

Efficient and Divergent Total Synthesis of (–)-Epicoccin G and (–)-Rostratin A Enabled by Double C(sp³)–H Activation

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Supporting Information

ABSTRACT: Dithiodiketopiperazines are complex polycyclic natural products possessing a variety of interesting biological activities. Despite their interest, relatively few total syntheses have been completed. We herein report the enantioselective, scalable, and divergent total synthesis of two symmetrical pentacyclic dithiodiketopiperazines, (–)-epiccocin G and (–)-rostratin A. A common intermediate was synthesized on a multigram scale from inexpensive, commercially available starting materials using an enantioselective organocatalytic epoxidation and a double C(sp³)–H activation as key steps, with the latter allowing the efficient simultaneous construction of the two five-membered rings. In addition to the *cis,cis*-fused target (–)-epiccocin G, the more challenging (–)-rostratin A, possessing two *trans* ring junctions, was obtained for the first time on a 500 mg scale through the optimization of each step and validation on multigram quantities. Both natural products were synthesized with high overall yields (13–20%). This study should facilitate access to this fascinating and yet understudied family of biologically active natural products.

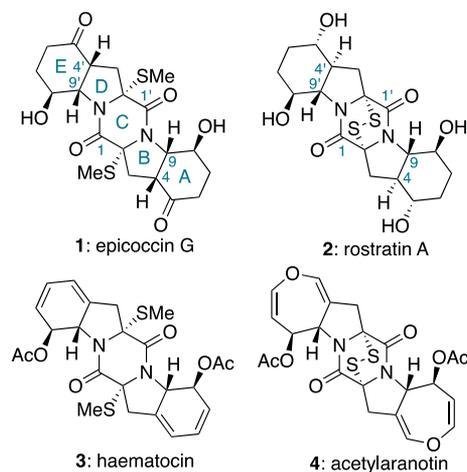


Figure 1. Examples of naturally occurring dithiodiketopiperazines with a pentacyclic framework.

Dithiodiketopiperazines (DTPs) constitute an abundant class of natural products exhibiting a great diversity of biological properties.¹ In particular, (–)-epiccocin G (**1**), isolated from the fungus *Epicoccum nigrum*, was shown to possess *in vitro* anti-HIV-1² and antiplasmodial activities,³ and (–)-rostratin A (**2**), isolated from the marine-derived fungus *Exserohilum rostratum*, was shown to be cytotoxic against HCT-116 cancer cells (Figure 1).⁴ These interesting bioactivities, combined with a challenging sulfurated fused pentacyclic framework, have attracted the attention of synthetic chemists in recent years. However, despite a significant number of synthetic studies,⁵ only three research groups have reported total syntheses of DTPs based on such a pentacyclic framework, and hence these molecules remain major synthetic challenges. On one hand, Nicolaou and co-workers reported the pioneering synthesis of several 6-5-6-5-6 DTPs, including epicoccin G (**1**) and haematocin (**3**).^{3,6} Shortly after, the groups of Reisman and Tokuyama disclosed the synthesis of the dihydrooxepine-containing 7-5-6-5-7 DTPs acetylaranotin (**4**)^{7,8} and acetylpoaranotin.⁹ Interestingly, all of these total syntheses proceed with the initial construction of the AB/DE bicyclic systems and assembly of the central DKP ring (C) at a later stage.

In recent years, C–H activation has gained increasing importance in total synthesis, offering step-economical access to key intermediates or allowing late-stage introduction of key functional groups.¹⁰ In this context, we and others developed an array of methods based on Pd⁰-catalyzed C(sp³)–H activation for the construction of various carbo- and heterocyclic systems¹¹ and demonstrated their applicability in natural product synthesis.¹² Herein, we report a new strategy based on double C–H activation for the concise and divergent enantioselective synthesis of (–)-epiccocin G (**1**) and (–)-rostratin A (**2**), which are synthesized for the second and first time, respectively. Structurally, these molecules differ from the oxidation degree at C5/C5', the nature of the sulfur substituents at C2/C2', and last but not least the presence of *cis* (**1**) or *trans* (**2**) A-B/D-E ring junctions.

