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General Approach to Epipolythiodiketopiperazine Alkaloids: Total Synthesis of (+)-Chaetocins A, C and (+)-12,12′-Dideoxychetracin A

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Abstract

A highly stereoselective and systematic strategy for the introduction of polysulfides in the synthesis of epipolythiodiketopiperazines is described. We report the first total synthesis of dimeric epitri- and epitetrathiodiketopiperazines.

Dimeric epipolythiodiketopiperazine alkaloids comprise the core bioactive constituents of the highly cytotoxic extracts from fungi of the *Chaetomium* genus.[1,2] Studies have recognized the central role of the polysulfide bridge in the virulence of this class of metabolites,[3c,d] noting an increase in potency with a corresponding increase in the degree of sulfuration among related isolates.[2] While the total synthesis of both monomeric[4,5] and dimeric[6,7] epidithiodiketopiperazine alkaloids have been addressed in previous reports, the late stage selective and efficient access to higher order polysulfides continues to remain a challenge.[8] In 2009, we reported the first total synthesis of a dimeric epidithiodiketopiperazine (+)-12,12′-dideoxyverticillin A (**1**),[6,9] and recently, Sodeoka reported the total synthesis of (+)-chaetocin A (**3**).[7,10] To date, there are no reported total syntheses of dimeric epitri- and epitetrathiodiketopiperazines. Herein, we present a general approach to the dimeric epipolythiodiketopiperazine alkaloids via syntheses of the di-, tri-, and tetrasulfides (+)-chaetocin A (**3**), (+)-chaetocin C (**5**), and (+)-12,12′-dideoxychetracin A (**7**), respectively.

Complete stereochemical control in thiolation and precision in the degree of sulfidation served as the central tenets of our retrosynthetic strategy toward epipolythiodiketopiperazines as delineated in Scheme 1. We envisioned that all sulfur homologs of epipolythiodiketopiperazines could be derived selectively and systematically from the corresponding polysulfanes by final stage intramolecular cyclization onto a C15-iminium ion such as **10**. Recognizing dithiol **11** as a key intermediate, we strived to access all the necessary polysulfanes by oxidation and subsequent application of an advanced stage stereo- and regioselective C11-sulfuration of a common dimeric diketopiperazine intermediate **12**. Such a solution would enable the controlled synthesis of tetra-, hexa-, and octasulfurated congeners.

Our synthesis of dimeric diketopiperazine (−)-**18**, a common precursor to target epipolythiodiketopiperazines **3**–**7**, is illustrated in Scheme 2. Bromocyclization of the

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Supporting Information Available: Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, crystal structure of (+)-**7**, and reassignments of several resonances for (+)-**3**, (+)-**4**, and (+)-**6.** This material is free of charge via the Internet at http://pubs.acs.org.

diketopiperazine (−)-**13**,[11a] which was synthesized in three steps from commercially available *N*-Boc-L-tryptophan and L-serine methyl ester hydrochloride,[12] afforded the *endo*-tetracyclic bromide (+)-**14** in 59% with high diastereoselectivity.[13] Subsequent efforts to accomplish an *N*-methylation using our previously developed conditions (K_2CO_3, MeI, acetone)[11a] suffered from elimination of the β-siloxy group; however, kinetic deprotonation followed by methylation at –40 °C effectively circumvented the problem and afforded (+)-**15** in 86% yield. A single-step exchange of the silyl ether for an acetate then provided the key dimerization substrate (+)-**16** in 85% yield, and $CoCl(PPh_3)_3$ mediated reductive radical dimerization provided the dimeric diketopiperazine (−)-**17** in 49% yield.[11] The dimer was selectively tetrahydroxylated[6] using Py_2AgMnO_4 to provide our key intermediate (−)-**18** in 55% yield. The high chemo- and stereoselectivity of these transformations allowed facile gram-scale access to advanced intermediates.

