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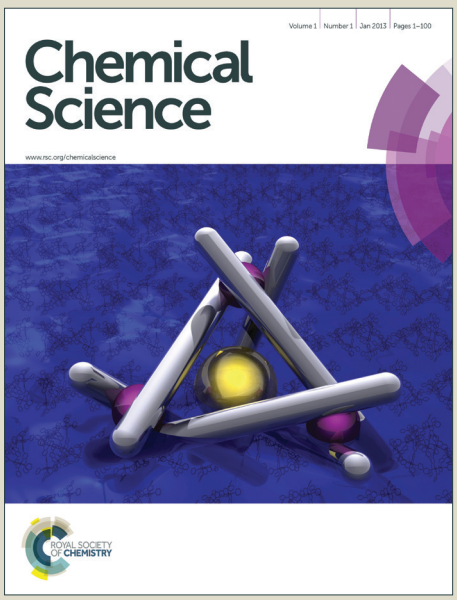

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EDGE ARTICLE

Development of a Route to Chiral Epidithiodioxopiperazine Moieties and Application to the Asymmetric Synthesis of (+)-Hyalodendrin

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The epidithiodioxopiperazine skeleton is found in a variety of biologically active compounds. Despite numerous attempts at constructing this highly functionalized structure within a bicyclo[2.2.2]octane skeleton, asymmetric synthesis of this unique functionality remains problematic. Our synthetic studies have led to the development of efficient methods for asymmetric preparation of an epidithiodioxopiperazine skeleton, which was successfully applied to the first asymmetric synthesis of (+)-hyalodendrin.

Introduction

Epidithiodioxopiperazine (ETP) alkaloids possess a unique architecture involving a central bicyclo[2.2.2]octane moiety containing a disulfide bridge, that is believed to be causative of a broad spectrum of bioactivities (Figure 1, **1**–**6**).[1] In addition to displaying antifungal and selective antimyeloma activities,[2] ETP alkaloids display antitumor activity via the inhibition of several molecular targets.[3] Considerable interest from the synthetic community has inspired the development of several synthetic strategies for preparing the core bicyclo[2.2.2]octane structure. We began our research of the ETP natural products in an effort to develop a novel methodology for the enantioselective construction of an ETP core structure that would facilitate access to these intriguing molecules. To this end, we selected hyalodendrin (**1**), one of the simplest members of this class of alkaloids, as an initial synthetic target. Hyalodendrin (**1**) was isolated in 1974 from *Hyalodendron sp.* (FSC-601) by Strunz *et al*.[4] and was shown to display a broad spectrum of antimicrobial activity.[5] The isolation of the opposite enantiomer, A26771A (**2**), from *Penicillium turbatum* was reported, and **2** was found to display antiviral and antibacterial activity,[6] further underscoring the mysterious biogenetic nature of the source of the epidisulfide moiety.[7,8]

In the recent total synthesis of ETP alkaloids, the sulfur atoms of the epidisulfide moiety were introduced to the diketopiperazine core by taking advantage of the steric effects of the neighboring stereo center(s) in the molecule, as shown in the transformation from **7** to **8** (Scheme 1a). The resultant stereochemistry of the epidisulfide is not necessarily associated with the original stereochemistry derived from the diketopiperazine or amino acids. Thus, a majority of the reports describing the enantioselective construction of an ETP core involved a rigid framework that provided stereocontrol over the product.[9] On the other hand, most synthetic studies conducted without such rigid frameworks resulted in racemic mixtures of the ETPs.[10,11]