Our retrosynthetic analysis is depicted in Figure 2. Target compounds **1** and **2** were thought to arise from the common intermediate **5** through manipulation of the C4–C5/C4'–C5' double bonds and late-stage introduction of the sulfur atoms at C2/C2', as advised in earlier studies.^{3,6–8} For the synthesis of **2**, we anticipated that the control of the contra-thermodynamic *trans* ring junctions would be a significant challenge. Indeed, the *cis,cis* 6-5-6-5-6 pentacyclic system was calculated to be more stable than the *trans,trans* system by 5 kcal mol^{–1} by DFT (Supporting Information, Figure S1), and no such *trans*-

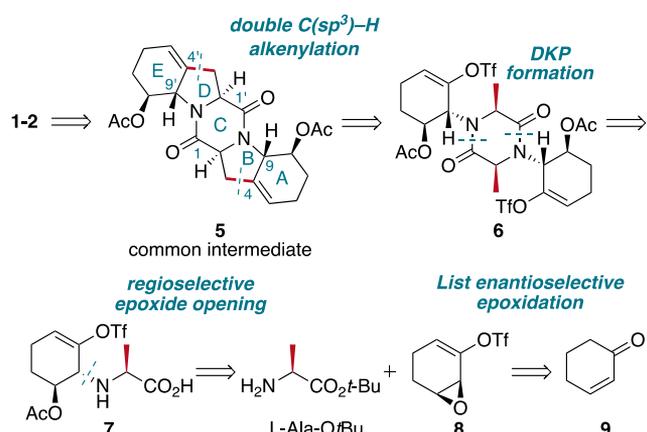


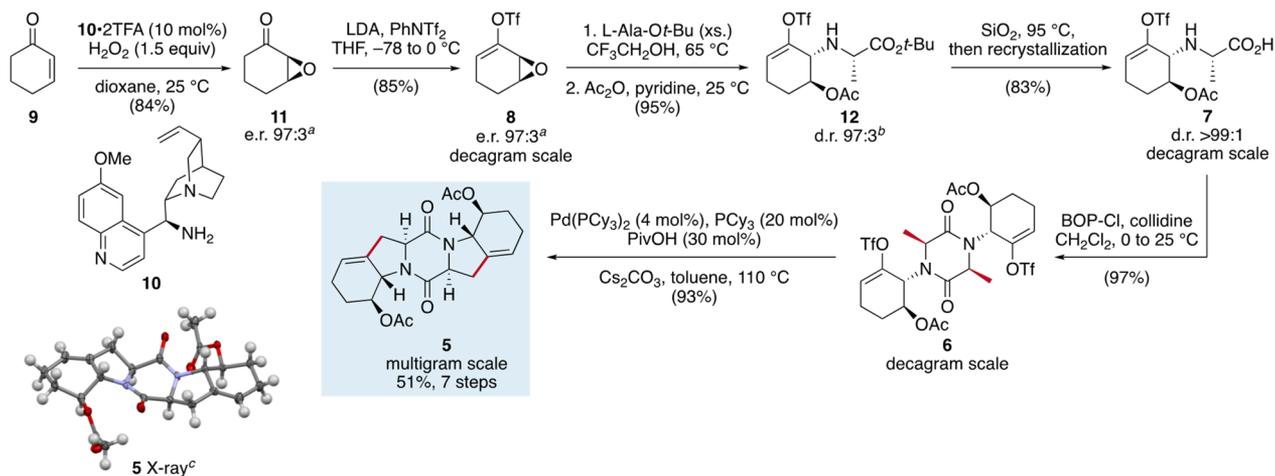
Figure 2. Retrosynthetic analysis.

