The mechanism we have described requires only a few general materials characteristics, in particular that at temperatures where a liquidus exists, the more slowly evaporating component accumulates as a liquid on the surface. Therefore, comparable behavior is expected in other III-V semiconductors such as InAs (*23*) and perhaps in many other systems. Evaporation is used in the cleaning of GaAs, and Ga droplets are central to droplet epitaxy (*15*–*18*). The intrinsic droplet motion observed here may therefore have important technological consequences and may open up new extensions for the droplet epitaxy technique.

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Total Synthesis of (+)-11,11'-Dideoxyverticillin A

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The fungal metabolite (+)-11,11'-dideoxyverticillin A, a cytotoxic alkaloid isolated from a marine *Penicillium* sp., belongs to a fascinating family of densely functionalized, stereochemically complex, and intricate dimeric epidithiodiketopiperazine natural products. Although the dimeric epidithiodiketopiperazines have been known for nearly 4 decades, none has succumbed to total synthesis. We report a concise enantioselective total synthesis of (+)-11,11'-dideoxyverticillin A via a strategy inspired by our biosynthetic hypothesis for this alkaloid. Highly stereo- and chemoselective advanced-stage tetrahydroxylation and tetrathiolation reactions, as well as a mild strategy for the introduction of the epidithiodiketopiperazine core in the final step, were developed to address this highly sensitive substructure. Our rapid functionalization of the advanced molecular framework aims to mimic plausible biosynthetic steps and offers an effective strategy for the chemical synthesis of other members of this family of alkaloids.

The fungal metabolite (+)-11,11'-dideoxyverticillin A (**1**, Fig. 1) (*1*) is a member of the epidithiodiketopiperazine alkaloids, a large family of natural products that has received substantial attention from the scientific community for its rich biological activity and complex molecular architecture (*2*–*7*). The dimeric subset of alkaloids to which the title compound belongs has been known for nearly 4 decades with the isolation of (+)-chaetocin A (**2**) (*8*) and (+)-verticillin A (**3**) (*9*). Reflective of the daunting challenges posed by molecular structures replete with sterically congested stereogenic centers and highly acid-, base-, and redox-sensitive functional groupings (*5*), no dimeric epidithiodiketopiperazine alkaloid has yet succumbed to total synthesis. Herein we describe a concise strategy for the enantioselective total synthesis of the dimeric epidithiodiketopiperazine alkaloid (+)-**1**. Our biosynthetically inspired synthesis features stereo- and chemoselective advanced-stage tetrahydroxylation and tetrathiolation reactions, providing a generalizable solution to the epidithiodiketopiperazine substructure found in the broader family of these alkaloids.

At the outset of our synthetic studies, structural similarities among members of this alkaloid family combined with Kirby's radio-labeled amino acid feeding experiments and his hypothesis for gliotoxin biosynthesis (*10*) prompted us to consider the possibility that the epidisulfides of (+)-**1** are assembled by enzymes that exploit the inherent chemistry of dimeric diketopiperazines. Our retrosynthetic analysis of (+)-**1** imitates a plausible biosynthetic sequence of events linking dimeric epidithiodiketopiperazines to common α-amino acid precursors (Fig. 2). We envisioned preparation of (+)-**1** by mild oxidation of the tetrathiol **5**, which could be accessed via stereoselective tetrathiolation of an octacyclic tetraol **6**. In contrast to a previous biosynthetic hypothesis for monomeric epidithiodiketopiperazines invoking thiolation via an N-hydroxylation–dehydration sequence (*11*), we speculated that a postdimerization C_α-hydroxylation would enable substrate-directed hemiaminal thiolation through the intermediacy of an acyliminium ion. Intermediate **7**, which we hypothesized to arise from a dimerization event, could be assembled from the readily available *cyclo*-dipeptide **8** by using the concise cobalt-mediated dimerization strategy reported from our laboratories (*12*, *13*). The imposing challenges associated with quadruple C_α-methine hydroxylation of **7** and the tetrathiolation of inter-

