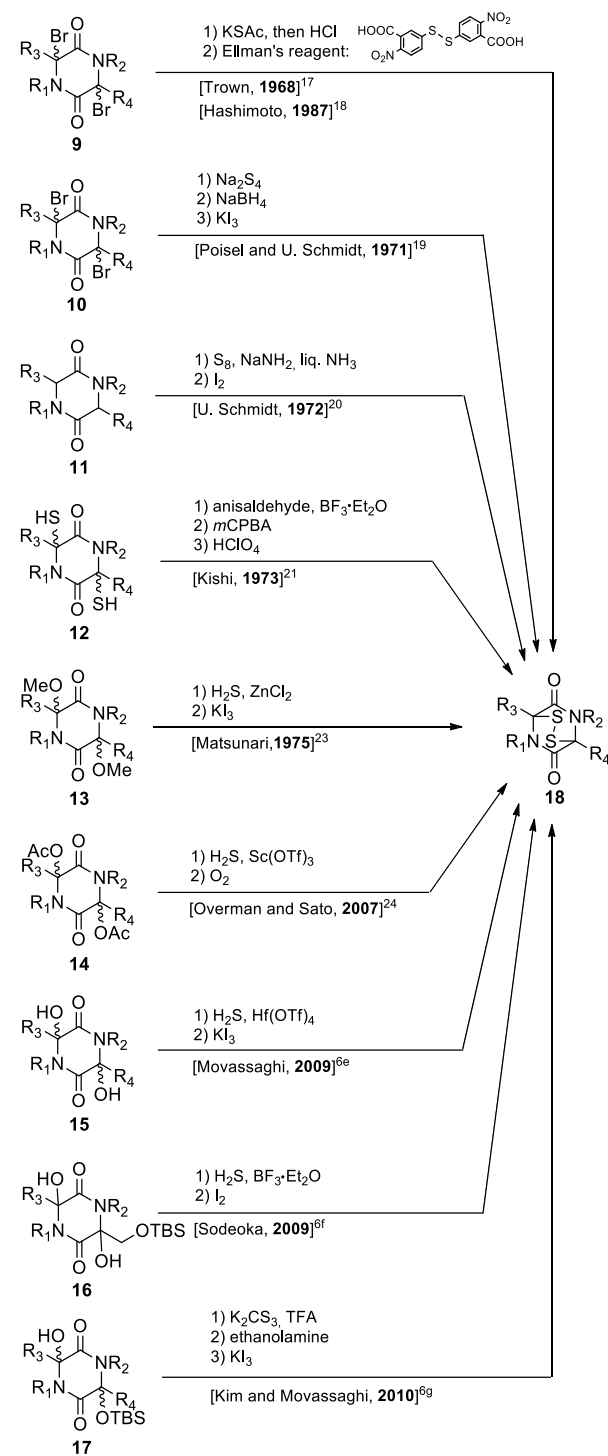
Figure 1. Selected naturally occurring epidithio-, epitetrathio- and bis-(methylthio)diketopiperazines.

RESULTS AND DISCUSSION

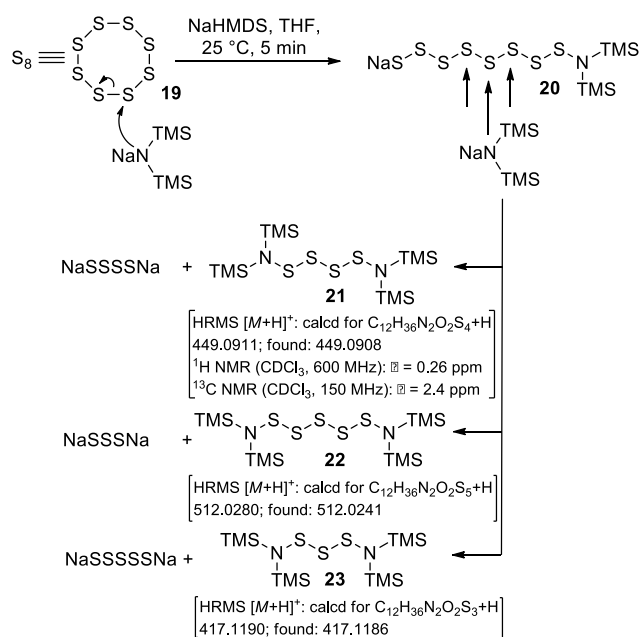
Methodology Development. Recognizing the deficiencies of the then available sulfenylation methods of 2,5-diketopiperazines, we set as part of our goals the development of improved sulfenylation methods to construct epidithiodiketopiperazines and bis-(methylthio)diketopiperazines. Figure 2 depicts a number of selected sulfenylation methods of 2,5-diketopiperazines known at the outset of our investigations. Thus, as early as 1968, Trown,¹⁷ and subsequently Hashimoto¹⁸ (1987), pioneered the use of 3,6-dibromodiketopiperazines (**9**) as substrates and KSAc as a sulfur source to prepare epidithiodiketopiperazines (**18**). In 1971, Poisel and U. Schmidt¹⁹ introduced the use of sodium tetrasulfide (Na_2S_4) as a source of sulfur to produce epidithiodiketopiperazines (**10**→**18**, Figure 2), and in 1972 the classical U. Schmidt method²⁰ for the synthesis of these compounds from 2,5-diketopiperazines employing sulfur (S_8) and NaNH_2 in liq. NH_3 (**11**→**18**, Figure 2) was reported. In 1973, Kishi²¹ reported a method of masking 3,6-dithiodiketopiperazines with anisaldehyde and then generating the desired epidithiodiketopiperazines at a later stage (**12**→**18**, Figure 2), a tactic that he elegantly applied to synthesize gliotoxin (**3**).^{6h,6i} In 1975, Matsunari²³ utilized 3,6-dimethoxydiketopiperazines as substrates in conjunction with H_2S as a source of sulfur to prepare epidithiodiketopiperazines (**13**→**18**, Figure 2), whereas in 2002 Overman and Sato²⁴ employed the corresponding bis-acetates and H_2S in their quest of similar epidithiodiketopiperazines (**14**→**18**, Figure 2). In 2009, Movassaghi^{6e} and

Sodeoka^{6f} applied the use of 3,6-dihydroxydiketopiperazines (**15** and **16**, respectively, Figure 2) and H_2S to construct the epidithiodiketopiperazine structural motifs (**18**, Figure 2) of their synthetic targets, 11,11'-dideoxyverticillin A and chaetocin, respectively. In 2010, Kim and Movassaghi described the use of potassium trithiocarbonate (K_2CS_3) to generate an epidithiodiketopiperazine moiety from monosilylated 3,6-dihydroxydiketopiperazine intermediate (**17**→**18**, Figure 2) in their elegant synthesis of chaetocins A and C and 12,12'-dideoxychetracin A.^{6g}

Inspired by the U. Schmidt method²⁰ of introducing sulfur atoms into 2,5-diketopiperazines directly using S_8 and NaNH_2 in liq. NH_3 , we opted to employ S_8 and NaHMDS or LiHMDS as the base in THF. Our expectations included not only the convenience of carrying out the sulfenylation reaction in an organic solvent rather than liq. NH_3 , but also the possibility of generating more well-defined sulfenylating species to effect the desired reaction more efficiently and with stereocontrol. In retrospect, we realized that the reaction of S_8 with NaHMDS had already been studied by M. Schmidt^{24a-c} in the 1960s, a study^{24a} that we inadvertently missed in our preliminary communications.^{7,8} Our investigations with this reaction are summarized in Scheme 1. Thus, from the reaction of S_8 (**19**) and NaHMDS , we were able to isolate, chromatographically, and characterize three reactive species: tetrasulfide **21** [40% yield, ^1H NMR (CDCl_3 , 600 MHz): δ = 0.26 ppm; ^{13}C NMR (CDCl_3 , 150 MHz): δ = 2.4 ppm; HRMS $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{12}\text{H}_{36}\text{N}_2\text{O}_2\text{S}_4+\text{H}$: 449.0911; found: 449.0908], pentasulfide **22** [5% yield, HRMS $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{12}\text{H}_{36}\text{N}_2\text{O}_2\text{S}_5+\text{H}$: 512.0280; found: 512.0241], and trisulfide **23** [8% yield, HRMS $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{12}\text{H}_{36}\text{N}_2\text{O}_2\text{S}_3+\text{H}$: 417.1190; found: 417.1186]. Their formation, presumably through intermediate **20**, may be explained as shown in Scheme 1 and it is consistent with the observations of M. Schmidt *et al.*²⁴ The predominance of the tetrasulfide **21** is most likely due to steric shielding and charge repulsion during the second nucleophilic attack by the $(\text{TMS})_2\text{N}^-$ species on the sulfur chain (see **20**, Scheme 1). The reaction of the resulting mixture with 2,5-diketopiperazines as exemplified with substrate **24** in the presence of excess base (NaHMDS) as shown in Scheme 2 is consistent with the presence of these species, although only epidi- and epitetrasulfides were isolated. Reduction of the mixture (presumably containing additional sulfenylated species, such as epitri- and epipentasulfides as well as open-chain oligosulfides) with NaBH_4 followed by oxidation of the resulting dithiolate **26** (aq. NH_4Cl ; then KI_3) led to a good yield of the epidithiodiketopiperazine **27** (69%). The same result was obtained from the pure tetrasulfide **25** (obtained in 22% yield from **24**, see Scheme 2) upon reduction/oxidation (94%). Reaction of dithiolate **26** with MeI furnished bis-(methylthio)diketopiperazine **28** in 72% overall yield from **24**. In support of the proposed mechanism (Scheme 2), we found that only mono-deuteration occurs upon quenching the initially formed species from substrate **24** and NaHMDS (2.2 equiv). Also in support of the intramolecular nature of the second C-S bond formation are the good yields of the epidithio- and epitetrathiodiketopiperazine products observed.

