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Enantioselective Total Synthesis of (−)-Acetylaranotin, a Dihydrooxepine Epidithiodiketopiperazine

Julian A. Codelli, Angela L. A. Puchlopek, and Sarah E. Reisman*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: The first total synthesis of the dihydrooxepine-containing epidithiodiketopiperazine (ETP) (−)-acetylaranotin (**1**) is reported. The key steps of the synthesis include an enantioselective azomethine ylide (1,3)-dipolar cycloaddition reaction to set the absolute and relative stereochemistry, a rhodium-catalyzed cycloisomerization/chloride elimination sequence to generate the dihydrooxepine moiety, and a stereoretentive diketopiperazine sulfenylation to install the epidisulfide. This synthesis provides access to (−)-**1** in 18 steps from inexpensive, commercially available starting materials. We anticipate that the approach described herein will serve as a general strategy for the synthesis of additional members of the dihydrooxepine ETP family.

The epidithiodiketopiperazine (ETP) natural products are a large and structurally diverse family of biologically active fungal metabolites that beautifully exemplify the interplay between molecular structure and function in nature (Figure 1).[1] One structural subgroup of the ETPs is characterized by the presence of a seven-membered dihydrooxepine ring and includes acetylaranotin (**1**),[2] MPC1001B (**2**),[3] and emethallicin A (**3**).[4] Compounds **1**−**3** exhibit an array of biological activities, ranging from the inhibition of viral RNA polymerase[2,5] to antiproliferative[3] and apoptotic[6] activity against various human cancer cell lines. The labile ETP core, in combination with the complex peripheral structures, renders these molecules challenging candidates for chemical synthesis. Indeed, ETPs containing the dihydrooxepine ring at their periphery have remained elusive as synthetic targets,[7] despite the fact that **1** was first isolated over 40 years ago and that the first synthesis of the biosynthetically related compound gliotoxin (**4**) was reported in 1976.[8] As part of a research program aimed at advancing the chemistry and biology of ETP natural products, we sought to develop a general strategy for the synthesis of the dihydrooxepine ETPs. In this communication, we report the results of our synthetic efforts, which have culminated in the first enantioselective total synthesis of (−)-acetylaranotin (**1**).

Our synthetic planning began with the retrosynthetic simplification of (−)-acetylaranotin (**1**) to a C_2-symmetric diketopiperazine intermediate, **8** (Scheme 1). In the forward sense, this disconnection reserves installation of the redox-active epidisulfide for the final stage of the synthesis and highlights the first tactical consideration: identification of conditions for oxidation of the diketopiperazine C−H bonds in the presence of the

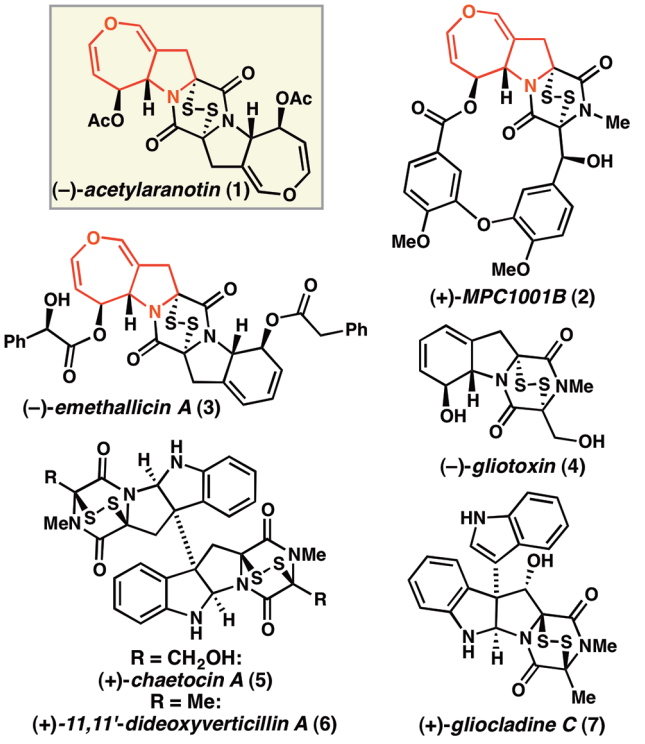

Figure 1. Epidithiodiketopiperazine (ETP) natural products.