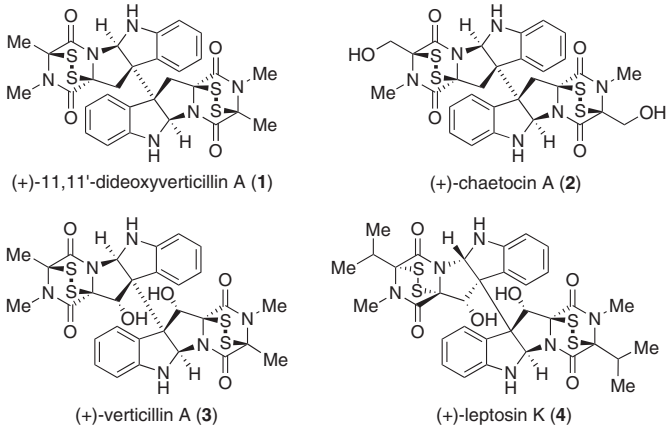

Fig. 1. The molecular structure of (+)-11,11'-dideoxyverticillin A (**1**) and representative dimeric epidithiodiketopiperazine alkaloids.

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mediate **6** notwithstanding, the need for absolute and relative stereochemical control (Fig. 2) of the six tetrasubstituted carbons of (+)-**1** posed noteworthy strategic concerns. We envisioned the introduction of the C3 and the C3′ vicinal quaternary stereocenters as a prelude to stereochemical control of the four thiolated-carbon stereogenic centers of (+)-**1** in a strategy reminiscent of Seebach's self-reproduction of chirality (*14*). Such a final-stage tetrathiolation followed by immediate disulfide formation would obviate the need to mask the notoriously sensitive epidithiodiketopiperazine functional grouping in the early stages of the synthesis.

The dimeric diketopiperazine (+)-**13** was assembled in six steps from commercially available amino acid derivatives (Fig. 3) [supporting online material (SOM) text]. The sequential treatment of amide (–)-**9** with trifluoroacetic acid followed by cyclization with morpholine readily afforded access to the desired *cis*-diketopiperazine (–)-**10** in 84% yield (>20 g). Exposure of *cyclo*-L-tryptophan-L-alanine (–)-**10** to molecular bromine in acetonitrile at 0°C furnished the desired monomeric tetracyclic bromide (+)-**11** in 76% isolated yield (SOM text). Treatment of tetracyclic bromide (+)-**11** with methyl iodide and potassium carbonate gave the base-sensitive dimerization precursor (+)-**12** in 77% yield (*15*). Reductive dimerization of the tertiary benzylic bro-

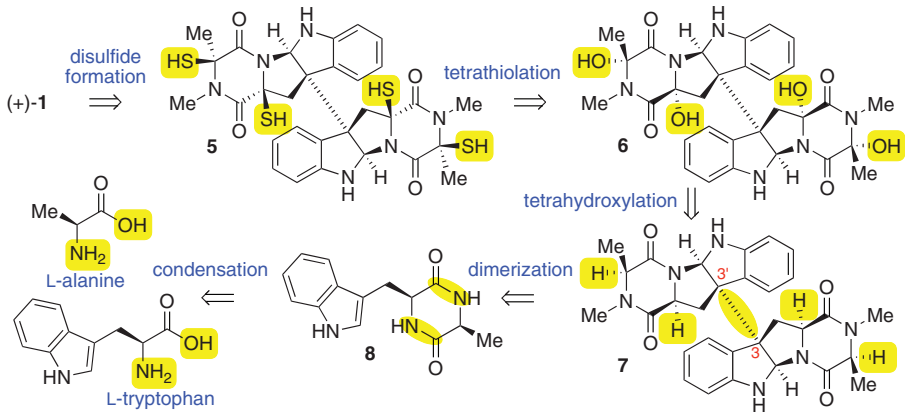

Fig. 2. Retrosynthetic analysis of (+)-11,11'-dideoxyverticillin A (**1**) based on a biosynthetic hypothesis.