Our initial attempts to introduce two pairs of sulfur atoms in a *cis*-selective fashion proved ineffective due to the intransigence of the C15- and C15′-hydroxyls toward acid promoted ionization conditions. Both stereoelectronic and inductive factors of the serine side chain adversely influenced the ionization potential of the hemiaminals, and while solvent and field effects proved influential, harsher ionization conditions were incompatible with nearly all of our previously examined *cis*-thiolation strategies.[15] Development of milder conditions for the desired chemoselective and stereocontrolled thiolation chemistry proved imperative.[16]

The innate reactivity differences between the C11- and the C15-hemiaminals permitted a regio- and stereoselective introduction of sulfur critical to our general route to epidi-, epitri-, and epitetrathiodiketopiperazines (Scheme 2). Exposure of tetraol (−)-**18** to trifluoroacetic acid in hydrogen sulfide–saturated nitromethane generated the sensitive bisthiohemiaminal **20** in a highly diastereoselective fashion.[17] Concentration of the reaction mixture followed by addition of isobutyryl chloride[18] afforded the octacyclic bisthioisobutyrate (+)-**21** in 53% yield (2-steps). The isobutyrates served the dual role of preventing detrimental hemiaminal opening under polar protic conditions and activating the C15-hemiaminal function in an anticipated mild ionization.

The unique challenges of C11-ionization in the presence of the C2-aminal substructure in this system compelled the precedence of C11-thiolation over N1-desulfonylation, a sequence opposite to our previously established methodologies for synthesis of epidithiodiketopiperazines.[6] Nonetheless, we discovered that irradiating a solution of (+)-**21** with a black light phosphor coated lamp in the presence of the photosensitizer 1,4-dimethoxynaphthalene and the terminal reductant L-ascorbic acid cleanly provided the desired diaminodithioisobutyrate (+)-**22** in 51% yield.[19,20] Chemoselective hydrazinolysis of the thioesters in the presence of the primary acetates provided dithiol (+)-**23**, which served as a strategic point of divergence en route to the various polysulfide homologs.

Formation and sulfenylation of dithiol (+)-**23**, which could be performed in a single step, afforded the corresponding bis(triphenylmethanedisulfide) (+)-**24** in 90% yield (X=S, Scheme 2).[21] Subsequent ionization of the isobutyrates and efficient cyclization with concomitant loss of a triphenylmethyl cation was accomplished (82% yield) to give (+)-chaetocin A diacetate (**4**), a derivative used in the isolation and characterization[1] of (+)-**3**. *Synchronized loss of the triphenylmethyl cation was essential in accessing the rapidly disproportionating polysulfanes, a central component of our synthetic strategy.* Mild methanolysis of the acetates using Otera's catalyst at 85 °C in toluene afforded the natural product (+)-chaetocin A (**3**) in 92% yield as a white solid.[10] All spectroscopic data for (+)-**3** and (+)-**4** matched those reported in the literature.[1]

We proceeded to examine our stereoselective thiolation strategy in the synthesis of more highly sulfurated and challenging epipolythiodiketopiperazines. Bis(triphenylmethanetrisulfide) (+)-**26** was smoothly obtained in 86% yield via the common dithiol (+)-**23** when chloro(triphenylmethane)disulfane (X=SS, Scheme 2) was used as the sulfenylating agent. Attempts to cyclize (+)-**26** to form the corresponding epitrithiodiketopiperazine using the protocol developed for the bisdisulfide (vide supra) were, however, unsuccessful. The slower rate of cyclization for formation of a larger ring may have enabled competing decomposition pathways involving active participation of the N1 lone pair. Trifluoroacetylation of the amines imparted sufficient stability to allow subsequent C15-iminium ion formation, affording trithiodiketopiperazine (+)-**28** in 91% yield. Methanolysis of the acetates followed by in situ hydrazinolysis of the trifluoroacetamides provided (+)-chaetocin C (**5**) in 95% yield, offering the first total synthesis of a dimeric epitrithiodiketopiperazine alkaloid. (+)-Chaetocin C (**5**) was converted to (+)-chaetocin C diacetate (**6**) for direct comparison with data reported in the isolation report.[2] All spectroscopic data for (+)-**6** matched those reported in the literature.[2,22]

Interestingly, (+)-chaetocin C (**5**), which contains two epitrisulfide bridges, exists as a 1:2.4:5.5 mixture of three distinct conformers in chloroform at room temperature with the intermediate conformer being of heterodimeric constitution.[23] The distribution changes by structure, however, as variable temperature NMR studies carried out on the more stable derivative (+)-**28** demonstrated that its three conformers exist in a 1:1.5:2.4 ratio in toluene-d_8 at 90 °C[24] with the major conformer lacking a C_2 symmetry axis. An activation barrier of *ca.* 23 kcal/mol was determined[12] for their interconversion in 1,3,5-trimethylbenzene-d_{12}.[25] We report the first complete characterization data for all three conformers of (+)-**5** and (+)-**6**.[12]