Figure 2. Selected sulfonylation methods of 2,5-

diketopiperazines.

Scheme 1. Reaction of Sulfur (S₈) with NaHMDS [NaN(TMS)₂]^a

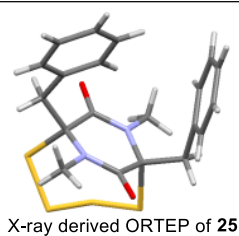
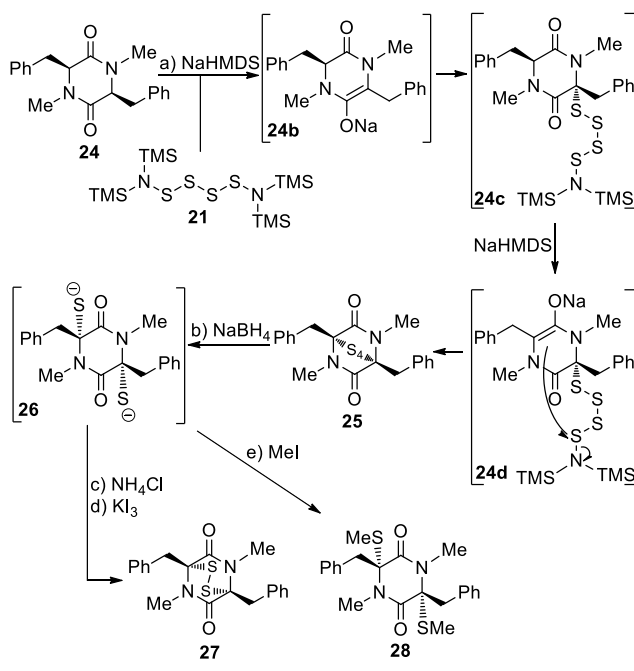
^aReagents and conditions. NaHMDS (0.6 M in PhMe, 3.0 equiv), S₈ (1.0 equiv), THF, 25 °C, 5 min, **21**: 40%, **22**: 5%, **23**: 8%.

The generality and scope of the sulfonylation reaction was explored with a variety of substrates. These explorations led to a series of epidithiodiketopiperazines (Table 1) and *bis*-(methylthio)diketopiperazines (Table 2). Thus, under the reaction conditions shown in Table 1, 3,6-unsubstituted diketopiperazines such as **29** (entry 1) reacted to form epidithiodiketopiperazines (i.e. **30**, entry 1), albeit in modest yield (40%), the latter observation being attributed to possible unhindered intermolecular reactions of the intermediate sulfur species. This speculation is supported by the higher yields observed with 3,6-mono- and 3,6-disubstituted substrates (e.g. entries 2–5). The relatively low yield of epidithiodiketopiperazine **38** (entry 6) is most likely due to the steric congestion at the sites of sulfonylation (i.e. positions 3 and 6). It is notable that both *syn* (entries 4, 8, 10–12) and *anti* (entries 3 and 9) 3,6-disubstituted diketopiperazine systems enter the reaction equally well. These include monocyclic (entries 3–7) and polycyclic (entries 8–12) systems. The fact that sulfonylation occurs from the same side of the molecule in both the *syn* and the *anti* series provides support for the intramolecular nature of the second C-S bond formation (see **24d**→**25**, Scheme 2). All epidithiodiketopiperazine products shown in Table 1 are racemic as a consequence of the enolate intermediacy in these reactions. Enantiopure compound **45** (entry 10) gave a mixture of enantiopure diastereoisomers (ca. 1.4:1 dr) due to the additional chiral centers within the structure.

Employment of the reaction conditions shown in Table 2 on the indicated substrates led to the corresponding *bis*-(methylthio)diketopiperazines. All products were isolated as single racemic *syn* compounds with the exception of **55** (entry 6), which was formed as a mixture of enantiopure diastereoisomers (ca. 1.4:1 dr) due to the additional stereocenters within the substrate. Again, the observation of only the *syn* product provides support for the intramolecularity of the second sulfonylation step. The excellent stereoselectivity and good yields obtained in this sulfonylation reaction and its epidithiodiketop-

iperazine-forming counterpart (see Table 1) demonstrate the superiority of this method in comparison to the traditional U. Schmidt process that often leads to mixtures of the *syn* and *anti* products in lower yields.

Scheme 2. Sulfenylation of 2,5-Diketopiperazines with [NaHMDS-S₈]. Preparation of Epitetrathiodiketopiperazine 25, Epidithiodiketopiperazine 27 and bis-(Methylthio)diketopiperazine 28^a



^aReagents and conditions. a) NaHMDS (0.6 M in PhMe, 3.0 equiv), S₈ (1.0 equiv), THF, 25 °C, 1 min; then 24 (1 M in THF, 1.0 equiv), 1 min; then NaHMDS (0.6 M in PhMe, 2.0 equiv), 25 °C, 30 min; b) NaBH₄ (25 equiv), THF/MeOH (1:1), 0→25 °C, 45 min; c) NH₄Cl aq. (1.0 M), 25 °C; d) KI₃ aq. (1.4 M), 25 °C, 10 min, 69% over the four steps from 24; e) MeI (50 equiv), 25 °C, 15 h, 72% over the three steps from 24.

$\begin{array}{c} \text{R}^1 \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{N}-\text{R}^4 \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{R}^2 \end{array} \quad \xrightarrow[\text{c) aq. KI}_3]{\text{a) [NaHMDS-S}_8\text{], THF} \\ \text{b) NaBH}_4\text{, THF/EtOH}} \quad \begin{array}{c} \text{R}^1 \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{N}-\text{R}^4 \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{R}^2 \end{array}$			
Entry	Substrate	Product ^b	Overall Yield [%] ^c
1			40
2			63
3			70
4			69
5			65
6			45
7			43
8			65
9			68
10			55 ^d
11			68
12			70

Table 1. Preparation of Epidithiodiketopiperazines^a

^aReactions were performed on 100 mg scale at 25 °C. ^bRacemic mixture unless otherwise stated. ^cYield of isolated products after chromatography. ^dca. 1.4:1 dr.

Entry	Substrate	Product ^b	Overall Yield [%] ^c
1			70
2			72
3			63
4			51
5			64
6			58 ^d
7			61
8			67

Table 2. Preparation of bis-(Methylthio)diketopiperazines^a

^aReactions were performed on 100 mg scale at 25 °C. ^bRacemic mixture unless otherwise stated. ^cYield of isolated products after chromatography. ^dca. 1.4:1 dr.

The effect of the alkali metal in the base on the efficiency of the reaction was then examined. Thus, KHMDS, NaHMDS and LiHMDS were used in the sulfenylation protocol shown in Table 1 using diketopiperazine substrates **24**, **41** and **2-epi-43** to generate epidithiodiketopiperazines **27**, **42** and **44**, respectively. As shown in Table 3, the results consistently point to NaHMDS as the preferred base for this reaction, although all three bases gave good yields of the epidithiodiketopiperazine

products. As we shall see below, however, this is not always the case, especially with more sensitive substrates (see Table 4).