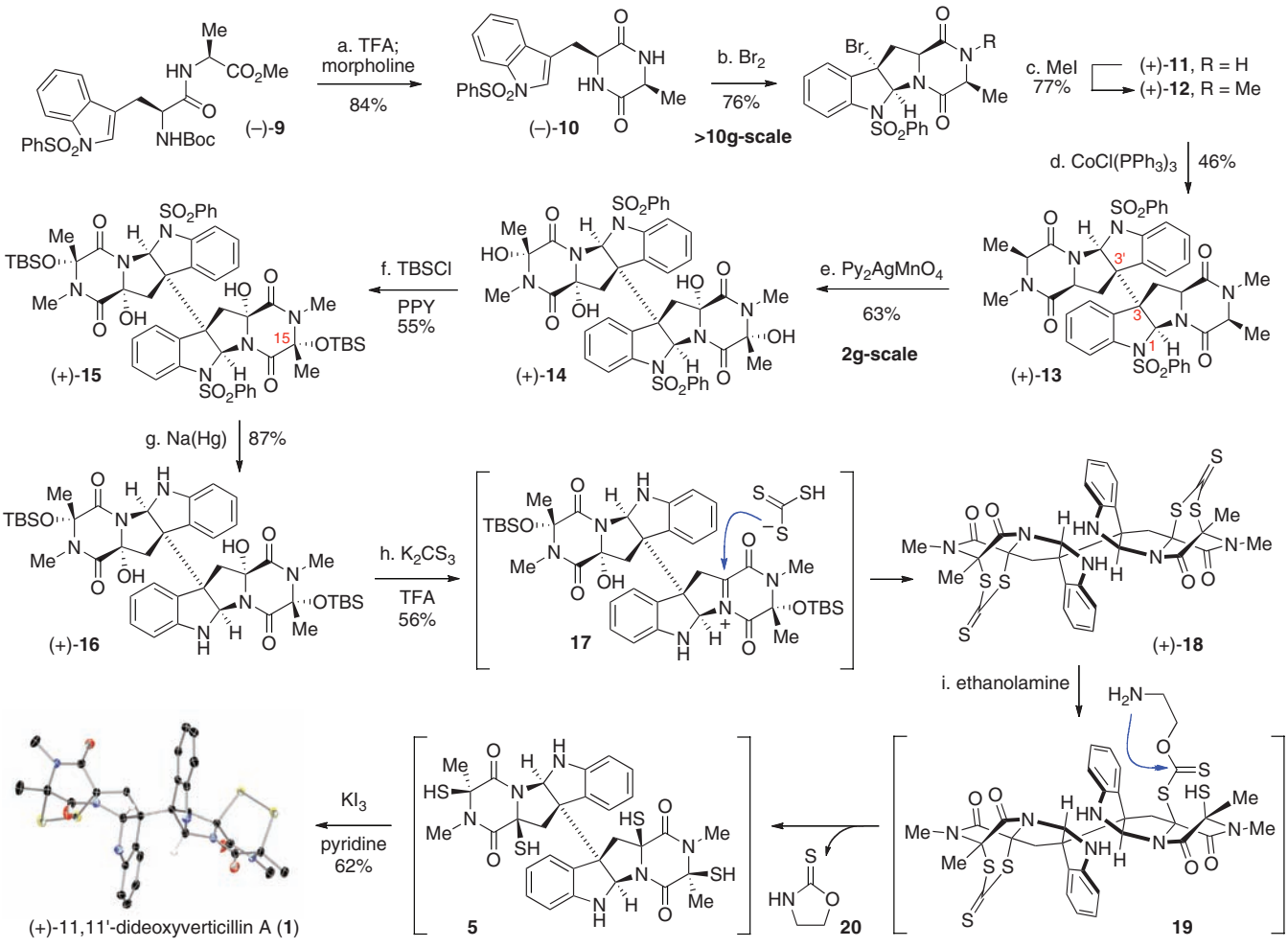

Fig. 3. Concise enantioselective total synthesis of (+)-11,11'-dideoxyverticillin A (**1**). Isolated yields are given for each step. Reaction conditions are as follows: (a) trifluoroacetic acid (TFA), dichloromethane (CH_2Cl_2), 23°C, 4 hours; *tert*-butanol (^tBuOH), morpholine, 23°C, 48 hours. (b) Br_2, acetonitrile (MeCN), 0°C, 5 min. (c) methyl iodide (MeI), K_2CO_3, acetone, 23°C, 5 days. (d) tris(triphenylphosphine)cobalt(I) chloride [$CoCl(PPh_3)_3$], acetone, 23°C, 30 min. (e) bis(pyridine)silver(I) permanganate (Py_2AgMnO_4), CH_2Cl_2, 23°C, 2 hours. (f) *tert*-butyl(chloro)dimethylsilane (TBSCl), PPY 5 mole %, triethylamine (Et_3N), *N*,*N*-dimethyl formamide (DMF), 23°C, 30 min. (g) 5% Na(Hg), NaH_2PO_4, methanol (MeOH), 23°C. (h) K_2CS_3, TFA, CH_2Cl_2, 23°C, 28 min. (i) ethanolamine, acetone, 23°C; KI_3, pyridine, CH_2Cl_2, 23°C. The thermal ellipsoid representation of synthetic (+)-**1** from x-ray crystallographic analysis is shown with most hydrogens omitted for clarity.

mide (+)-**12** with tris(triphenylphosphine)cobalt(I) chloride in acetone provided the key dimeric octacyclic intermediate (+)-**13** in 46% yield (*16*). Preference for cis-fusion on 5,5-ring systems made this an effective strategy for simultaneously securing the two vicinal C3 and C3′ quaternary stereocenters (*12*). This chemistry is amenable to multigram scale synthesis of (+)-**13** (e.g., 43% yield on 8 g scale).

Guided by our biosynthetic hypothesis for late-stage functionalization of the diketopiperazines (i.e., **7**→**5**, Fig. 2), we sought methods for C_α-oxidation of the dimeric octacycle (+)-**13**. Initially, we focused on the oxidation of the readily accessible enol tautomers or corresponding enolates of (+)-**13** (SOM text). Unfortunately, these strategies were plagued by formation of partially oxidized and diastereomeric