2012. 11. 22 Hiroki Sato

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 Dicscovery of New Antiviral and Antimalarial Agents

K. C. Nicolaou,* Min Lu, Sotirios Totokotsopoulos, Philipp Heretsch, Denis Giguere, Ya-Ping Sun, David Sarlah, Thu H. Nguyen, Ian C. Wolf, Donald F. Smee, Craig W. Day, Selina Bopp, and Elizabeth A. Winzeler

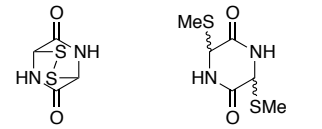
J. Am. Chem. Soc. **2012**, *134*, 17320–17332

1. Introduction

1.1. Sulfur containing derivatives of 2,5-diketopiperazines (Figure 1).

• Epidithio-diketopiperazine (**1**) and bis-(methylthio)diketopiperazines (**2**) show good biological activity: antiviral, antibacterial, antiallergic, antimalarial, and cytotoxic properties.

• They remain largely unexplored due to their natural scarcity and the synthetic laboratory challenge they pose: S–S bridge is sensitive to the reductive, basic, and strongly acidic condition.



1: Epidithio-diketopiperazine

2: bis-(methylthio) diketopiperazines

Figure 1.

1.2. Previous Work (Figure 2) and its Problems

Synthesis of epidithio-diketopiperazine (**1**)

• narrow variety of the products and low yield (a, c).

• many steps and overreaction (b).

Synthesis of bis-(methylthio)diketopiperazines (**2**)

• poor stereocontrol (d).

1.3. This Work

• Improved method for the sulfenylation reaction

- Use of mixture of bis[bis(trimethylsilyl)amino] sulfide [$(TMS)_2N(S)_nN(TMS)_2$] prepared from S element with NaHMDS *in situ*) as sulfenylating species
- Broader substrate scope.
- Desired products were obtained with perfect stereocontrol.
- Product are obtained in high yield (~70%).

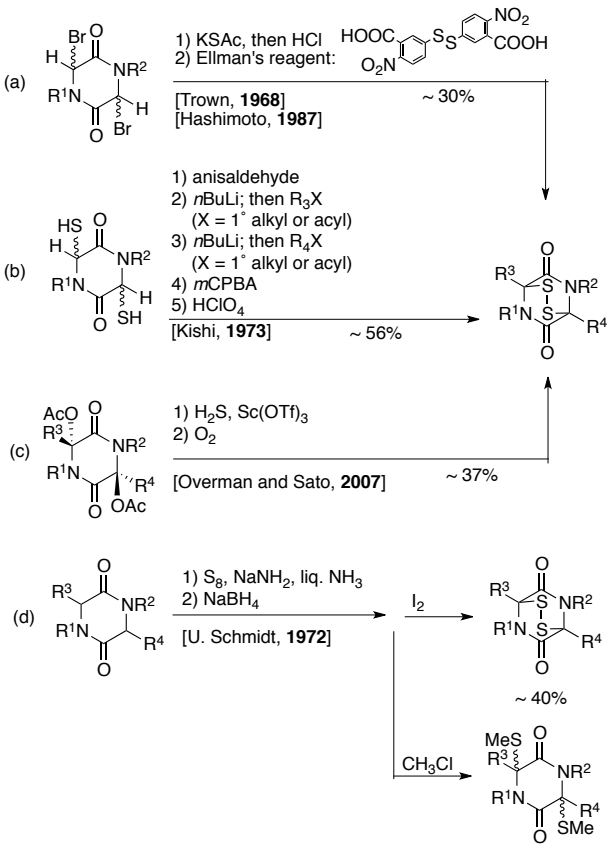


Figure 2. Selected sulfenylation methods of 2,5-diketopiperazines

• Total synthesis of several interesting natural products (Figure 3).

• Biological evaluation of the synthesized compounds and discovery of potent antipoliovirus and anti *Plasmodium falciparum* （マラリヤ原虫，悪性疟原虫）componds.