Our general strategy for stereocontrolled synthesis of epipolythiodiketopiperazines proved effective even for the synthesis of congeners possessing a tetrasulfide bridge, a motif found in natural products such as (+)-chetracin A (**8**). The versatile dithiol intermediate (+)-**23** was converted to the bis(triphenylmethanetetrasulfide) (−)-**29** in 80% yield using chloro(triphenylmethane)trisulfane (X=SSS, Scheme 2). In contrast to the disulfide series, cyclization of the resulting tetrasulfide required conditions that were more favorable for the reversible disengagement of the neighboring acetate from the acyliminium ion. An adjusted window of reactivity was also observed for the resulting product during post-cyclization transformations. For example, while N1-trifluoroacetylation of (−)-**29** followed by ionization provided the octasulfated homolog of **28**, removal of the trifluoroacetamides proved ineffective under a variety of nucleophilic and basic conditions. After significant experimentation, we recognized that the epitetrasulfides were marginally tolerant toward acidic reaction conditions. Thus, conversion of diamine (−)-**29** to bisformamide **30** not only enabled successful synthesis of dimeric epitetrathiodiketopiperazine (+)-**31**, but also allowed rapid removal of the acetyl and formyl groups by acid catalyzed methanolysis to provide (+)-12,12′-dideoxychetracin A (**7**) in 52% yield. Unlike the epitrisulfides, the epitetrasulfide appears as a single conformer in solution on the NMR timescale at room temperature. The preferred helicity of the staggered sulfur atoms in the solid state was identified through the X-ray structure solution of (+)-**7**.[12]

We have developed a general approach to the dimeric epipolythiodiketopiperazines, with the solution yielding the first total synthesis of dimeric epitri- and epitetrathiodiketopiperazines. The hallmark of our synthesis of (+)-chaetocin A (**3**), (+)-chaetocin C (**5**), and (+)-12,12′-dideoxychetracin A (**7**) is the high level of stereochemical control and chemoselectivity in sulfidation of a common dimeric diketopiperazine to access dimeric epipolythiodiketopiperazines, a strategy consistent with a biogenetic hypothesis for

divergent sulfidation of a common diketopiperazine precursor.[12] We have exploited our understanding of the reactivity and structure of epipolythiodiketopiperazines to guide the development of the chemistry. The chemo- and stereoselective nature of this synthesis offers facile access to compounds with promising biological function.[3]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. See Supporting Information for details.

13. Diastereocontrol was derived from dipole minimization effects in low dielectric constant media; the silyl ether function was imperative for the solubility of the notoriously insoluble diketopiperazines.
14. For the systematic positional numbering system used throughout this report, see page S3 of the Supporting Information.
15. For discussions of our first and second generation solutions to dimeric epidithiodiketopiperazines, see ref. 6.
16. For challenges in purification of a diastereomeric mixture of intermediates in a route related to our first generation solution to epidithiodiketopiperazine synthesis see page S7–14, S27–28 of ref. 7.
17. Exceptional control in the thiolation was achieved by stereoinduction from the proximal C3 stereocenter. Significant adverse C15 stereoinduction via anchimeric stabilization of the acyliminium ion by the acetate was minimized in high dielectric constant media.
18. An acetate proved too labile at C11 under the subsequent desulfonylation step while attempts to use a pivaloate resulted in premature ionization.
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20. The thioesters proved stable to the reductive photochemical conditions in contrast to the corresponding thiols and polysulfides.
21. For epidithiodiketopiperazine synthesis using sulfenyl chlorides such as chloro(triphenylmethane)disulfane for thiol protection, see ref. 5d. For preparation of this reagent see: Williams CR, Britten JF, Harpp DN. J Org Chem. 1994; 59:806.
22. The ^{1}H NMR shift reported for one of the diastereotopic protons at C12 of the major isomer is 3.60 ppm, but we found the resonance to be at 3.33 ppm.
23. It is heterodimeric with respect to the conformation of the two trisulfides.
24. The ratio was obtained at this temperature because trifluoroacetamide rotamer derived peak broadening at lower temperatures prevented accurate integration of the peaks for the separate entities.
25. Low dielectric constant media were crucial for these studies, particularly when heating to 160 °C for ^{1}H NMR signal coalescence.