dihydrooxepine moiety. The recent syntheses of pyrroloindoline ETPs (such as **5**, **6**, and **7** in Figure 1) have utilized strategies involving diketopiperazine oxidation and thiol trapping of presumed acyliminium intermediates under acidic conditions to achieve late-stage C−S bond formation.[9] Because of the sensitivity of dihydrooxepines to both oxidative and acidic conditions, this strategy was not expected to be feasible for the preparation of **1**. Since the dihydrooxepines of **8** were anticipated to be stable under basic conditions, we instead envisioned utilizing a modification of Schmidt's protocol for diketopiperazine enolization and trapping with S_8.[10]

Diketopiperazine **8** was envisioned to arise from the dimerization of two equivalents of protected amino ester **9** through a standard peptide coupling sequence. The preparation of **9** raises the second key tactical consideration: construction of the dihydrooxepine moiety. Relatively few general methods for dihydrooxepine

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formation have been disclosed, and these methods are typically constrained to substitution patterns that are undesirable in the context of preparing **1**.[11,12] Inspired by recent examples of transition metal-catalyzed heterocycloisomerization reactions of alkynes,[13] we envisioned preparing dihydrooxepine **9** from alkynal **10** (or an aldehyde surrogate) through a metal vinylidene-mediated 7-*endo* cycloisomerization.[14,15] Alkynal **10** was expected to arise from pyrrolidine **11**, the product of a catalytic asymmetric (1,3)-dipolar cycloaddition reaction between *tert*-butyl acrylate (**12**) and the azomethine ylide derived from ethyl glycinate (**14**) and cinnamaldehyde (**13**).

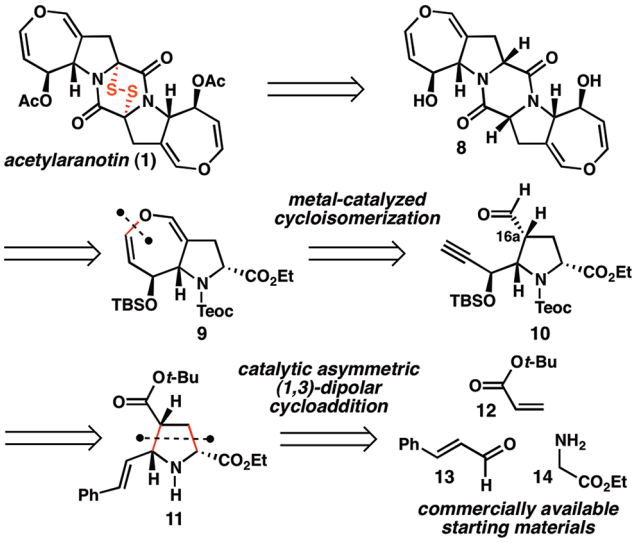
In the forward sense, exposure of cinnamaldimine **15**, which was pregenerated from ethyl glycinate (**14**) and cinnamaldehyde (**13**), to *tert*-butyl acrylate (**12**) in the presence of catalytic copper iodide and brucin-OL[16] as the chiral ligand provided the corresponding *endo*-pyrrolidine in 50% yield with 96% ee (Scheme 2). Subsequent cleavage of the *tert*-butyl group using trifluoroacetic acid (TFA) furnished TFA salt **16**. Notably, during the trituration process utilized to isolate **16**, the enantiomeric excess was enriched to >98%. Although the yield of the (1,3)-dipolar cycloaddition reaction was modest, the inexpensive starting materials and catalyst system employed in this transformation meant that it could be routinely conducted on a multigram scale to furnish ample quantities of **16**. Protection of the amine as the trimethylsilylethyl carbamate and ozonolytic cleavage of the alkene delivered hydroxylactone **17** in 77% yield over two steps.