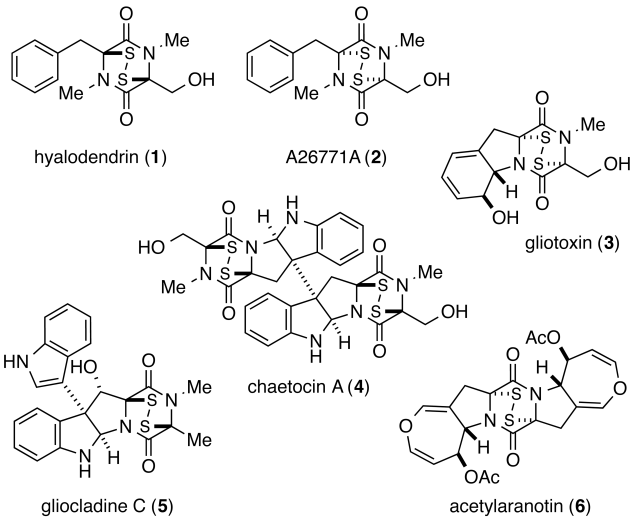
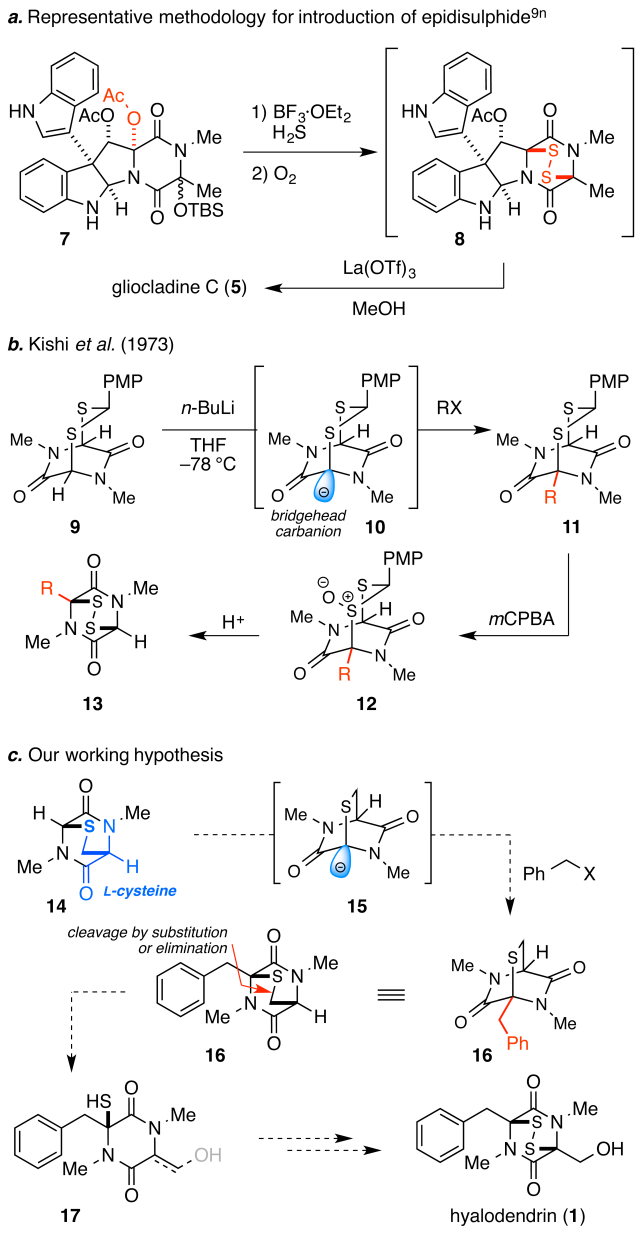


Figure 1. Epidithiodioxopiperazine Alkaloids.

Previous syntheses of hyalodendrin were racemic[12] due to the absence of neighboring structures that could direct the stereochemistry of the thiohemiaminal. The enantioselective synthesis of hyalodendrin (**1**) as well as A26771A (**2**) is challenging and offers a chance to develop a novel methodology for the construction of an epidithiodioxopiperazine moiety.

Our strategy for the synthesis of **1** relies upon the configurational stability of the highly nucleophilic bridgehead anion which was inspired by the unique protocol reported by Kishi[13] for constructing an ETP core structure (Scheme 1b). The procedure involves the *in situ* generation of a bridgehead anion **10** which reacted with an electrophile to provide **11**, and subsequent oxidation and acidic treatment of the sulfoxide **12** afforded the functionalized ETP **13**. We thus hypothesized that the L-cysteine-derived bicyclo[2.2.2]octane unit **14** would serve as a precursor to the bridgehead carbanion **15** (Scheme 1c). Alkylation at the bridgehead position would establish the