fused pentacyclic DTP natural product has been synthesized to date, to the best of our knowledge. A twofold application of our C(sp³)-H activation transform to the C3-C4 and C3'-C4' bonds in 5 would then lead to the ditriflate precursor 6. The intramolecular C(sp³)-H alkenylation of cyclohexenyl bromides¹³ and triflates¹⁴ has been reported, but such a double C(sp³)-H alkenylation reaction is unprecedented.¹⁵ Diketopiperazine formation by cyclodimerization would allow building intermediate 6 from monomeric amino acid 7. The latter would arise from the regioselective and stereospecific opening of enantiomerically pure epoxide 8 with L-alanine *tert*-butyl ester.¹⁶ Finally, epoxide 8 would be obtained from cyclohexenone 9 by using List's organocatalytic enantioselective epoxidation.¹⁷ This retrosynthetic plan differs from most previous approaches^{5,6} by constructing simultaneously rings B and D from A-C-E precursor 6 instead of constructing ring C last,^{5d,g} while minimizing nonstrategic functional group manipulations. This should result in a significant overall step-economy for the synthesis of targets 1 and 2.

The enantiopure dialkene intermediate 5 was synthesized in high overall yield from inexpensive starting materials according to the seven-step sequence depicted in Scheme 1. The most effective method to access epoxide 8 was found to be List's asymmetric epoxidation of cyclohexenone 9, catalyzed by

cinchona amine 10 and using aqueous hydrogen peroxide as the oxidant.¹⁷ This method was routinely performed on a decagram scale and provided an excellent yield and enantioselectivity (e.r. 97:3) for keto-epoxide 11. The triflation of 11 was performed via formation of the lithium enolate and reaction with phenyl triflimide to give alkenyl triflate 8, which was sensitive and rapidly engaged in the next step. The epoxide was opened via nucleophilic substitution by an excess of L-alanine *tert*-butyl ester in trifluoroethanol at 65 °C. The ring-opening occurred with complete regioselectivity, consistent to a related example.¹⁶ Of note, 50–60% of the initially engaged L-alanine *tert*-butyl ester could be easily recovered. The secondary alcohol was then acetylated to give compound 12 as a 97:3 diastereoisomeric mixture matching the enantiomeric purity of epoxide 8, as expected from the stereospecificity of the epoxide opening. Cleavage of the *tert*-butyl ester under mildly acidic conditions furnished amino acid 7, which was isolated as a single diastereoisomer after recrystallization (79% overall yield from epoxide 8). Cyclodimerization of 7 mediated by BOP-Cl and collidine furnished the C₂-symmetric diketopiperazine 6 in high yield on a decagram scale. Bis-triflate 6 was then submitted to the key double C(sp³)-H alkenylation reaction. Reaction conditions were optimized, starting with standard conditions that proved successful in previous complex settings (see the Supporting Information for details).^{12b,c} In particular, use of the well-defined Pd(PCy₃)₂ complex (4 mol %), supplemented with free tricyclohexylphosphine (20 mol %), was found to be key to avoid premature catalyst decomposition, leading to unproductive mixtures including 5, unreacted 6, the mono-C-H alkenylation product, and protodetriflated products. Moreover, epimerization at the DKP ring was observed without additional free ligand when the reaction was carried out at the high concentrations required for upscaling. With this important modification, the double C-H activation occurred in high yield (93%) and in a reproducible manner on multigram quantities (8–9 g of 5 was typically isolated per batch). This contributed to a short and efficient (51% over seven steps) synthesis of intermediate 5, the structure and absolute configuration of which were confirmed by X-ray diffraction analysis.