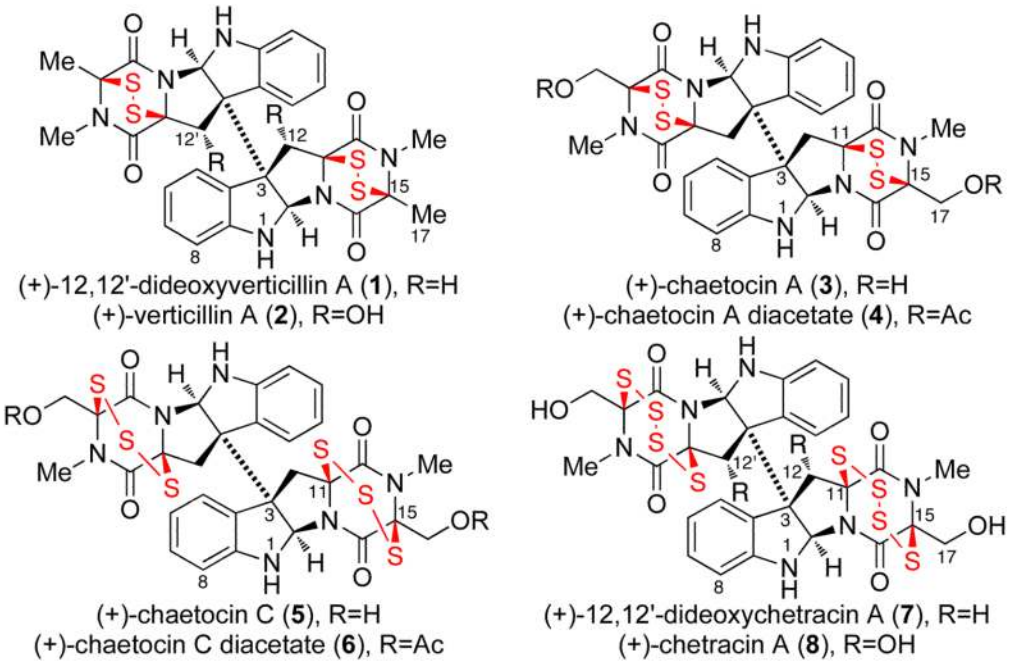
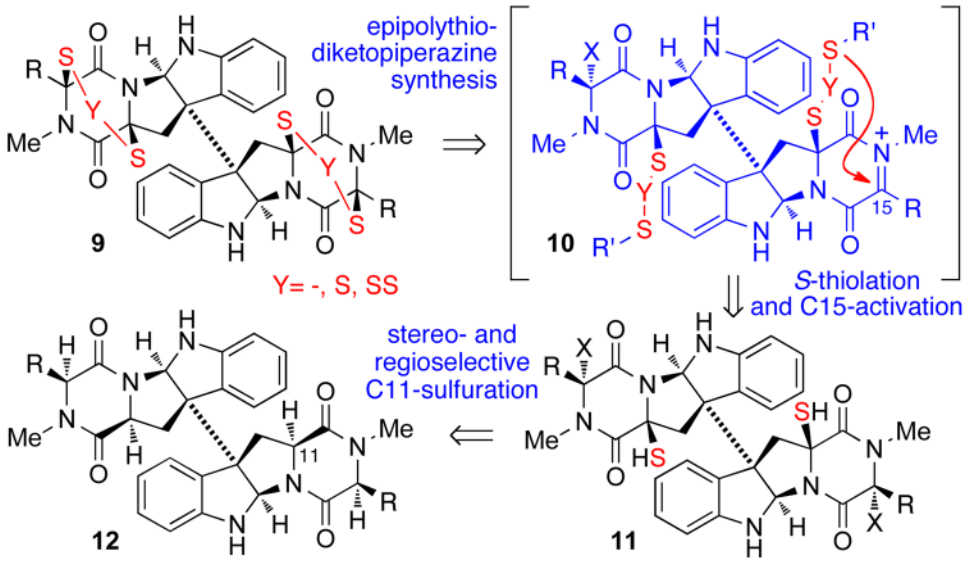
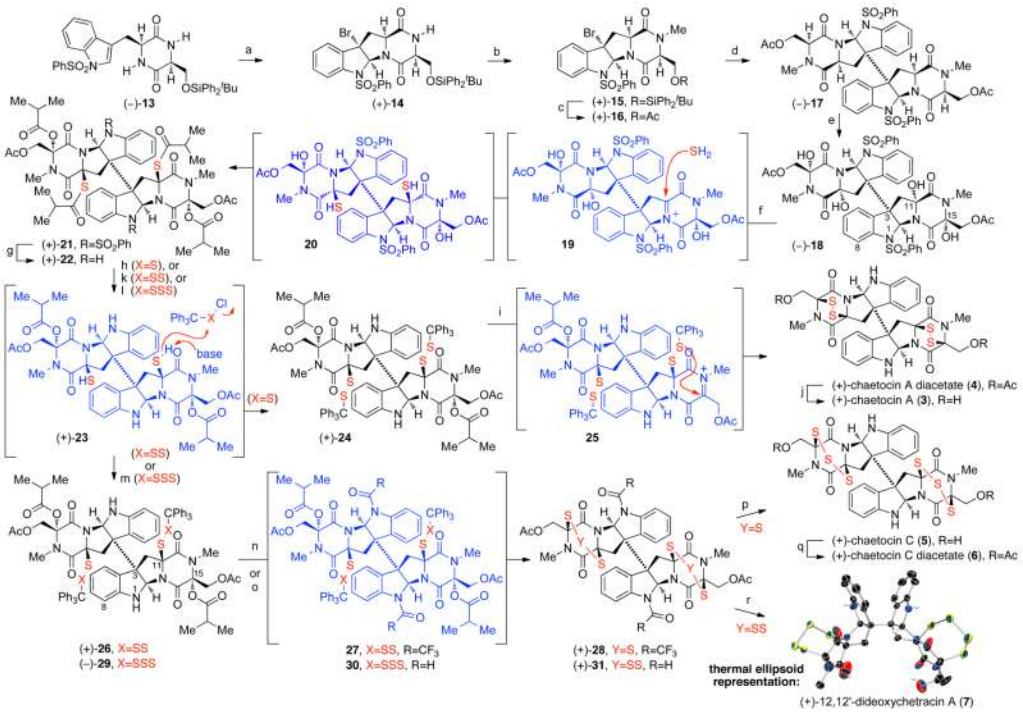