products in addition to substantial competing decomposition. Likewise, a variety of soft-enolization and electrophilic amide activation strategies failed to provide the necessary C_α-methine oxidation. Although we ultimately developed conditions for dihydroxylation (or didehydrogenation) of a model monomeric tetracyclic diketopiperazine **21** (Fig. 4A) along with its conversion to the corresponding monomeric epidithiodiketopiperazine **23** (SOM text), none of these methodologies proved effective when applied to the more-challenging dimeric octacyclic bisdiketopiperazine (+)-**13**, likely because of additional modes of C3–C3′ bond fragmentation and/or unfavorable interactions between the tetracyclic subunits.

Careful analysis of the bond dissociation energies (*17*) involved in our successful radical-based abstraction of C_α-methines in the model tetracycle **21** (SOM text) suggested weak C_α–H bonds resulting from stabilization of the ensuing C_α-radicals in diketopiperazines. Thus, the use of mild oxidants typically reserved for hydrogen atom abstraction from formyl groups became a focus of our efforts in pursuit of an effective strategy for single-step tetrahydroxylation of dimeric octacycle (+)-**13**. After extensive experimentation, we found that the treatment of the diketopiperazine **21** with tetra-*n*-butylammonium permanganate (3.0 equiv) (*18*) in pyridine at 23°C for 2 hours provided the desired tetracyclic diol **22** in 78% yield primarily as one diastereomer. Application of these conditions to the oxidation of the more-challenging dimeric octacycle (+)-**13** resulted in 40% yield of the desired tetraol as a complex mixture of hemiaminal diastereomers. Because this tetrahydroxylation was fraught with competing epimerization of C_α-methines and incomplete oxidation leading to complex product mixtures (SOM text), we sought to refine this reaction.