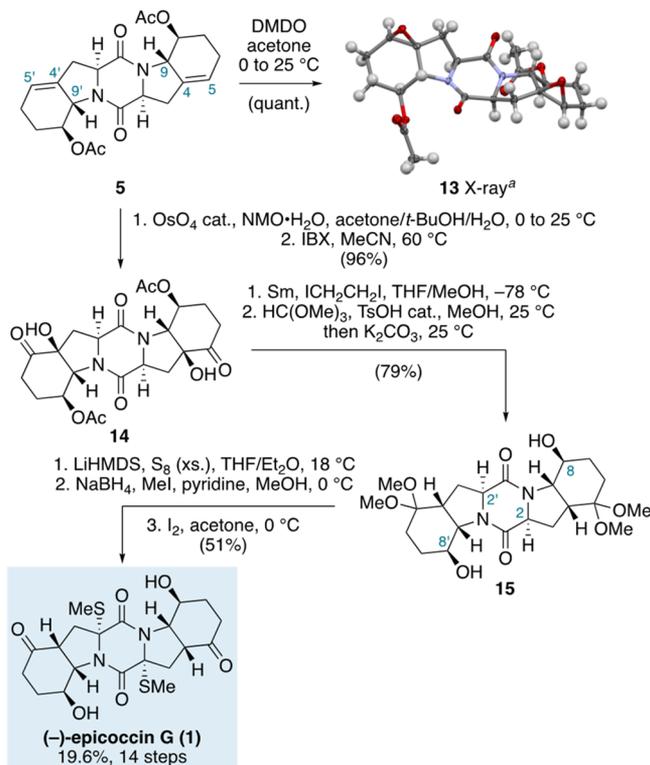
Scheme 1. Seven-Step Synthesis of Intermediate 5



^aMeasured by GC on a chiral stationary phase. ^bMeasured by ¹⁹F NMR. ^cThermal ellipsoids shown at 50% probability. BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphonic chloride.

After having secured an efficient access to intermediate **5**, we turned to the synthesis of (–)-epiccocin G (Scheme 2). Initial

Scheme 2. Synthesis of (–)-Epiccocin G



^aThermal ellipsoids shown at 50% probability. DMDO = dimethyldioxirane; NMO = *N*-methylmorpholine *N*-oxide; IBX = 2-iodoxybenzoic acid; LiHMDS = lithium bis(trimethylsilyl)amide.

attempts to perform the hydroboration/oxidation of the C4–C5/C4′–C5′ alkenes with various boranes were met with little success. In contrast, epoxidation occurred with high efficiency when DMDO was used, leading to the bis-epoxide **13** with complete *cis* diastereoselectivity with respect to the angular C9/C9′ hydrogens, as confirmed by X-ray diffraction analysis. However, attempts at regioselective ring-opening of these epoxides in the presence of various Lewis or Brønsted acids failed to provide useful synthetic intermediates.