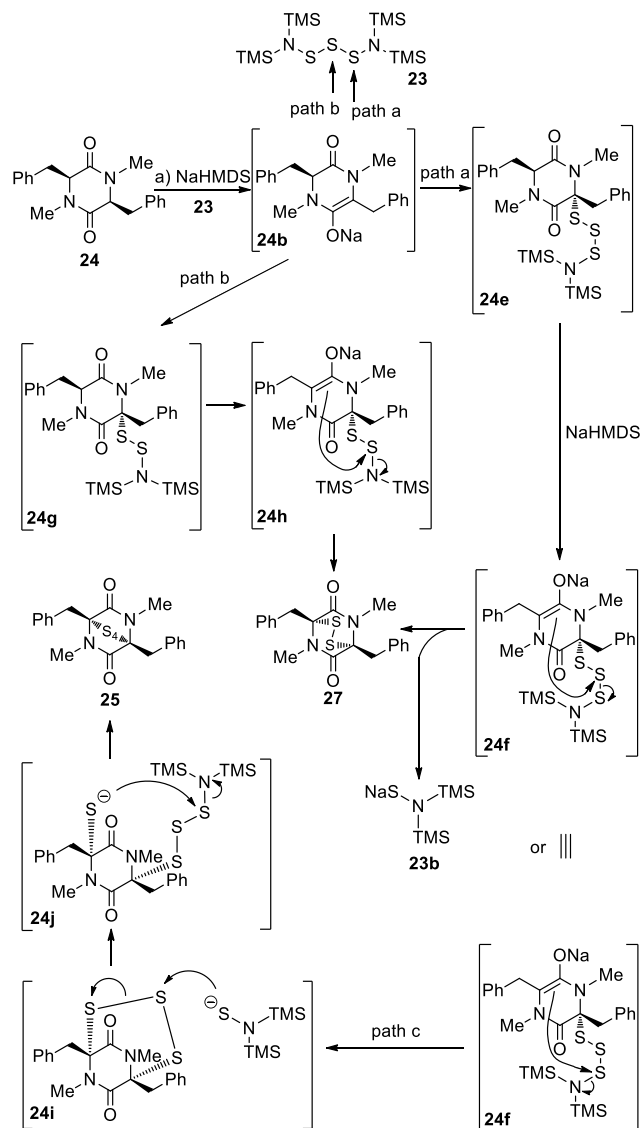
Table 3. Influence of the Base in the Sulfenylation of Selected Epidithiodiketopiperazines^a

Entry	Substrate	Product ^b	LiHMDS	NaHMDS	KHMDS
Yield [%] ^c					
1			45	69	50
2			50	65	53
3			53	69	43

^aReactions were performed on 50 mg scale at 25 °C. ^bRacemic mixtures were obtained. ^cYield of isolated products after chromatography.

Previously known^{24a} bis[bis(trimethylsilyl)amino]trisulfide (**23**, Scheme 3) was prepared and investigated for its suitability as a sulfenylation agent of 2,5-diketopiperazines in the presence of base. Thus, pure **23** reacted with diketopiperazine **24** in the presence of NaHMDS in THF at ambient temperature to produce a mixture of epidithiodiketopiperazine **27** (43%) and epitetrathiodiketopiperazine **25** (22%). A speculative mechanism for the formation of these products is shown in Scheme 3.²⁵ Thus, the initially formed enolate **24b** may react with trisulfide **23** through path a (attack at terminal S) to afford trisulfide intermediate **24e**, which may then suffer intramolecular attack by the second enolate (**24f**) to afford epidithiodiketopiperazine **27** and (TMS)₂NSNa (**23b**). The same product (**27**) could be formed from enolate **24b** and trisulfide **23** through path b (attack at the central S) via the intermediacy of species **24g** and **24h** by intramolecular attack as shown in the scheme. Alternatively, trisulfide intermediate **24f** may undergo different intramolecular collapse to generate, through path c, epitetrathiodiketopiperazine **24i**,²⁶ whose opening with (TMS)₂NS⁻ as shown may form epitetrathiodiketopiperazine **25** via intermediate species **24j**.

Scheme 3. Reaction of Diketopiperazine 24 with *bis*[*bis*(trimethylsilyl)amino]trisulfide [(TMS)₂SSS(TMS)₂] and NaHMDS and Mechanistic Considerations. Direct Formation of Epidithio- and Epitetraethiodiketopiperazines^a



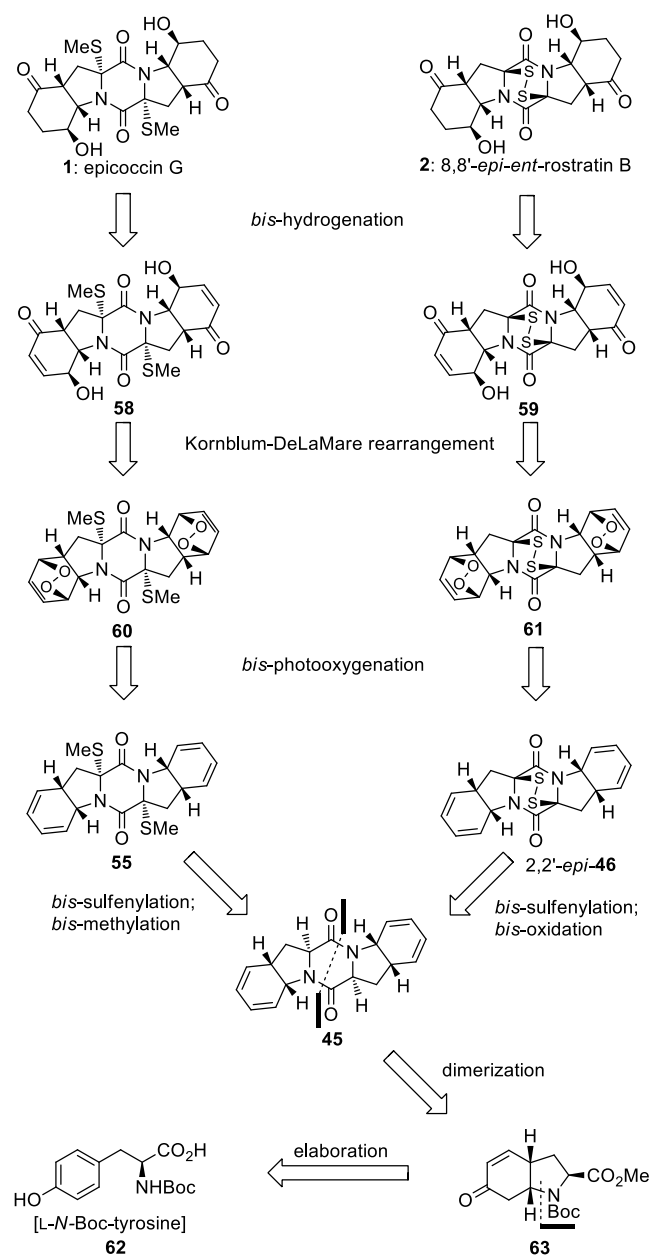
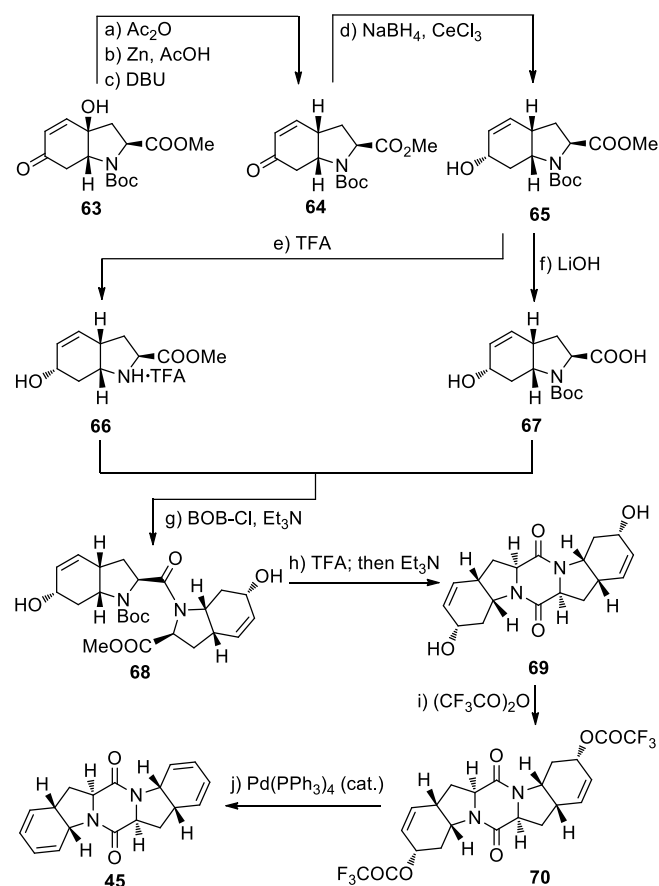
^aReagents and conditions. a) (TMS)₂NSSN(TMS)₂ (4.0 equiv), NaHMDS (0.6 M in PhMe, 4.0 equiv), THF, 25 °C, 30 min, **25**: 22%, **27**: 43%.