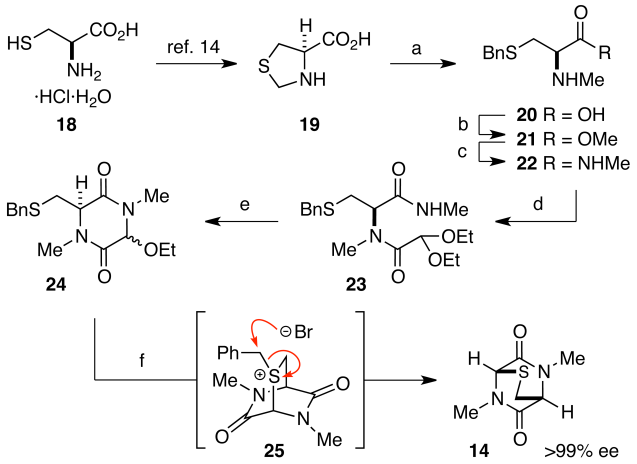
stereochemistry of the hemithioaminal moiety in **16**. Since introduction of the second sulfur atom in ETP has been shown to take place preferentially from the same side of the first sulfur atom,[10c] cleavage of the bicyclic core of **16** via a ring-opening transformation was envisioned en route to the introduction of the second sulfur atom onto **17**. This step would allow the formation of the epidisulfide to form the ETP core structure of **1**.



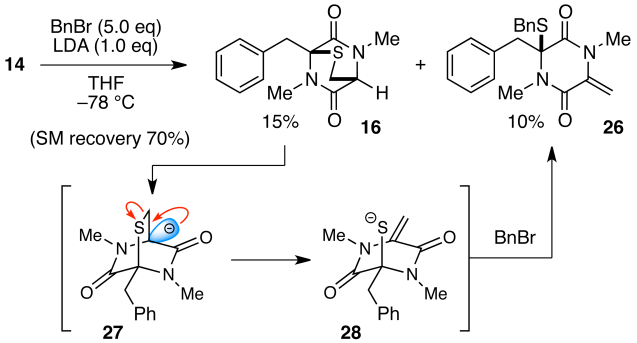
Scheme 1. Strategy for the construction of the ETP Core.

Results and discussion

Our approach to **1** commenced with the synthesis of the key intermediate **14** bearing an unprecedented bicyclo[2.2.2]octane structure (Scheme 2). L-cysteine hydrochloride monohydrate (**18**) was transformed in one step to the thiazolidine-4-carboxylic acid (**19**).[14] Reduction of the C–S bond under the Birch reduction conditions gave a thiolate that was directly benzylated to afford **20**.[15] The carboxylic acid **20** was converted to *N*-methyl amide **22** via the aminolysis of the methyl ester **21**. To construct the diketopiperazine core structure as well as the bridging hemithioaminal moiety, installation of a glyoxylate unit was envisioned. After examining the ring closure reaction in an effort to assemble the thioaminal bridgehead of the bicyclo[2.2.2]octane moiety, we identified the conditions that promoted an efficient two-step transformation to **14**. Thus, diethoxyacetate **23** was synthesized and first treated with *p*-TsOH to form the diketopiperazine core in **24**. This was then subjected to a cyclization reaction using TMSBr as a uniquely effective reagent. An acyliminium ion, generated by trimethylsilylation of the ethoxy group, was intercepted by the benzyl sulfide to form the bicyclic sufinium ion **25**, which underwent debenzylation to form the desired bicyclo[2.2.2]octane product **14**.