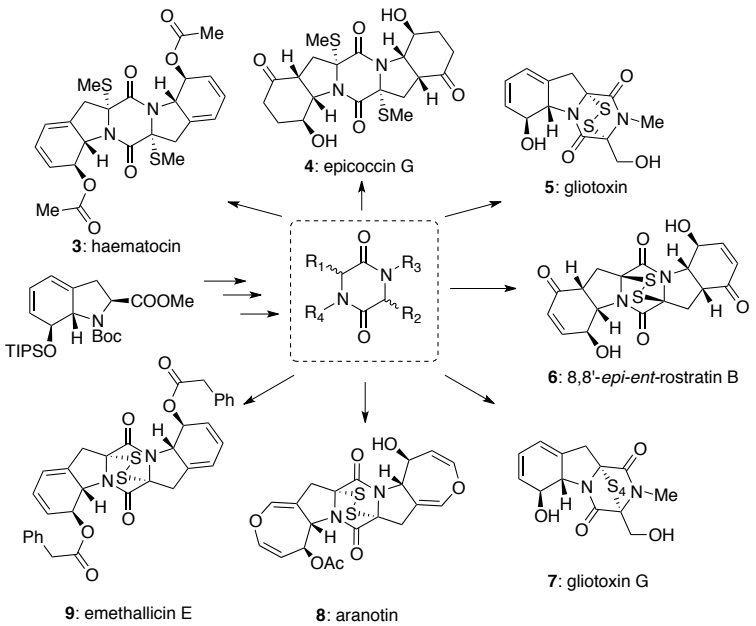
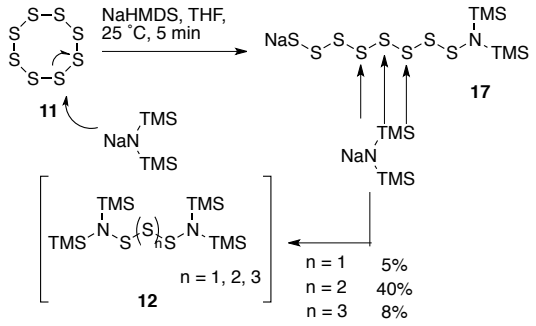


Figure 3. Compounds synthesized in this report.

2. Results and discussion

2.1. Development of the sufenylation reaction (Scheme 2).

Scheme 1. Reaction of Sulfur (S_8) with NaHMDS



Preparation of sulfenylating species

- The reaction of elemental sulfur with NaHMDS produced mainly three reactive species (Scheme 1).
- The reaction mixture reacted with 2,5-diketopiperazine *in situ* (Scheme 2). Presumably not only tetrasulfide (**12**)but also tri-, penta-, and oligo- sulfide effected the sulfenylation reaction.

• Intramolecular sulfenylation with $[NaN(TMS)_2]$ (**10c → 10d)**.

- This gave only *syn*- type desired products (**16**).

Perspective

• Applicable to a variety of the substrates (Tables 1 and 2, only selected substrates).

• Perfect stereoselectivity

- disubstituted diketopiperazine (**10**) gave the desired products (Tables 1 and 2)

- Both *syn*- and *anti*- 3,6-disubstituted diketopiperazine (**10**) systems give only *syn*- products (**16**) with the same yield (For example, Table 1, entries 2 and 3).

• Pure bis[bis(trimethylsilyl)amino]trisulfide([$(TMS)_2N(S)_3N(TMS)_2$]) was added instead of ([$(TMS)_2N(S)_nN(TMS)_2$]).

- Tetrasulfide (**13**) and disulfide (**15**) were produced as same.
- The reaction occurred intramolecularly.

Scheme 2. Sulfenylation of 2,5-Diketopiperazines with [NaHMDS-S_8]