Figure 1.
Representative dimeric epipolythiodiketopiperazines.[14]



Scheme 1.
Retrosynthetic analysis.



Scheme 2.

Enantioselective total synthesis of dimeric epipolythiodiketopiperazines (+)-**3**–**7**.[a]

[a]Conditions: (a) Br_2, PhH, 59%. (b) LHMDS, MeI, DMPU–THF, −78 → −40 °C, 86%. (c) HF·py, THF, py; AcCl, 85%. (d) $CoCl(PPh_3)_3$, CH_2Cl_2, 49%. (e) Py_2AgMnO_4, CH_2Cl_2, 55%. (f) H_2S, TFA, $MeNO_2$; $^{i}PrCOCl$, CH_2Cl_2, 53% (2-steps). (g) hν (350 nm), L-ascorbic acid, 1,4-dimethoxynaphthalene, H_2O, MeCN, 51%. (h) N_2H_4, THF, 0 °C; NaH, Ph_3CSCl, 90%. (i) $BF_3{\cdot}OEt_2$, 2,6-di-^{t}Bu-4-Me-pyridine, Et_3SiH, CH_2Cl_2, 82%. (j) Otera's cat., MeOH, PhMe, 85 °C, 92%. (k) N_2H_4, THF, 0 °C; TrSSCl, NEt_3, 86%. (l) N_2H_4, THF, 0 °C, 93%. (m) TrSSSCl, NEt_3, 80%. (n) TFAA, 2,6-di-^{t}Bu-4-Me-pyridine, MeCN; $BF_3{\cdot}OEt_2$, 91%. (o) HCO_2Ac; MeCN, $BF_3{\cdot}OEt_2$, 60%. (p) Otera's cat., MeOH, PhMe, 90 °C; N_2H_4, 95%. (q) Ac_2O, CH_2Cl_2, 70%. (r) HCl, MeOH, 52%.