Total Syntheses of Epicoccin G (**1**), 8,8'-*epi-ent*-Rostratin B (**2**), Gliotoxin (**3**), Gliotoxin G (**4**), Emethallicin E (**5**) and Haematocin (**6**). Empowered with the improved sulfonylation method^{7,8} we were able to synthesize a number of biologically active sulfonylated diketopiperazine natural products⁸ (Figure 1), including the antiviral agent epicoccin G⁹ (**1**), the 8,8'-*epi-ent*-isomer (**2**) of the cytotoxic agent rostratin B,¹⁰ the antiviral and antibiotic gliotoxin¹¹ (**3**), and its epitetrathio counterpart gliotoxin G¹² (**4**), the immunosuppressant emethallicin E¹³ (**5**), and the antifungal agent haematocin¹⁴ (**6**). The designed synthetic strategies employed to construct these molecules are exemplified with those depicted for epicoccin G [**1**, a *bis*-(methylthio)diketopiperazine] and 8,8'-*epi-ent*-rostratin B (**2**, an epidithiodiketopiperazine), in retrosynthetic format, in

Scheme 4. Thus, epicoccin G (**1**) was disconnected retrosynthetically to its *bis*-unsaturated precursor **58** through a *bis*-hydrogenation step. The latter intermediate was then traced to *bis*-endoperoxide **60** through the rarely used Kornblum–DeLaMare rearrangement,²⁷ anticipating a regioselective rupture of the endoperoxide moieties under basic conditions. Steric control in the latter process was envisioned to furnish the desired regioisomer (**58**). Through a *bis*-photooxygenation/*bis*-sulfonylation sequence, *bis*-endoperoxide **60** was traced back to *bis*-diene diketopiperazine **45** through the intermediacy of *bis*-diene **55**. Similar retrosynthetic analysis of 8,8'-*epi-ent*-rostratin B (**2**) led to the same precursor (**45**) as shown in Scheme 4. The latter was envisioned to arise from L-*N*-Boc-tyrosine (**62**) via bicyclic intermediate **63**²⁸ (see Scheme 4) through appropriate elaboration and dimerization procedures.

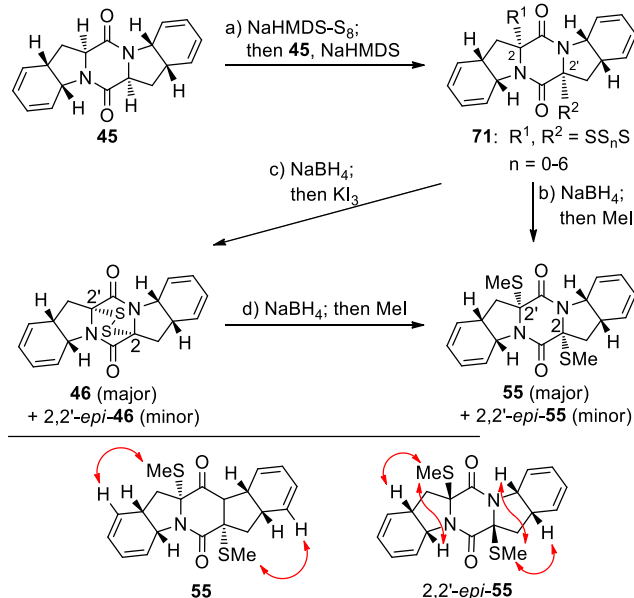
The synthesis of the *bis*-diene **45** from the known tyrosine-derived hydroxy enone **63**²⁸ is shown in Scheme 5. Thus, acetylation of **63** followed by treatment with Zn and AcOH in MeOH at 65 °C and exposure to DBU led to the deoxygenation product bicyclic enone **64** possessing the desired *syn* ring junction (51% yield for the three steps). Luche reduction²⁹ of the latter (NaBH₄, CeCl₃) gave allylic alcohol **65** (possessing the α configuration as expected on steric grounds; inconsequential) in 92% yield. In preparation for the pending cyclodimerization, key intermediate **65** was separately processed with LiOH and TFA to afford coupling partners **66** (99% yield, TFA salt) and **67** (99% yield), respectively. *N*-Boc carboxylic acid **67** and amine methyl ester TFA salt **66** were coupled in the presence of BOP-Cl and Et₃N to afford amide **68** in 86% yield. Treatment of the latter with TFA followed by exposure to Et₃N led to the formation of pentacyclic diketopiperazine **69** in 77% yield for the two steps. The desired *bis*-dehydration of *bis*-allylic alcohol **69** was achieved through the intermediacy of *bis*-allylic trifluoroacetate **70** formed by treatment of the former with (CF₃CO)₂O in the presence of Et₃N and 4-DMAP (69% yield). The latter intermediate (**70**) was smoothly converted to the targeted *bis*-diene **45** upon exposure to catalytic amounts of Pd(PPh₃)₄ in the presence of K₂CO₃ (90% yield).³⁰

The advancement of *bis*-diene **45** to the desired sulfonylated intermediates epidithiodiketopiperazine **46** and *bis*-(methylthio)diketopiperazine **55** and their diastereoisomers is summarized in Scheme 6. Thus, sulfonylation of **45** according to the developed procedure [NaHMDS-S₈] furnished a mixture of oligosulfides (**71**) from which emerged epidithiodiketopiperazines **46** and 2,2'-*epi*-**46** and *bis*-(methylthio)diketopiperazines **55** and 2,2'-*epi*-**55** upon reduction/oxidation (NaBH₄; KI₃; 55% combined yield for **46** and 2,2'-*epi*-**46**, ca. 1.4:1 dr) and reduction/methylation (NaBH₄; MeI; 58% overall yield for **55** and 2,2'-*epi*-**55**, ca. 1.4:1 dr). The stereochemical configurations of these chromatographically separated products were deciphered by NOESY correlations as indicated in Scheme 6 (bottom).

Scheme 4. Retrosynthetic Analysis of Epicoccin G (1) and 8,8'-*epi-ent*-Rostratin B (2)**Scheme 5. Synthesis of *bis*-Diene Diketopiperazine 45^a**

^aReagents and conditions. a) Ac₂O (2.0 equiv), Et₃N (3.0 equiv), 4-DMAP (0.2 equiv), CH₂Cl₂, 0→25 °C, 4 h; b) Zn (8.0 equiv), AcOH (2.0 equiv), MeOH, 65 °C, 30 min; c) DBU (5.0 equiv), PhMe, 65 °C, 3 h, 51% for the three steps; d) NaBH₄ (1.1 equiv), CeCl₃·7H₂O (1.0 equiv), MeOH, -78→0 °C, 1 h, 92%; e) TFA/CH₂Cl₂ (1:1), 0→25 °C, 30 min, 99%; f) aq. LiOH (1.0 M)/THF (4:1), 0→25 °C, 3 h, 99%; g) **66**, **67** (1.0 equiv each), BOP-Cl (1.1 equiv), Et₃N (3.0 equiv), CH₂Cl₂, 0→25 °C, 15 h, 86%; h) TFA (32 equiv), CH₂Cl₂, 0→25 °C, 1.5 h; then Et₃N (5.0 equiv), CH₂Cl₂, 0→25 °C, 15 h, 77% for the two steps; i) (CF₃CO)₂O (4.0 equiv), Et₃N (6.0 equiv), 4-DMAP (0.3 equiv), MeCN, -40→25 °C, 1 h, 69%; j) Pd(PPh₃)₄ (0.1 equiv), K₂CO₃ (2.1 equiv), dioxane, 65 °C, 30 min, 90%.

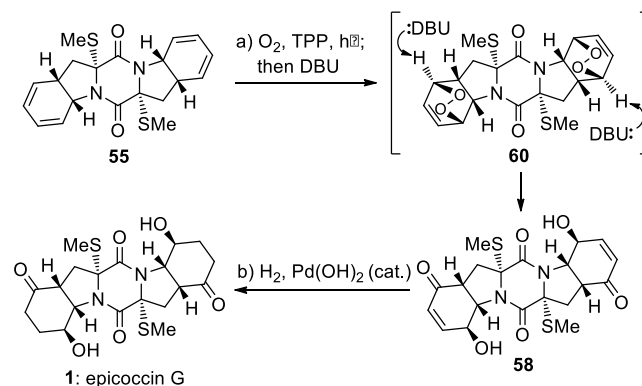
Scheme 6. Synthesis of Dithiodiketopiperazines **46 and **2,2'-epi-46**, and *bis*-(Methylthio)diketopiperazines **55** and **2,2'-epi-55**^a and Stereochemical Assignments of **55** and **2,2'-epi-55** by NOESY Studies (Arrows Designate NOESY Correlations)**



^aReagents and conditions. a) NaHMDS (0.6 M in PhMe, 3.0 equiv), S₈ (1.0 equiv), THF, 25 °C, 1 min; then **45** (1 M in THF, 1.0 equiv), 1 min; then NaHMDS (0.6 M in PhMe, 2.0 equiv), 25 °C, 30 min; b) NaBH₄ (25 equiv), THF/MeOH (1:1), 0→25 °C, 45 min; then MeI (50 equiv), 25 °C, 15 h, 58% over the three steps from **45** (**55**:**2,2'-epi-55** ca. 1.4:1 dr); c) NaBH₄ (25 equiv), THF/MeOH (1:1), 0→25 °C, 0.75 h; then KI₃ aq. (1.4 M), 25 °C, 10 min, 55% over the three steps from **45** (**46**:**2,2'-epi-46** ca. 1.4:1 dr); d) NaBH₄ (25 equiv), THF/MeOH (1:1), 0→25 °C, 45 min; then MeI (50 equiv), 25 °C, 15 h, 65% from **46** (**55**:**2,2'-epi-55** ca. 1.4:1 dr).