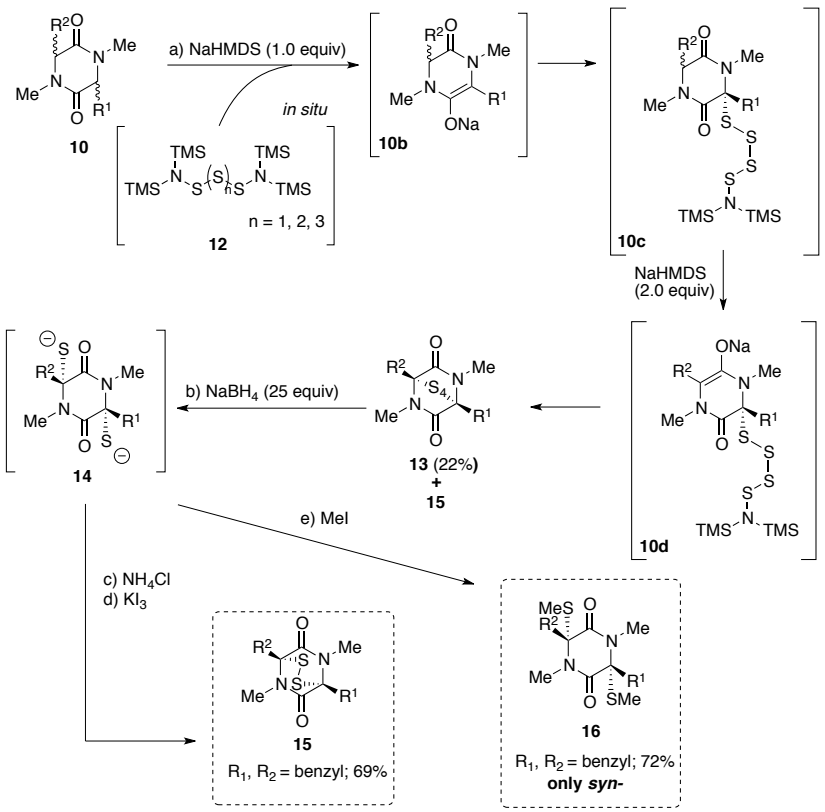
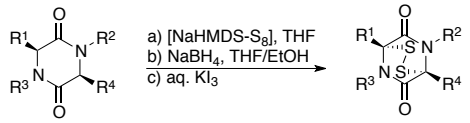
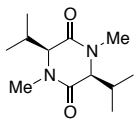
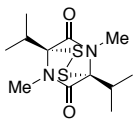
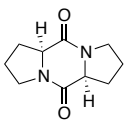
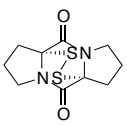
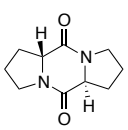
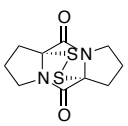


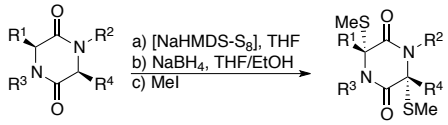
Table 1. Preparation of Selected Epidithiodiketopiperazines

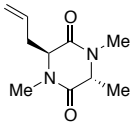
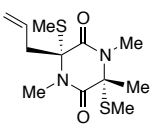
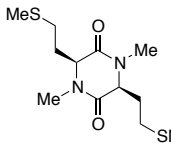
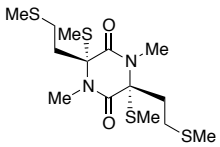
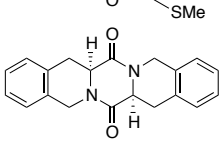
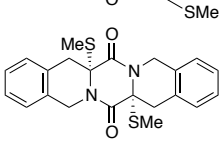