Further studies revealed that bis(pyridine)-silver(I) permanganate (Py_2AgMnO_4) (*19*) oxidized dimeric octacycle (+)-**13** selectively and efficiently. Under optimal conditions, treatment of dimer (+)-**13** with Py_2AgMnO_4 (4.8 equiv) in dichloromethane at 23°C for 2 hours afforded the desired dimeric octacyclic tetraol (+)-**14** in 63% yield as a single diastereomer (Fig. 3). The high level of diastereoselection (SOM text) is consistent with a fast abstraction-rebound mechanism (*20*, *21*), as suggested by hydroxylation of the radical-clock hydantoin **24** (74%) (Fig. 4A) and x-ray diffraction analysis of tetraol (+)-**14**. Oxidation of the corresponding *cyclo*-D-Trp-L-Ala derivatives under these conditions resulted only in oxidation at the alanine C_α(L-Ala)-methines, leaving the C_α(D-Trp)-methines unchanged (SOM text). This observation, which has important consequences for the choice of natural or unnatural amino acid precursors, is attributed to a nonoptimal conformation of the C–H bond for abstraction and/or the sterically disfavored approach of the oxidant from the concave face of the 5,5-ring system.

The dimeric octacyclic tetraol (+)-**14** proved highly acid- and base-sensitive. Its treatment with Brønsted acids led to formation of tetraene **26** (Fig. 4B) (*22*), whereas its exposure to base resulted in either decomposition or conversion to hemiaminal diastereomers (SOM text). The high sensitivity of tetraol (+)-**14** to base may be attributed to reversible ring opening at the C15-aminal, allowing deleterious side reactions of the alpha-keto amide derivative **27** (Fig. 4B). Unexpectedly, even dissolution of (+)-**14** in methanol at ambient temperature led to slow decomposition.

With multigram access to dimeric octacyclic tetraol (+)-**14**, we focused on its conversion to alkaloid (+)-**1**. Removal of the benzenesulfonyl groups with sodium amalgam in methanol buffered with dibasic sodium phosphate unveiled an unstable diaminotetrahemiaminal **28** (Fig. 4C). Immediate exposure of this labile compound to condensed hydrogen sulfide at –78°C with a Lewis acid (*6*), followed by warming, resulted in formation of the corresponding tetrathiol **29** as a mixture of hemithioaminal diastereomers. Oxidation of the crude mixture of tetrathiols with potassium triiodide resulted in (+)-11,11'-dideoxyverticillin A (**1**), albeit in low overall yields (2 to 15%, three steps) from tetraol (+)-**14**.

The fragility of tetraol (+)-**14** and derivatives **28** and **29**, the poor mass balance of this capricious three-step sequence, and our preference to avoid the use of pressurized toxic hydrogen sulfide led us to seek a superior strategy for the synthesis of the epidithiodiketopiperazine substructure of this family of alkaloids. After substantial experimentation, we realized that a simple tactical conversion of the tetraol (+)-**14** to the diol (+)-**15** (Fig. 3) imparted considerable stability to this structure, consistent with prevention of an undesired diketopiperazine ring opening. The use of Fu's (*R*)-(+)-4-pyrrolidinopyridinyl(pentamethylcyclopentadienyl)-iron (PPY) catalyst (5 mole %) (*23*) was optimal