To incorporate the required alkyne for the cycloisomerization reaction, hydroxylactone **17** was treated with excess ethynylmagnesium bromide; a standard acidic workup resulted in spontaneous lactonization. Unfortunately, the major lactone diastereomer (not shown) possessed the undesired stereochemistry at C13 (acetylaranotin numbering) for elaboration to the natural product.[17] Whereas efforts to override the observed diastereoselectivity by varying the reaction parameters failed to produce synthetically useful quantities of **18**, a procedure involving in situ Mitsunobu lactonization[18] of the transiently formed hydroxy acid was more fruitful, delivering **18** in 76% isolated yield. Lactone **18** was then reduced to diol **19** with $NaBH_4$ in EtOH, and bis-silylation with TBSOTf followed by selective cleavage of the primary silyl ether furnished alcohol **20**. Finally, oxidation of the primary alcohol with Dess–Martin periodinane (DMP)[19] afforded aldehyde **10** (see Scheme 1) in excellent yield.[20]

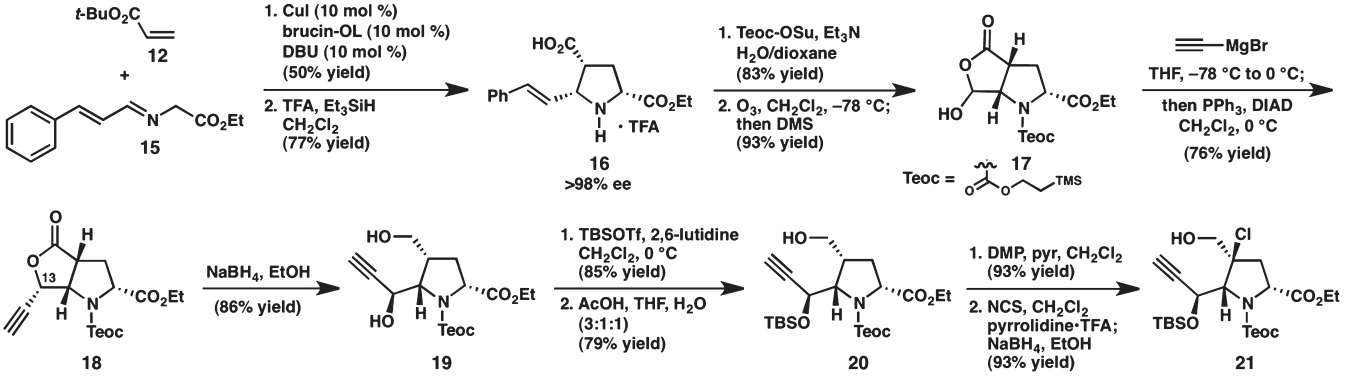
With access to aldehyde **10**, we were poised to study the key cycloisomerization reaction. Unfortunately, dihydrooxepine formation was not observed under any of the conditions screened; in all cases, the substrate was either recovered as a mixture with its C16a epimer or underwent complete decomposition.[21] We therefore set out to design an aldehyde surrogate that would demonstrate the desired reactivity but would also incorporate the correct oxidation state for conversion to the dihydrooxepine. Given that alkynols have been shown to undergo vinylidene-mediated cycloisomerization under a variety of conditions,[14] we turned our attention to chlorohydrin **21** as a potential substrate. Treatment of aldehyde **10** with *N*-chlorosuccinimide (NCS) and pyrrolidine·TFA gave the α-chloroaldehyde as a single diastereomer, which was reduced in situ with $NaBH_4$ to deliver alkynol **21** in excellent yield (Scheme 2). After screening several catalysts and solvents, we were pleased to find that exposure of a solution of **21** in *N*,*N*-dimethylformamide (DMF) to catalytic $[Rh(cod)Cl]_2$ and tris(4-fluorophenyl)phosphine at 85 °C provided the corresponding chlorotetrahydrooxepine **22** in 88% yield (Scheme 3).[22] After considerable experimentation, elimination of the chloride was achieved using LiCl and Li_2CO_3 at 100 °C in DMF, yielding the desired dihydrooxepine **9**.