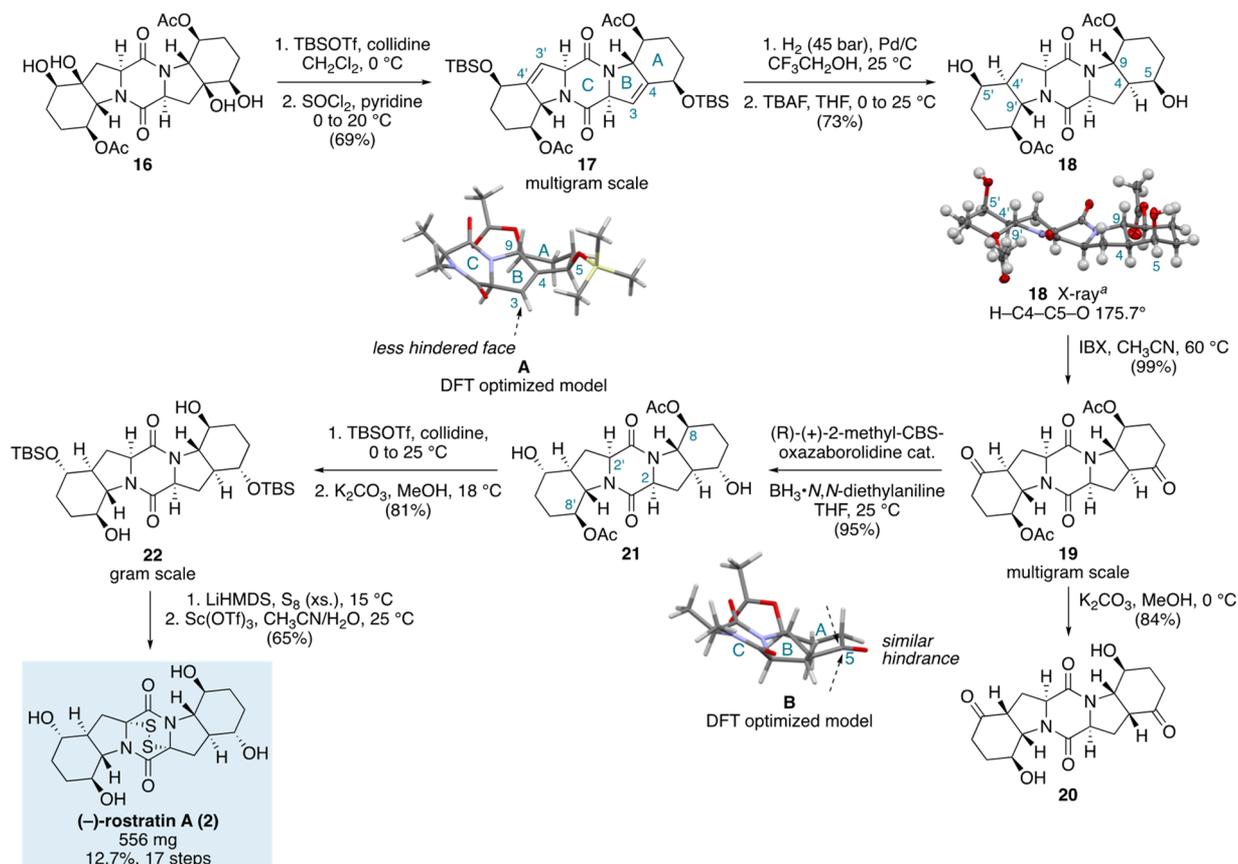
The best option was to perform an Upjohn dihydroxylation, which likewise occurred with complete *cis* diastereoselectivity, followed by oxidation of the secondary alcohols at C5/C5′ with IBX, which gave bis- α -hydroxyketone **14** in excellent yield (96% for two steps). Samarium(II) iodide-mediated reduction of these hydroxyketones¹⁸ then led to the thermodynamically favored *cis,cis*-fused diketone, which was protected as a dimethoxyketal and deacetylated in a one-pot fashion (**15**). The next important step was the introduction of the C2/C2′ thiomethyl groups, which was performed under conditions adapted from Nicolaou and co-workers.^{3,6} However, whereas the latter obtained a 1.4:1 mixture of *cis* diastereoisomers epimeric at both C2 and C2′ from a different precursor, the thiolation of **15** occurred with a high diastereoselectivity in favor of the desired C2 _{α} /C2′ _{α} diastereoisomer. This behavior could arise from a directing effect of the C8 and C8′ hydroxy groups, which according to molecular models are spatially close to the C2′ and C2 positions, respectively, and which were not present at the sulfuration stage in the Nicolaou synthesis.

Finally, iodine-mediated cleavage¹⁹ of the C5/C5′ ketals led to epiccocin G (**1**) in 51% yield for three steps. Overall, (–)-epiccocin G (**23** mg) was synthesized in 19.6% yield over 14 steps from cyclohexenone **9**, which represents a major improvement compared to the first synthesis (1.5% over 17 steps).^{3,6}

We then set out to explore the synthesis of (–)-rostratin A (Scheme 3). Different strategies were considered to install the challenging *trans,trans* ring junctions. In particular, attempts at performing directed hydrogenations of C3–C4/C3′–C4′ double bonds from allylic C5 _{α} /C5′ _{α} or C2 _{α} /C2′ _{α} hydroxy groups failed to provide the desired relative configuration. These failures led us to consider a sterically controlled hydrogenation of C3–C4/C3′–C4′ alkenes using C5 _{β} /C5′ _{β} -protected hydroxy groups. To this purpose, tetraol **16**, obtained from the above-mentioned Upjohn dihydroxylation of intermediate **5**, was protected as a bis-silyl ether, and SOCl₂-mediated dehydration furnished dialkene **17** in good yield on a multigram scale.