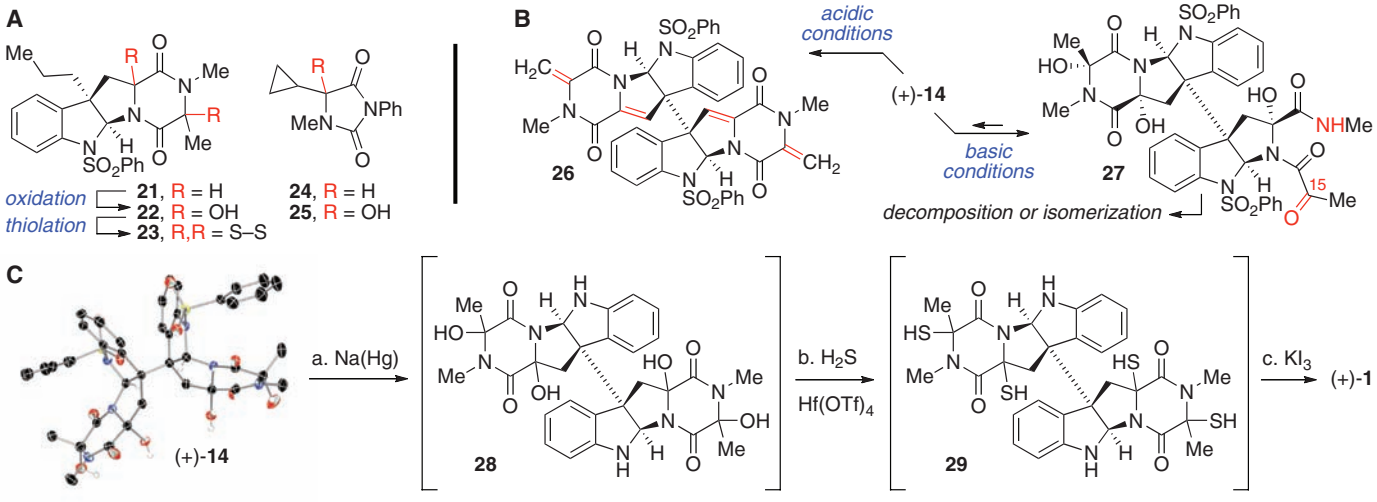

Fig. 4. Key observations enabling our first-generation synthesis of (+)-11,11'-dideoxyverticillin A (**1**). (**A**) Functionalization of exploratory models. (**B**) Sensitivity of dimeric octacyclic tetraol (+)-**14** to both acidic and basic conditions. (**C**) Thermal ellipsoid representation of (+)-**14**. Synthesis of alkaloid (+)-**1** from dimeric tetraol (+)-**14**. Conditions: (a) 5% Na(Hg), Na_2HPO_4, MeOH, 23°C. (b) H_2S, CH_2Cl_2, hafnium(IV) trifluoromethanesulfonate [$Hf(OTf)_4$], –78→23°C, 14 hours. (c) KI_3, pyridine, CH_2Cl_2, 23°C, 2 to 15% for three steps.

for the selective derivatization of both alanine-derived hemiaminals of (+)-**14** (SOM text). Treatment of a methanolic solution of diol (+)-**15** containing monobasic sodium phosphate with sodium amalgam cleanly unveiled the stable diaminodiol (+)-**16** in 87% yield as a surrogate for our hypothetical biosynthetic intermediate **6** (Fig. 2).

At this juncture, we envisioned that coordinating the introduction of the two sulfur atoms on each diketopiperazine ring would provide greater stereochemical control and structural stability. Inspired by the Woodward-Prévost cis-dihydroxylation of alkenes with carboxylate ions (*24*) and cognizant of the observation from Kishi's seminal synthesis of gliotoxin that epidithiodiketopiperazines are acutely sensitive toward basic, reductive, oxidative, and strongly acidic conditions (*5*), we reasoned that the use of a trithiocarbonate (*25*) would deliver a sulfurated product poised for mild unveiling of the targeted tetrathiol at an advanced stage. In the event, treatment of diaminodiol (+)-**16** with potassium trithiocarbonate and trifluoroacetic acid in dichloromethane resulted in rapid formation and isolation of the desired dimeric bisdithiepanethione (+)-**18** in 56% yield (*26*) (SOM text), likely via kinetic trapping of iminium ion **17** followed by intramolecular dithiepanethione formation. In this single operation, four carbon-oxygen bonds are exchanged for four carbon-sulfur bonds, the stereochemistry at all four tertiary thiols is secured, and the targeted *cis*-dithiodiketopiperazine substructure of **5** is attained.