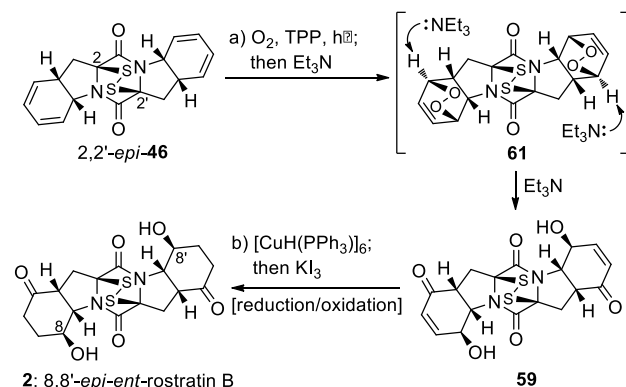
The correct diastereoisomers **55** and **2,2'-epi-46** were elaborated to the target molecules epicoccin G (**1**) and 8,8'-*epi-ent*-rostratin B (**2**) through similar pathways as shown in Schemes 7 and 8, respectively. Thus, reaction of *bis*-(methylthio)diketopiperazine *bis*-diene with singlet oxygen (generated from triplet oxygen and UV light in the presence of tetraphenylporphyrin sensitizer)³¹ in CH₂Cl₂ at -45 °C furnished *bis*-endoperoxide **60**, which was treated with DBU (-45→0 °C) without isolation to afford *bis*-hydroxy enone **58** as the major product (52% overall yield, Scheme 7). The latter compound was subjected to catalytic hydrogenation [H₂, 20% Pd(OH)₂/C] to give smoothly epicoccin G in 86% yield. Processing epidithio *bis*-diene **2,2'-epi-46** with singlet oxygen (0 °C) followed by treatment of the resulting *bis*-endoperoxide (**61**) with Et₃N (0→25 °C) furnished epidithio *bis*-hydroxy enone **59** in 55% overall yield (Scheme 8). The sensitivity of the epidithiodiketopiperazine structural motif within **59** dictated the use of Stryker's reagent³² [CuH(PPh₃)₆] (as opposed to the hydrogenation conditions employed for the conversion of **58** to epicoccin G, Scheme 7) for the required reduction of the olefinic bonds, followed by re-oxidation with KI₃ to regenerate the partially cleaved epidithio moiety, thereby furnishing 8,8'-*epi-ent*-rostratin B (**2**) in 82% overall yield.

Scheme 7. Completion of the Total Synthesis of Epicoccin G (1**)^a**



^aReagents and conditions. a) O₂, TPP (0.02 equiv), CH₂Cl₂, -45 °C, 45 min; then DBU (10.0 equiv), -45→0 °C, 1 h, 52% from **55**; b) H₂, Pd(OH)₂/C (20% w/w, 0.4 equiv), MeOH, 25 °C, 1 h, 86%.

Scheme 8. Completion of the Total Synthesis of 8,8'-*epi-ent*-Rostratin B (2**)^a**

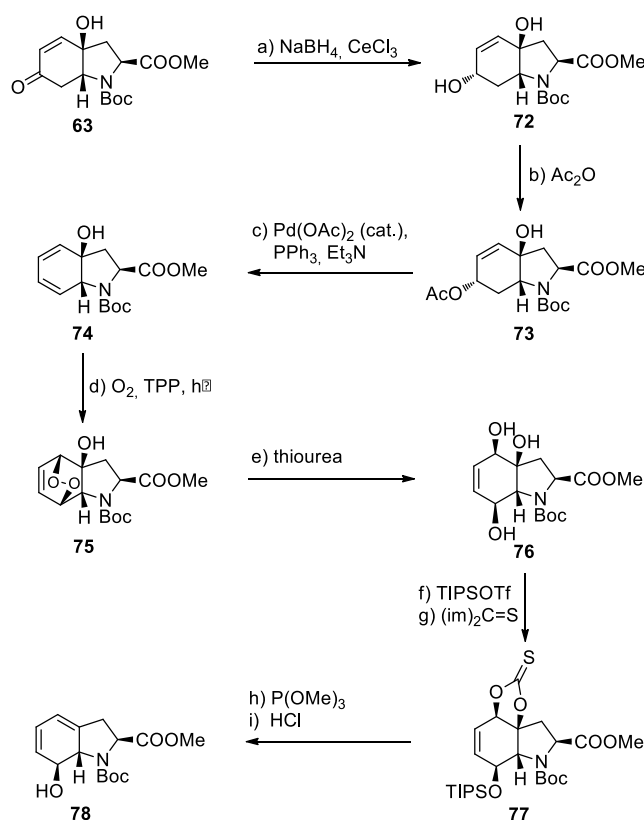


^aReagents and conditions. a) O₂, TPP (0.02 equiv), CH₂Cl₂, 0 °C, 2 h; then Et₃N (5.0 equiv), 0→25 °C, 3 h, 55% for the two steps; b) [CuH(PPh₃)₆] (10.0 equiv), benzene, 25 °C, 30 min; then KI₃ aq. (1.4 M), 25 °C, 10 min, 82%.

As further demonstrations of the applicability of the present improved sulfenylation method, we pursued the enantioselective total synthesis of gliotoxin (**3**) and gliotoxin G (**4**), as well as emethallicin E (**5**) and haematocin (**6**) (Figure 1). The devised synthetic strategy toward these target molecules envisioned bicyclic hydroxy diene **78** (see Scheme 9) as a common intermediate. This key building block was obtained in multi-gram quantities from the tyrosin-derived hydroxy enone *N*-Boc methyl ester **63** as shown in Scheme 9.³³ Thus, Luche reduction (NaBH₄, CeCl₃) of **63**²⁸ gave diol **72** stereoselectively (99% yield), which was smoothly acetylated to afford hydroxy acetate **73** in 91% yield. The latter was converted to hydroxy diene **74** through palladium-catalyzed elimination [Pd(OAc)₂ (cat.), PPh₃ (cat.), Et₃N, 86%]. Photooxygenation of this diene (O₂, TPP, hν, 73%) generated hydroxy endoperoxide **75**, whose reduction with thiourea afforded triol **76** in 84% yield. Selective monosilylation of the latter (TIPSOTf, 96% yield) followed by engagement of the 1,2-diol system into a thionocarbonate moiety [(im)₂C=S, 90% yield] fur-

nished intermediate **77**. The latter was deoxygenated [$\text{P}(\text{OMe})_3$, 82% yield] and desilylated (aq. HCl , 98% yield) to afford the desired building block hydroxy diene **78**.

Scheme 9. Synthesis of Common Key Building Block **78**^a



^aReagents and conditions. a) NaBH_4 (2.0 equiv), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.3 equiv), MeOH , $-20 \rightarrow 0^\circ\text{C}$, 3 h, 99%; b) Ac_2O (2.0 equiv), Et_3N (3.0 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2 , 0°C , 1 h, 91%; c) $\text{Pd}(\text{OAc})_2$ (0.02 equiv), PPh_3 (0.1 equiv), Et_3N (1.2 equiv), PhMe , $25 \rightarrow 110^\circ\text{C}$, 3 h, 86%; d) O_2 , TPP (0.0036 equiv), CH_2Cl_2 , 25°C , 24 h, 73%; e) thiourea (2.0 equiv), MeOH , 25°C , 2 h, 84%; f) TIPSO Tf (1.1 equiv), Et_3N (2.0 equiv), CH_2Cl_2 , 0°C , 30 min, 96%; g) $(\text{im})_2\text{C}=\text{S}$ (1.2 equiv), PhMe , 110°C , 3 h, 90%; h) $\text{P}(\text{OMe})_3$, 111°C , 12 h, 82%; i) HCl aq. (1.0 M), $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (1:1), 0°C , 10 min, 98%.