What remained in the synthesis of **1** was diketopiperazine formation, acetylation, and installation of the epidisulfide. Our original plan called for conversion of **9** to the corresponding amino acid and dimerization of two identical monomers. To this end, chemoselective cleavage of the Teoc group in the presence

Scheme 1. Retrosynthetic Analysis for Acetylaranotin (1)



Scheme 2. Enantioselective Synthesis of Pyrrolidine 21



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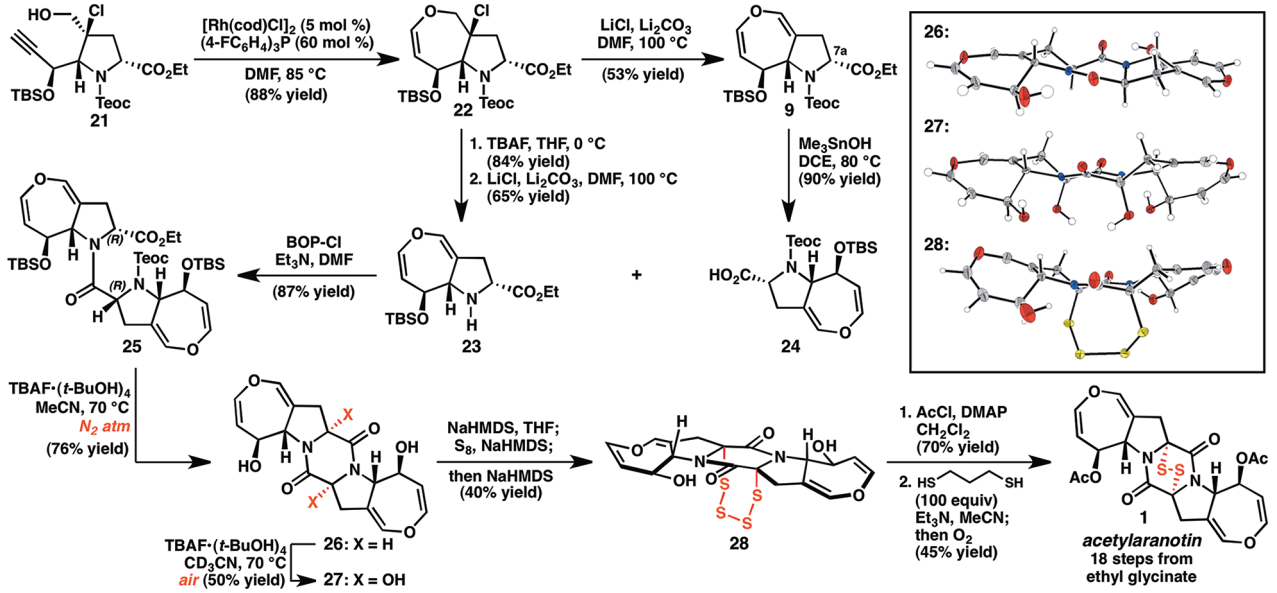
Scheme 3. Completion of the Synthesis of Acetylaranotin (1)



of the TBS ether was necessary. Unfortunately, exposure of **9** to a variety of conditions provided mixtures of mono- and bis-desilylated products. In contrast, treatment of chlorotetrahydrooxepine **22** with tetrabutylammonium fluoride (TBAF) at 0 °C cleanly provided the free amine (Scheme 3). Subjection of the amine to the previously optimized chloride elimination conditions delivered dihydrooxepine **23** in 65% yield. Hydrolysis of the ethyl ester using lithium hydroxide in methanol gave the corresponding amino acid, but attempts to form the diketopiperazine by direct dimerization were unfruitful.