The examination of the DFT-optimized structure of an A-B-C truncated model **A** indicated that the β face of the C3–C4/C3′–C4′ alkenes should be efficiently shielded by the silyloxy groups. Consistent with this analysis, the hydrogenation of **17** led to the desired *trans,trans*-fused product, as determined by NOESY NMR. TBAF-mediated deprotection provided diol **18**, the *trans,trans* configuration of which was confirmed by X-ray diffraction analysis. At this stage, attempts to invert the configuration of the C5/C5′ alcohols by Mitsunobu or related reactions failed, due to the propensity of compound **18** to undergo dehydration, regenerating the C4–C5/C4′–C5′ double bonds. Indeed, the X-ray structure of **18** shows that the C5OH and C5′OH groups lie at axial positions of the chairlike rings A and E with a mean dihedral angle H–C4(C4′)–C5(C5′)–O of 175.7°, hence almost perfectly aligned for *anti*-elimination. To solve this problem, we turned to an oxidation–reduction strategy. IBX-mediated oxidation of diol **18** led to diketone **19**, which easily epimerized at C4/C4′ in the presence of acids or bases to give the thermodynamic *cis,cis* diastereoisomer, as shown with the formation of **20** upon transesterification from **19**. The truncated DFT-optimized model **B** showed no particular steric preference for the reduction of the C5 ketone in favor of the C5 _{α} alcohol, and indeed attempts at reducing diketone **19** with standard achiral reagents furnished unproductive diastereomeric mixtures. Consequently, we turned to the use of a reagent-based stereochemical control and found that the use of catalytic (*R*)-(+)-2-methyl-CBS-oxazaborolidine in combination with the borane-2,6-diethylaniline complex, conditions well adapted to aliphatic ketones,²⁰ afforded the desired C5 _{α} /C5′ _{α} diol **21** exclusively and without epimerization at C4/C4′. The cleavage of the C8/C8′ acetates led to the corresponding tetraol, but the latter was found to be insoluble in usual aprotic solvents required for the subsequent step. Overcoming this additional problem required a more indirect strategy. TBS diprotection and acetate cleavage afforded a less polar diol **22**, which was submitted to sulfuration with LiHMDS and S₈ as above for **15** in the synthesis of epiccocin G. However, in contrast to **15**, which provided a mixture of C2/C2′ epipolysulfides as reported by Nicolaou and co-workers,^{3,6} the desired 2,2′-epidissulfide was the major product of the sulfuration of the TBS-protected diol **22**. This fortunate result suppressed the need for an additional reduction/reoxidation sequence, which would have been otherwise necessary.

Scheme 3. Synthesis of (–)-Rostratin A



^aThermal ellipsoids shown at 50% probability. TBS = *tert*-butyldimethylsilyl; TBAF = *n*-Bu₄NF.

In addition, similar to epicoccin G, the sulfuration of **22** occurred with exclusive C2_α/C2'α diastereoselectivity. Finally, the scandium triflate-mediated²¹ mild cleavage of the TBS groups directly provided (–)-rostratin A (**2**), the physical properties of which matched the reported data.⁴ Rostratin A was synthesized for the first time in 12.7% yield over 17 steps. This synthetic sequence was reproducible and scalable, allowing to obtain 556 mg of synthetic rostratin A.

In conclusion, we successfully achieved the enantioselective total synthesis of the natural dithiodiketopiperazines (–)-epicoccin G and (–)-rostratin A in 14 and 17 steps, respectively, and with high overall yields from inexpensive starting materials. The common precursor to both target molecules was readily synthesized using an enantioselective organocatalytic epoxidation and a double C(sp³)–H activation as key steps. The most challenging target, rostratin A, possessing two *trans* ring junctions, was synthesized for the first time on a 500 mg scale thanks to a careful analysis of steric features and through a combination of substrate- and reagent-based stereochemical control. This study further demonstrates the power of C–H activation to, combined with more established methods, streamline the access to complex biologically active natural products.

■ ASSOCIATED CONTENT

Experimental procedures; spectral and characterization data for all compounds (PDF)

X-ray diffraction data for **5** (CIF)

X-ray diffraction data for **13** (CIF)

X-ray diffraction data for **18** (CIF)

Coordinate files for computational modeling (XYZ)

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Notes

The authors declare no competing financial interest.

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