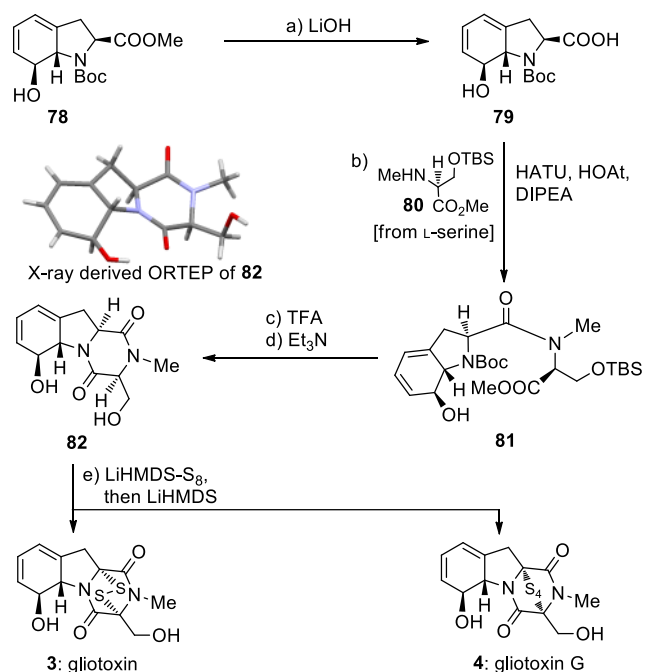
The enantioselective total synthesis of gliotoxin (**3**) and gliotoxin G (**4**) from the common building block **78** is summarized in Scheme 10. Thus, hydrolysis of the methyl ester within **78** (LiOH) led to carboxylic acid **79** (99% yield), which was coupled with L-serine derivative **80**³⁴ (HATU, HOAt, DIPEA) to afford amide **81** in 88% yield. Removal of the Boc group from the latter and exposure of the resulting amino ester to Et_3N furnished tricyclic diketopiperazine **82** (63% overall yield), whose structure was proven beyond doubt through X-ray crystallographic analysis (see ORTEP, Scheme 10). Sulfenylation of the latter required the use of S_8 and LiHMDS , conditions that furnished directly gliotoxin (**3**, 23% yield) and gliotoxin G (**4**, 33% yield) (plus 6% recovered starting material **82**). Interestingly, attempts to effect the sulfenylation of **82** with $[\text{NaHMDS}-\text{S}_8]$ failed to produce gliotoxin or gliotoxin G, leading instead to aromatization of the cyclohexadiene ring and decomposition. These results underscore the subtle differences in reactivity of the various alkali metal HMDS bases and point to the importance of thorough experimentation in at-

tempting to achieve certain transformations, including the present sulfenylation.

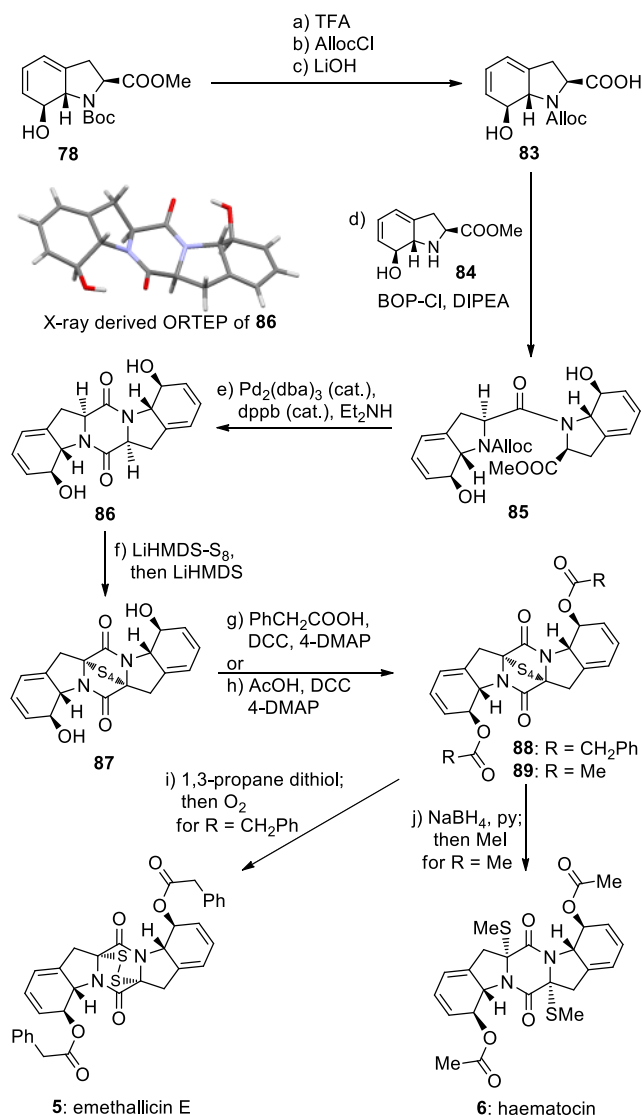
Scheme 11 summarizes the enantioselective total syntheses of emethallicin E (**5**) and haematocin (**6**) from common intermediate **78**. Thus, a three-step sequence involving replacement of the Boc protective group with Alloc (TFA, 95% yield; then AllocCl , 88% yield) followed by saponification of the methyl ester group (LiOH) furnished hydroxy carboxylic acid **83** in high yield. Coupling of building blocks **83** and **84** (obtained in the first step of the above sequence **78** \rightarrow **83**) under the influence of BOP-Cl and DIPEA led to amide **85** in 83% yield over the two steps. Pentacyclic *bis*-hydroxy diketopiperazine **86** was generated from amide **85** in 84% overall yield upon cleavage of the Alloc protecting group [$\text{Pd}_2(\text{dba})_3$ (cat.)] in the presence of Et_2NH . The structure of intermediate **86** was unambiguously confirmed by X-ray crystallographic analysis (see ORTEP, Scheme 11). Sulfenylation of *bis*-hydroxy diketopiperazine **86** with $[\text{LiHMDS}-\text{S}_8]$ led to tetrasulfide **87** as the major product (46% yield, plus 43% recovered starting material **86**).

As in the case of the gliotoxins discussed above (Scheme 10), the standard $[\text{NaHMDS}-\text{S}_8]$ conditions failed to produce the sulfenylated product from substrate **86** in satisfactory yield, leading only to 10% yield of epitetrasulfide **87** (Scheme 11). This observation prompted a systematic investigation to optimize the yield of this sulfenylation reaction varying the HMDS base and the solvent. The results of this study, shown in Table 4, revealed LiHMDS in THF as the optimum conditions (entry 5/ LiHMDS). The formation of the epitetrasulfide as the predominant product in this case is also of interest. This example underscores once again the importance of careful optimization of conditions to achieve the best results in diketopiperazine sulfenylation reactions. It is also noteworthy that the use of *bis*[*bis*(trimethylsilyl)amino]trisulfide (**23**, Scheme 3) as a sulfenylating reagent in the presence of LiHMDS as a base proved less reactive than the corresponding *in situ* generated species $[\text{LiHMDS}-\text{S}_8]$, leading to recovery of 80% of starting material (**86**) and no epidisulfide or epitetrasulfide products. The use of NaHMDS or KHMDS and trisulfide **23** led primarily to aromatization under the same sulfenylation conditions.

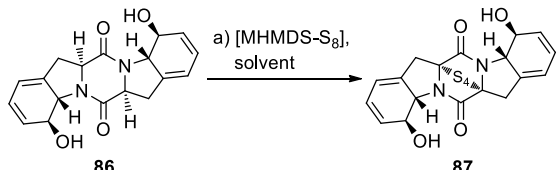
The stereochemical configuration of the epitetrasulfide **87** was based on NMR spectroscopic studies and was confirmed by the successful synthesis of the natural products **5** and **6**. Indeed, intermediate **87** served as a common precursor to emethallicin E (**5**) and haematocin (**6**) as shown in Scheme 11. Thus, *bis*-esterification of **87** with phenylacetic acid (PhCH_2COOH) in the presence of DCC and 4-DMAP gave *bis*-phenylacetate **88** (71% yield, plus 26% recovered starting material **87**), whose reduction/oxidation (1,3-propane dithiol; then O_2) furnished the desired product emethallicin E (**5**) in 54% overall yield. Alternatively, *bis*-acetylation of **87** (AcOH , DCC, 4-DMAP, 71% yield, plus 24% recovered starting material **87**) followed by reduction/methylation (NaBH_4 ; then MeI) of the resulting *bis*-acetate afforded haematocin (**6**) in 97% overall yield. The use of the DCC/4-DMAP esterification protocol instead of the more conventional acid anhydride or chloride methods was dictated by the sensitivity of the substrate (**87**) and products (**88**, **89**) under the reaction conditions, especially toward aromatization.