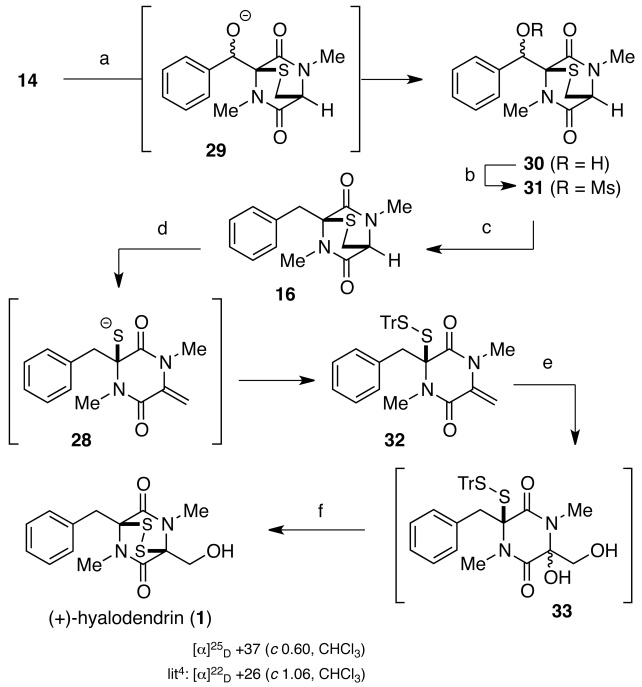
Scheme 2. Construction of the bicyclo[2.2.2]octane moiety. (a) Na/NH_3, H_2O, –78 °C; NH_4Cl, BnCl; (b) $SOCl_2$, MeOH, reflux; $NaHCO_3$ aq., 84% (2 steps); (c) $MeNH_2$, MeOH, rt; (d) $(EtO)_2CHCOOH$, DCC, CH_2Cl_2, rt, 84% (2 steps); (e) CSA, toluene, 80 °C; (f) TMSBr, MeCN, reflux, 75% (2 steps).



Scheme 3. Attempted direct alkylation and unexpected ring opening reaction.

With the key intermediate **14** in hand, we next examined the alkylation of the bridgehead anion **15** (Scheme 3). Quite unexpectedly, in addition to the desired benzylated compound **16**, the ring-opened byproduct **26** was obtained. Our deuteration experiment of **14** (LDA (1.0 eq), THF, –78 °C, 5 min; CD_3OD) indicated the selective deprotonation at the thioaminal bridgehead (47% deuteration). Thus the formation of **26** could be explained

by the ring cleavage of the bridgehead anion **27**, generated by deprotonation of the benzylated product **16**, and the subsequent benzylation of the resultant thiolate **28**. This result clearly implicated the difficulties associated with the low reactivity of alkylation and competing facile ring opening of **16**.



Scheme 4. Alkylation of a bridgehead anion and endgame. (a) PhCHO, LDA, THF, –78 °C, 56%; (b) MsCl, TMEDA, CH_2Cl_2, rt, 92%; (c) TMSOTf, Et_3SiH, CH_2Cl_2, reflux, 66%; (d) LDA, THF, –78 °C to 0 °C; TrSCl, 71%; (e) OsO_4, NMO, acetone, H_2O, rt; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 49% (2 steps).

We hypothesized that this obstacle could be circumvented by using an aldehyde as an electrophile, which would lead to the formation of the electron-rich alkoxide **29**, thereby retarding deprotonation at the opposite bridgehead (Scheme 4). Eventually, this strategy successfully gave the desired secondary alcohol **30** as the only product. The hydroxy group situated at the benzylic position was activated as the mesylate **31** and was reduced by treatment with TMSOTf and Et_3SiH. Upon treatment with 1.0 equivalent of LDA at –78 °C, **16** underwent a facile ring cleavage to give the thiolate **28**. Since the corresponding thiol was unstable under the aerobic conditions, tritylsulfenyl chloride (TrSCl)[16] was added to the reaction mixture to furnish the stable trityl disulfide **32**. Since the disulfide in **32** did not survive the epoxidation conditions, dihydroxylation of the olefin using a catalytic amount of OsO_4 with NMO was performed, instead, to give a diastereomeric mixture of diols **33**. Finally, the first enantioselective synthesis of (+)-hyalodendrin (**1**) was completed by treatment of **33** with $BF_3{\cdot}OEt_2$ according to Movassaghi's protocol.[9d]

Conclusions

We have established a novel method for the construction of the epidithiodioxopiperazine moiety. The chemistry of the bridgehead anion was used in such a way that the stereochemistry of the ETP product was derived solely from the stereochemistry of the natural L-cysteine, regardless of the neighboring stereocontrolling moieties present within the molecule. This concept has been clearly exemplified in the first asymmetric synthesis of (+)-hyalodendrin (**1**).

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