Entry	Substrate	Product[a]	Overall Yield [%]
1			45
2			65
3			68

[a]Racemic mixture

Table 2. Preparation of Selected bis-(Methylthio)diketopiperazines

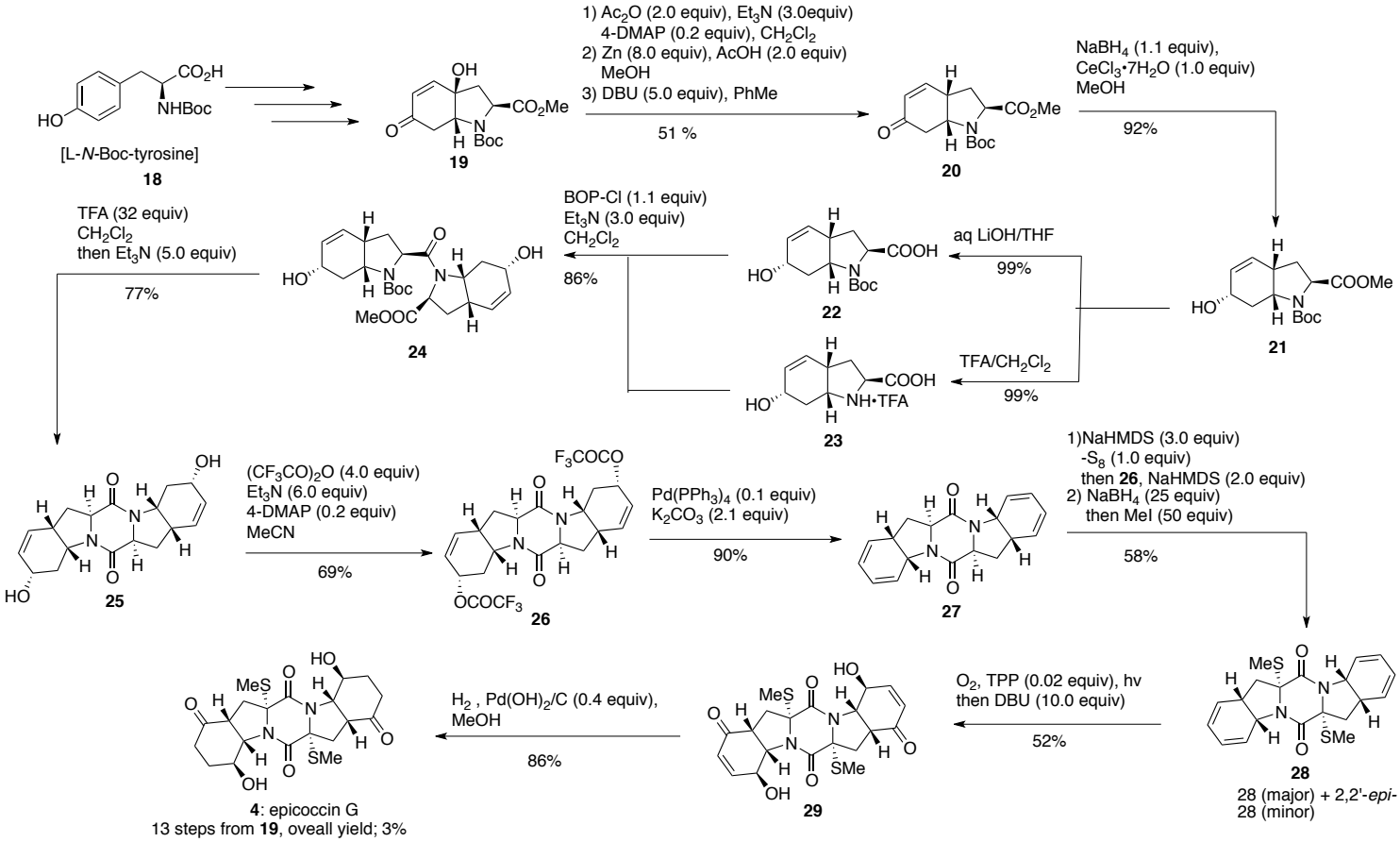


Entry	Substrate	Product[a]	Overall Yield [%]
			70
			51
			67

[a]Racemic mixture

2.2. Total synthesis of epicoccin G (4) (Scheme 4).

Scheme 3. Total Synthesis of Epicoccin G



• Stereoretention through deoxygenation with DBU (Figure 4) (**19→ 20**)

• Stereoselective reduction (**20→ 21**)

• Intermediate **21** was separately processed with LiOH and TFA to afford coupling partners **22** and **23** respectively followed by condensation (**21→ 24**).

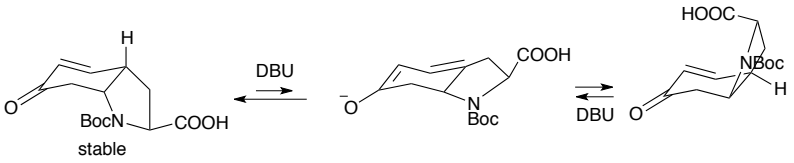


Figure 4. Thermodinamically more stable 20 was obtained stereoselectively

• Deprotection of Boc and ester hydrolysis followed by condensation to produce amide (**24 → 25**).

• Trifluoroacetate was obtained with bis-allylic alcohol and trifluoroacetic anhydride (**25 → 26**)

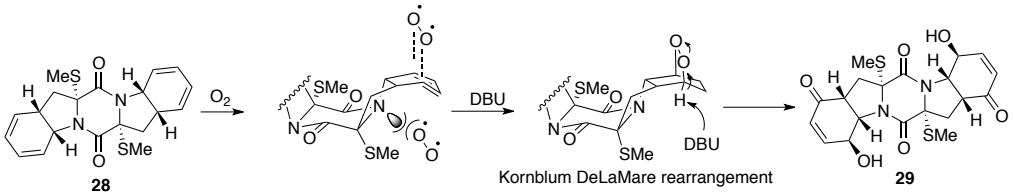


Figure 5

• Deprotonation in the presence of Pd cat. to produce diene (**26 → 27**).