Scheme 10. Completion of the Enantioselective Total Syntheses of Gliotoxin (3) and Gliotoxin G (4)^a

^aReagents and conditions. a) aq. LiOH (1.0 M)/THF (6:1), 0→25 °C, 5 h, 99%; b) 79 (1.0 equiv), 80 (2.0 equiv), HOAt (1.1 equiv), HATU (1.1 equiv), DIPEA (3.0 equiv), CH₂Cl₂, 0→25 °C, 15 h, 88%; c) TFA/CH₂Cl₂ (1:1), 0→25 °C, 3 h; d) Et₃N (5.0 equiv), CH₂Cl₂, 0→25 °C, 15 h, 63% for the two steps; e) LiHMDS (1.0 M in THF, 4.0 equiv), S₈ (8.0 equiv), THF, 25 °C, 5 min; then 82 (0.06 M in THF, 1.0 equiv) 5 min; then LiHMDS (1.0 M in THF, 4.0 equiv), 25 °C, 1.5 h, 3: 23%, 4: 33%, plus 6% recovered starting material 82.

Scheme 11. Completion of the Enantioselective Total Syntheses of Emethallicin E (5) and Haematocin (6)^a

^aReagents and conditions. a) TFA/CH₂Cl₂ (1:2.5), 25 °C, 4 h, 95%; b) AllocCl (1.7 equiv), NaHCO₃ (10.0 equiv), dioxane/H₂O (1:1), 0→25 °C, 3 h, 88%; c) LiOH aq. (1.0 M)/THF (1:1), 0→25 °C, 5 h; d) 83, 84 (1.0 equiv each), BOP-Cl (1.1 equiv), DIPEA (3.0 equiv), CH₂Cl₂, 0→25 °C, 15 h, 83% for the two steps; e) Pd₂(dba)₃ (0.02 equiv), dbpp (0.05 equiv), THF/Et₂NH (2:1), 25 °C, 2 h, 84%; f) LiHMDS (1.0 M in THF, 20 equiv), S₈ (37 equiv), THF, 25 °C, 5 min; then 86 (0.06 M in THF/Et₂O (9:1), 1.0 equiv), 5 min; then LiHMDS (1.0 M in THF, 20 equiv), 25 °C, 5 h, 46%, plus 43% recovered starting material 86; g) PhCH₂COOH (30 equiv), DCC (30 equiv), 4-DMAP (3.0 equiv), 0→25 °C, 15 h, 71%, plus 26% recovered starting material 87; h) AcOH (30 equiv), DCC (30 equiv), 4-DMAP (3.0 equiv), 0→25 °C, 15 h, 71%, plus 24% recovered starting material 87; i) 1,3-propane dithiol (90 equiv), Et₃N (0.32 equiv), MeCN/CH₂Cl₂ (25:1), 25 °C; then concentrate; then O₂, MeOH, 2 h, 25 °C, 54% overall; j) NaBH₄ (80 equiv), MeOH/py (1:1), 0 °C; then MeI (485 equiv) 0→25 °C, 4 h; 97% overall.

Table 4. Optimization Study of the Sulfenylation of Diketopiperazine **86^a**


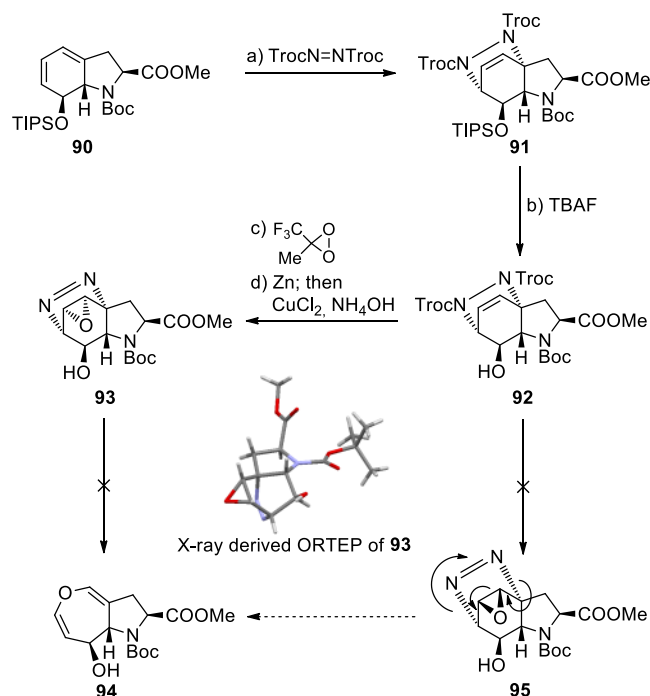
Entry	Solvent	LiHMDS	NaHMDS	KHMDS
Yield of 87 (%) [rsm] ^b				
1	THF	20 [70]	10 [40]	<5 [35]
2	CH ₂ Cl ₂	<5 [<5]	<5 [<5]	<5 [<5]
3	PhMe	15 [70]	<5 [45]	<5 [30]
4	Et ₂ O	25 [60]	15 [35]	<5 [35]
5	THF ^c	46 [43]	28 [30]	<5 [40]

^aReactions were performed on 5 mg scale at 25 °C. ^bYields of product and recovered starting material (rsm) are isolated yields after chromatography, <5% yield refers to no detectable product or starting material as determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. ^cReverse addition of preformed sulfenylation reagent to substrate and base.

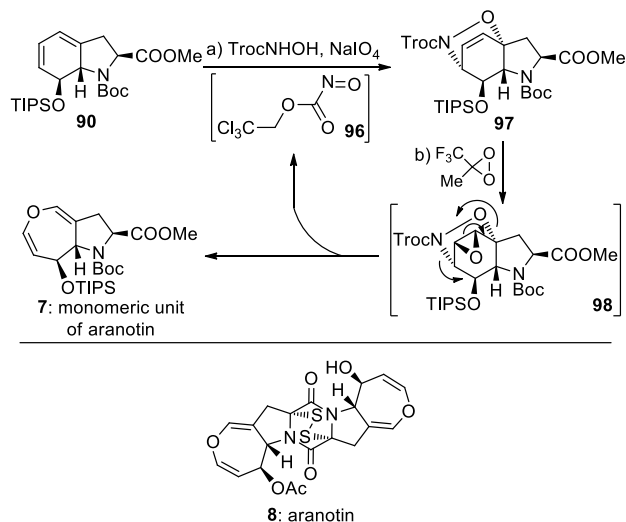
As part of a program directed toward the total synthesis of aranotin (**8**) we attempted to construct its monomeric unit (**7**, see Scheme 13) through diazo epoxide precursor **95** as shown in Scheme 12.³⁵ Thus, bicyclic diene system **90** (for its synthesis see Scheme 9, **77**→**78**, step h) was reacted with bis-trichloroethylazodicarboxylate (TrocN=NTroc) to afford Diels–Alder adduct **91** stereoselectively (steric control) and in 93% yield. Desilylation of the latter with TBAF gave hydroxy derivative **92** (92% yield), whose treatment with methyl(trifluoromethyl) dioxirane followed by sequential exposure to Zn and CuCl₂ in the presence of NH₄OH afforded diazo epoxide **93** as a single diastereoisomer (76% overall yield). The stereochemical configuration of **93** was established through X-ray crystallographic analysis (see ORTEP, Scheme 12). As expected, this epoxide did not enter the obligatory rearrangement with loss of N₂ by virtue of the *syn* arrangement of the diazo and epoxide moieties that does not allow for the proper orbital orientations.^{35a}

Our inability to reach the *anti* diazo epoxide **95** (Scheme 12), whose rearrangement to oxepin **94** was anticipated to be facile, prompted us to pursue the alternative pathway (Scheme 13) involving trichloroethyl nitrosoformate compound **96** (generated from TrocNHOH and NaIO₄) as the dienophile. The latter reacted with bicyclic diene **90** to give Diels–Alder adduct **97** (88% yield) diastereo- and regioselectively (presumably due to steric control).³⁶ The structure of **97** was assigned based on NMR spectroscopic analysis (COSY, NOESY, HMBC, HSQC). This intermediate was epoxidized with methyl(trifluoromethyl) dioxirane to afford directly oxepin system **7** (40% yield), presumably *via* the fleeting epoxide **98** through a retro-Diels–Alder/epoxide opening. Epoxide **98** apparently must be of the *anti* configuration with respect to the N–O bridge, which allows for the facile rearrange-

ment/extrusion of **96** (which undergoes disproportionation with expulsion of oxygen to form TrocN=N(Troc)).³⁶

Scheme 12. Attempted Synthesis of Oxepin **7 by Ring Expansion of a Diazo Epoxide^a**

^aReagents and conditions. a) TrocN=NTroc (1.2 equiv), CH₂Cl₂, 41 °C, 4 h, 93%; b) TBAF (1.0 M in THF, 2.0 equiv), THF, 0 °C, 30 min, 92%; c) 1,1,1-trifluoro acetone (62 equiv), Na₂EDTA, NaHCO₃ aq. (15 equiv), oxone[®] (38 equiv), MeCN, 0→25 °C, 15 h; d) Zn (21 equiv), MeOH/ NH₄Cl aq. (1.0 M) (4:1), 25 °C, 2 h; then NH₄OH aq. (15 M), CuCl₂ aq. (1.0 M), 25 °C, 5 min, 76% for the two steps.