Instead, a stepwise approach was pursued in which amine **23** was coupled with carboxylic acid **24** using standard peptide coupling conditions to give **25** (Scheme 3). After a survey of fluoride sources, we were pleased to find that treatment of dipeptide **25** with TBAF·$(t\text{-BuOH})_4$[23] in acetonitrile at 70 °C effected global desilylation and cyclization to deliver a C_2-symmetric compound as the major product (isolated in 27% yield). Interestingly, initial characterization of this compound using standard NMR techniques and high-resolution mass spectrometry suggested that it was a *syn*-diol, the result of a double C−H oxidation process. On the basis of the hypothesis that the oxidant was oxygen in the ambient atmosphere, the reaction was repeated under a nitrogen atmosphere using rigorously degassed solvent, which provided diketopiperazine **26** as a single diastereomer in 76% yield. The structure of **26** was confirmed by single-crystal X-ray diffraction (XRD). Notably, the (*S*,*S*)-stereochemistry of the central diketopiperazine is the result of epimerization at both of the diketopiperazine methine positions under the cyclization conditions. At this time, it is uncertain whether epimerization occurs prior to cyclization of the dipeptide—cyclization of the (*S*,*S*)-configured dipeptide could potentially be more facile than that of the starting (*R*,*R*)-diastereomer—or subsequent to diketopiperazine formation to give a thermodynamically favored product. Isolation and resubjection of **26** to TBAF·$(t\text{-BuOH})_4$ in deuterated acetonitrile at 70 °C under air provided the same oxidation product observed previously, which was confirmed by XRD analysis to be *syn*-diol **27**. Whether this double C−H oxidation proceeds through a radical or anionic mechanism is currently unclear, and understanding this process is the subject of ongoing research in our laboratory. Regardless, the high diastereoselectivity observed in the formation of diketopiperazine **26** is impressive considering the seemingly flat nature of the pentacyclic ring system. Moreover, the high apparent diastereoselectivity of the dihydroxylation suggested that the analogous dithiolation might also proceed stereoselectively.[24]

With diketopiperazine **26** in hand, our attention turned to the epidisulfide formation. In the event, a solution of **26** in tetrahydrofuran (THF) was treated with sodium hexamethyldisilazide (NaHMDS), and the resulting solution was added to a mixture of NaHMDS and S_8, after which additional NaHMDS was added (Scheme 3).[25] ^{1}H NMR analysis of the crude reaction mixture indicated that the major product was a C_2-symmetric compound. Upon isolation of this compound, single-crystal XRD determined it to be tetrasulfide **28**, in which C−S bond formation had occurred to give the relative stereochemistry found in **1**. Tetrasulfide **28** was unstable to most standard reductants; for example, exposure to $NaBH_4$ produced a complex mixture of decomposition products. Instead, bisacetylation of **28** using acetyl chloride furnished the diacetate, and the tetrasulfide was reduced under mild conditions using propanedithiol and triethylamine in acetonitrile. Aerobic oxidation of the resulting dithiol delivered the natural product, **1**. The spectroscopic data for synthetic (−)-acetylaranotin were identical to the original isolation data.

In conclusion, we have achieved the enantioselective total synthesis of (−)-acetylaranotin (**1**), the first total chemical synthesis of any dihydrooxepine-containing ETP natural product, in 18 steps from inexpensive, commercially available materials. Essential to the development of this route was the successful execution of a rhodium-catalyzed cycloisomerization/chloride elimination sequence to furnish the dihydrooxepine ring and complete the monomer subunit (**9**). This strategy allowed us to exploit the power of an azomethine ylide (1,3)-dipolar cycloaddition reaction in order to enantio- and diastereoselectively construct the densely functionalized pyrrolidine scaffold of the requisite alkynyl alcohol substrate **21**.

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Furthermore, we determined that upon global deprotection, dipeptide **25** could be readily cyclized with concomitant epimerization to afford diketopiperazine **26**. Notably, direct sulfenylation of diketopiperazine **26** occurs with *complete retention of stereochemistry* to provide epitetrathiodiketopiperazine **28**. Investigations directed toward the implementation of these strategies and methods for the synthesis of related dihydrooxepine-containing ETP natural products are ongoing.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization and spectral data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
reisman@caltech.edu

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(20) Lactone **18** could be selectively reduced to the corresponding lactol; however, we were unable to advance this compound to the required aldehyde **10**.

(21) Several transition metal catalysts in the presence and absence of ligands and additives were evaluated under a variety of conditions, including $[Rh(cod)Cl]_2$, $[Rh(cod)(MeCN)_2]BF_4$, $CpRuCl[(4\text{-}FC_6H_4)_3P]_2$, $(CO)_5W{=}C(OMe)Me$, AuCl, $Pd(OAc)_2$, CuI, and AgOTf.

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