Addition of ethanolamine to a solution of bisdithiepanethione (+)-**18** at 23°C rapidly afforded the proposed biosynthetic precursor diaminotetrathiol **5** (*27*), which is subject to mild oxidation to (+)-**1** upon exposure to air (SOM text). Under optimized conditions, after the formation of diaminotetrathiol **5**, partitioning of the reaction mixture between aqueous hydrochloric acid and dichloromethane and immediate addition of potassium triiodide to the organic layer provided (+)-11,11'-dideoxyverticillin A {$[\alpha]_D^{21} = +590$ (*c* 0.30, $CHCl_3$); for lit. $[\alpha]_D^{21} = +624.1$ (*c* 0.3, $CHCl_3$); where α is the specific rotation and c is concentration in g/100 ml} in 62% yield as a colorless solid. All spectroscopic data for (+)-**1** matched those reported in the literature (*1*). Furthermore, we unambiguously secured the structure of synthetic (+)-**1** by crystallographic analysis.

This concise strategy for the synthesis of (+)-**1** required a carefully choreographed sequence of events. In this sequence, the inherent chemistry of intermediates was maximally used in generation of chemical complexity and stereochemical control. For example, unveiling of the aniline nitrogen (N1) of (+)-**13** followed by attempted tetrahydroxylation led to complete decomposition under a variety of conditions. The challenges associated with the high sensitivity of (+)-**13** toward epimerization at the L-amino acid–derived C_α-stereocenters was compounded by the requirement for oxidation before epimerization (*vide supra*). Furthermore, thiolation of the oxidized diketopiperazines at an earlier stage led to substantial reductive cleavage or elimination of the sensitive carbon-sulfur bonds during subsequent transformations. These key insights guided our described strategy, whereby the conversion of diaminodiol (+)-**16** to dimeric dithiepanethione (+)-**18** enabled tetrathiolation with concomitant inversion of all four C_α-stereocenters, allowing rapid epidithiodiketopiperazine formation.

Collectively, our observations on the inherent reactivity of these structures hint at a plausible biosynthetic sequence for alkaloid (+)-**1** (Fig. 2). Whereas the viability of the proposed biosynthetic intermediates is supported through chemical synthesis, the successful implementation of our synthetic strategy offers a potential roadmap to the function of enzymes involved in the biosynthesis of epidithiodiketopiperazine alkaloids. For instance, Howlett's studies of the epidithiodiketopiperazine biosynthetic gene clusters (*28*, *29*) have identified genes encoding proteins with unassigned function that have sequence homology to cytochrome P450 mono-oxygenases. The mechanistic semblance of our permanganate diketopiperazine hydroxylation to the well-studied C–H abstraction-hydroxylation of substrates by P450 oxygenases (*30*, *31*) prompts consideration of the involvement of these genes in the C_α-oxidation of the diketopiperazine core.

Alkaloid (+)-**1** potently inhibits the tyrosine kinase activity of the epidermal growth factor receptor (median inhibitory concentration = 0.14 nM), exhibits antiangiogenic activity, and has efficacy against several cancer cell lines (*32*–*34*). The strategy and methodologies described here are expected to yield ready access to related compounds and provide an inroad to further biological studies. In this report, we have attempted to capture the power of biosynthetic considerations as a guiding principle for synthetic planning and as an inspiration for the development of new reactions.

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15. Sensitivity of diketopiperazine (+)-**11** to epimerization at the tryptophan-derived C_α-methine is highlighted by isolation of the corresponding diastereomer of **12** in 11% yield.
16. The major isolable side product is the C3-reduction product. Although the use of tetrahydrofuran (THF) as solvent provided a higher yield of dimer (+)-**13** (52%) on <1 g scale, the yields of larger scale reactions (>1 g scale) in THF were lower (40%).
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27. The expected 1,3-oxazolidine-2-thione (**20**) was observed in the product mixture.
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Supporting Online Material

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