Scheme 13. Synthesis of Oxepin (7**) by Ring Expansion of Nitroso Epoxide **98**^a**

^aReagents and conditions. a) TrocNHOH (2.5 equiv), NaIO₄ (1.0 equiv), TBAI (1.0 equiv), CH₂Cl₂/H₂O (4:1), 0→25 °C, 10 min, 88%; b) 1,1,1-trifluoro acetone (7.0 equiv), Na₂EDTA, Na-

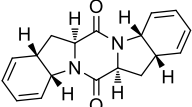
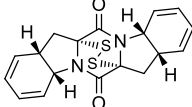
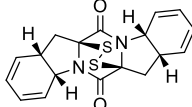
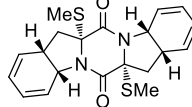
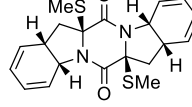
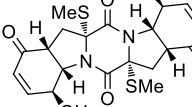
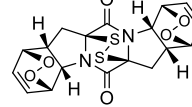
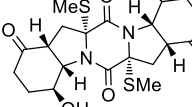
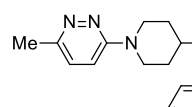
HCO₃ aq. (60 equiv), oxone^(R) (20 equiv), MeCN/H₂O (1:1), 0 °C, 15 h, 40%.

Biological Evaluation. Having synthesized various types of epidithio- and bis-(methylthio)diketopiperazines we selected a number of them for biological evaluation. Specifically, selected compounds were tested against poliovirus and *Plasmodium falciparum*.³⁷ Table 5 summarizes the results of these biological assays. Thus, in the anti poliovirus assays (carried out in the laboratory of D. F. S. under the auspices of the National Institute of Allergy and Infectious Diseases, NIAID), epidithiodiketopiperazines **46** (code number KCN-19), 2,2'-*epi*-**46** (code number KCN-2,2'-*epi*-19) and epidithio-bis-endoperoxide-diketopiperazine **61** (code number KCN-21) proved to be the most potent, exhibiting EC₅₀ = 101–115 nM, 107–123 nM, and EC₅₀ = 21.4 nM values, respectively, depending on the assay (see Table 5, entries 2, 3 and 7). Table 5 also displays selectivity indices (SI = CC₅₀/EC₅₀ or EC₉₀, with CC₅₀ = 50% cell-inhibitory, cytotoxic concentration determined in stationary cells and EC_{50/90} = 50%/90% poliovirus-

inhibitory, effective concentration) for some of these compounds. Compounds **46** (SI = 41–70), 2,2'-*epi*-**46** (SI = 27–75) and **61** (SI = 23–59) were the most impressive in this regard (see Table 5). The anti poliovirus drug Pirodavir^(R) (**99**, Table 5, entry 9), used as a control in this poliovirus assay, exhibited EC₅₀ = 1.58 μM, underscoring the significant activities of KCN-19 (**46**), KCN-2,2'-*epi*-19 (2,2'-*epi*-**46**), and KCN-21 (**61**).

In the anti *Plasmodium falciparum* assays (carried out in the laboratories of E. A. W. at TSRI), epidithiodiketopiperazines **46** (IC₅₀ = 3.6 μM, Table 5, entry 2), 2,2'-*epi*-**46** (IC₅₀ = 2.7 μM, entry 3), **59** (IC₅₀ = 4.5 μM; not included in the table, for structure see Scheme 4), **61** (IC₅₀ = 2.5 μM, entry 7), and bis-(methylthio)diketopiperazines **58** (IC₅₀ = 1.2 μM, entry 6), 2,2'-*epi*-**58** (IC₅₀ = 4.4 μM; not included in the table, for structure see Scheme 4), and epicoccin G (**1**, IC₅₀ = 2.5 μM) proved to be the most potent.

Table 5. Biological Evaluation of Selected Compounds in Poliovirus and *Plasmodium falciparum* Assays^a

Entry	Structure	Code Number	Poliovirus EC ₅₀ [visual; ^b neutral red ^c]	Poliovirus EC ₉₀ [virus yield ^d]	Selectivity Index (Poliovirus) [visual; ^b neutral red; ^c virus yield ^d]	<i>Plasmodium falciparum</i> IC ₅₀
1	 45	KCN-7	>50 μM; ^b n.d. ^{c,e}	n.d. ^{d,e}	n.d. ^e	>50 μM
2	 46	KCN-19	101 ± 59 nM; ^b 115 ± 59 nM ^c	149 ± 65 nM ^d	70 ± 48; ^b 56 ± 45; ^c 41 ± 23 ^d	3.6 μM
3	 2,2'-epi-46	KCN-2,2'-epi-19	107 ± 73 nM; ^b 123 ± 90 nM ^c	177 ± 45 nM ^d	59 ± 59; ^b 75 ± 92; ^c 27 ± 11 ^d	2.7 μM
4	 55	KCN-18	14.5 μM; ^b 25.6 μM ^c	n.d. ^{d,e}	5.7; ^b 3.4; ^c n.d. ^{d,e}	>50 μM
5	 2,2'-epi-55	KCN-2,2'-epi-18	56.9 μM; ^b >50 μM ^c	n.d. ^{d,e}	1.5; ^b n.d.; ^{c,e} n.d. ^{d,e}	>50 μM
6	 58	KCN-20	>50 μM; ^b n.d. ^{c,e}	n.d. ^{d,e}	n.d. ^e	1.2 μM
7	 61	KCN-21	21.4 ± 11.9 nM; ^b 21.4 ± 2.4 nM ^c	38.1 ± 7.1 nM ^d	59 ± 33; ^b 41 ± 17; ^c 23 ± 8 ^d	2.5 μM
8	 1: epicoccin G	KCN-1	>50 μM; ^b n.d. ^{c,e}	n.d. ^{d,e}	n.d. ^e	2.5 μM
9	 99: Pirodavis[®] f	—	n.d.; ^{b,e} 1.58 μM ^c	1.55 μM ^d	>18 ^c	n.d. ^e

^aAssays for entries 2, 3 and 7 were carried out as triplicates; mean and standard deviation are given. For experimental details of all assays, see Supporting Information. ^bVisual assay. ^cNeutral red assay. ^dVirus yield reduction assay. ^eNot determined. ^fStandard anti poliovirus drug used as a control.

CONCLUSION

An improved method for the sulfonylation of 2,5-diketopiperazines based on the use of alkali metal hexamethyldisilazide bases (i.e. NaHMDS, LiHMDS and KHMDS) and sulfur (S_8) in THF at 25 °C as a means to prepare epidithio-, epitetrahydro- and bis-(methylthio)diketopiperazines has been developed. A second method involving the use of bis[bis(trimethylsilyl)amino]trisulfide $[(TMS)_2NSSN(TMS)_2]$ and NaHMDS for the direct preparation of epidithio- and epitetrahydrodiketopiperazines has also been developed.

Application of these methods led to the synthesis of an array of sulfonylated diketopiperazine systems, including the natural products epicocin G (**1**), gliotoxin (**3**), gliotoxin G (**4**), emethallicin E (**5**), haematocin (**6**) and the 8,8'-*epi-ent*-isomer (**2**) of rostratin B. With the exception of gliotoxin (**3**),^{6h} these accomplishments represent the first enantioselective total syntheses of these natural products and their analogs and feature a number of novel synthetic strategies and reactions, including the [2+2] photooxygenation and the rarely used Kornblum–DeLaMare rearrangement.

Biological investigations of selected members of the synthesized compound libraries led to the discovery of a number of potent anti poliovirus agents (i.e. **46**, 2,2'-*epi*-**46** and **61**) and a series of anti *Plasmodium falciparum* lead compounds (i.e. **46**, 2,2'-*epi*-**46**, **58**, **61** and **1**) that may facilitate biological investigations and drug discovery efforts in the antiviral and antimalarial areas, respectively.

By blending total synthesis of natural products of biological and medical interest with method development endeavors and chemical biology studies, the work described herein exemplifies the modern paradigm of natural product synthesis and underscores its relevance and importance to chemistry, biology and medicine.

ASSOCIATED CONTENT

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

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