• Sulfenylation and reduction/methylation to produce **28** and 2, 2′-*epi*-**28**

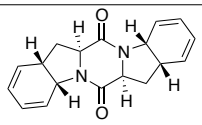
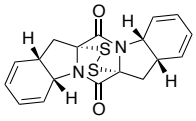
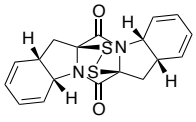
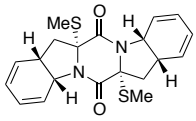
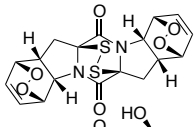
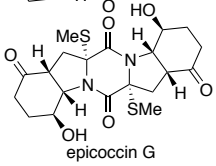
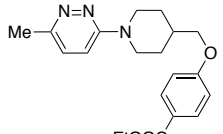
• Reaction with singlet dioxygen followed by Kornblum-DeLaMare rearrangement (Figure 6) (**28 → 29**).

• Reduction of alkene under dihydrogen in the presence of Pd cat (**29 → 30**)

2.3 Biological Evaluation (Table 3)

• Antipoliovirus assay; compounds possessing S–S bridge (**31**, **32, 34**) and compounds possessing disulfide (**4**) were most potent.
- These show better activity than standard poliovirus drug (**35**).
- S–S moieties may play an important role (Disulfide bridge can inactivate proteins, and catalytically produce toxic superoxide with dioxygen.)
• Anti P. *falciparum* assay; **31**, **32**, **33**, **34**, and epicoccin G (**4**) were most potent.
- **33** showed good activity despite the low activity against poliovirus.
- The reason is not clear.

Table 1. Biological Evaluation of Selected Compounds in Poliovirus and *P. falciparum* Assay[a]

Entry	Structure		Poliovirus EC_{50} [visual;[b] neutral red[c]]	Poliovirus EC_{90} [virus yield[d]]	*Plasmodium falciparum* IC_{50}
1		**30**	>50μM;[b] n.d.[c,e]	n.d.[d,e]	>50 μM
2		**31**	101±59 nM;[b] 115±59 nM[c]	149±65 nM[d]	3.6 μM
3		**32**	107±73 nM;[b] 123±90 nM[c]	177±45 nM[d]	2.7 μM
4		**33**	14.5 μM;[b] 25.6 μM[c]	n.d.[d,e]	1.2 μM
5		**34**	21.4±11.9 nM;[b] 21.4±2.4 nM[c]	38.1±7.1 nM[d]	2.5 μM
6	 epicoccin G	**4**	50 μM;[b] n.d.[c,e]	n.d.[d,e]	2.5 μM
7	 Pirodavir®[f]	**35**	n.d.[b,e] 1.58 μM[c]	1.55 μM[d]	n.d.[e]

[a]Assays for entries 2,3, and 7 were carried out as triplicates; mean and standard deviation are given.
[b]Visual assay. [c]Neutral red assay. [d]Virus yield reduction assay. [e]Not determined.
[f]Standard antipoliovirus drug used as a control.

3. Conclusion

• An improved method for the sulfenylation of 2,5-diketopiperazines has been developed with perfect stereocontrol of bis- (methylthio)diketopiperazines.
• Application of the method led to the total synthesis of an array of sulfenylated deketopiperazine systems.
• Biological investigation led to the discovery of potent anti polivirus agents and anti P. *falciparum* lead compounds.

4. References

1. Shimazaki, N.; Shima, I.; Hemmi, K.; Tsurumi, Y.; Hashimoto, M. *Chem. Pharm. Bull.* **1986**, *35*, 3527–3530.
2. Poisel, H.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 130–131.
3. Kishi, Y.; Fukuyama, T; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490–6492.
4. Overman, L. E.; Sato, T. *Org. Lett.* **2007**, *9*, 5267–5270.

Abbreviations

*m*CPBA: *m*-chloro-perbenzoic acid, Boc: *t*-butoxycarbonyl, NaHMDS: sodium bis(trimethylsilyl)amide, TMS: trimethylsilyl, 4-DMAP: *N,N*-dimethyl-4-aminopyridine, DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene, TFA: trifluoroacetic acid,
BOP: (benzoitriazol-1-yloxy)-tris(dimethylamino),
TPP: 5,10,15,20-tetraphenylporphyrin