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

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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.
intermediates under acidic conditions to achieve late-stage C-S bond formation. Due to the sensitivity of dihydrooxepines to both oxidative and acidic conditions, this strategy was not expected to be feasible for the preparation of acetylaranotin (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 S8.

Diketopiperazine 8 was envisioned to arise from the dimerization of two equivalents of protected amino ester 9 through a standard peptide coupling sequence. Preparation of 9 raises the second key tactical consideration: construction of the dihydrooxepine moiety. Relatively few general methods have been disclosed for dihydrooxepine formation, and these methods are typically constrained to substitution patterns that are undesirable in the context of preparing 1. Inspired by recent examples of transition metal-catalyzed heterocycloisomerization reactions of alkynes, we envisioned preparing dihydrooxepine 9 from alkylnal 10 (or from an aldehyde surrogate) through a metal vinylidene-mediated 7-endo cycloisomerization. Alkylnal 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, pre-generated from ethyl glycinate (14) and cinnamaldehyde (13), to tert-butyl acrylate (12) in the presence of catalytic copper iodide and brucin-OL as the chiral ligand provided the corresponding endo-pyrrolidine in 50% yield and 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 cyclodaddition reaction was modest, the inexpensive starting materials and catalyst system employed in this transformation meant that it could be routinely conducted on 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. 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 of the transiently formed hydroxy acid was more fruitful, delivering 18 in 76% isolated yield. Lactone 18 was then reduced to diol 19 with NaBH4 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 afforded aldehyde 10 (see Scheme 1) in excellent yield.

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. We therefore set out to design an aldehyde surrogate that would demonstrate the desired reactivity, but that 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, we turned our attention to chlorohydrin 21 as a potential substrate. Treatment of aldehyde 10 with NCS and pyrrolidine•TFA gave the α-chloroaldehyde as a single diastereomer, which was reduced in situ with NaBH4 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 the substrate (21) in DMF to catalytic [Rh(cod)Cl]₂ and tris-(4-fluorophenyl)-phosphine at 85 °C provided the corresponding chloro-tetrahydrooxepine (22) in 88% yield (Scheme 3). After considerable experimentation, elimination of the chloride was achieved using LiCl and Li₂CO₃ at 100 °C in DMF to yield 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 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 chloro-tetrahydrooxepine 22 with 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, however 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-BuOH)₄ in acetonitrile at 70 °C effected global desilylation and cyclization to deliver a C₂-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. Based on 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. 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-BuOH)₄ in deuterated acetonitrile at 70 °C under air provided the same oxidation product observed previously, which was confirmed to be syn-diol 27 by X-ray diffraction analysis. 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, attention turned to the epidisulfide formation. In the event, a THF solution of 26 was treated with sodium hexamethyldisilazide (NaHMDS) and the resulting solution was added to a mixture of NaHMDS and S₈, after which additional NaHMDS was added (Scheme 3).²⁵ ¹H NMR analysis of the crude reaction mixture indicated that the major product was a C₂-symmetric compound. Upon isolation of this compound, single crystal X-ray diffraction 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 sodium borohydride produced a complex mixture of decomposition products. Instead, bis-acetylation 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 are 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 requisite alkynyl alcohol substrate 21.

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 towards the implementation of these strategies and methods for the synthesis of related dihydrooxepine-containing ETP natural products are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


17. See Supporting Information for details.


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 metals 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)]2BF4, CpRuCl(4-FC6H4)P3, (CO)3W=C(OMe)Me, AuCl, Pd(OAc)2, CuI, and Ag-OTf.

22. Conditions were adapted from Trost’s conditions for the preparation of indoles and benzofurans: Trost BM, McClory A. Angew Chem, Int Ed. 2007; 46:2074–2077.


24. Efforts to convert diol 27 to the corresponding epi-disulfide through standard thiol exchange conditions were unsuccessful; decomposition of the starting material was observed under both Lewis and Brønsted acid-mediated conditions.

Figure 1.
Epidithiodiketopiperazine (ETP) natural products.
Scheme 1.
Retrosynthetic analysis for acetylaranotin (1).
Scheme 2.
Enantioselective synthesis of pyrrolidine 21.
Scheme 3.
Completion of the synthesis of acetylaranotin (1).