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A Modular Construction of Epidithiodiketopiperazines

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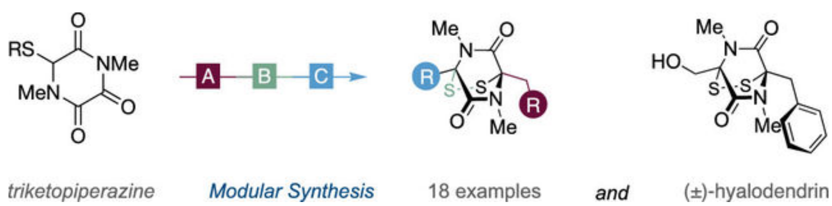
Abstract

Epidithiodiketopiperazines (ETPs) possess remarkably diverse biological activities and have attracted significant synthetic attention. The preparation of analogues is actively pursued; however, they are structurally challenging, and more direct and modular methods for their synthesis are desirable. To this end, the utility of a bifunctional triketopiperazine building block for the straightforward synthesis of ETPs is reported. A modular strategy consisting of enolate alkylation followed by site-selective nucleophile addition enables the concise synthesis of (±)-hyalodendrin and a range of analogues.

Graphical Abstract



Synthetic routes to epidithiodiketopiperazines (ETPs) have been intensely pursued. These fungal metabolites comprise 20 distinct families that are all characterized by a synthetically imposing disulfide-bridged diketopiperazine (DKP) (Figure 1a).[1] The unusually stable transannular disulfide embedded within this heteroatom-rich motif **1** possesses a **0**° CSSC dihedral angle, which demands a fully eclipsed arrangement of lone pairs on the adjacent S atoms and confers significant strain energy.[2] This allows ETPs to engage in redox cycling to produce reactive oxygen species, ligate and eject Zn(II), or participate in rapid and reversible disulfide exchange reactions with the cysteine residues of proteins.[3] The ETP core is solely responsible for the diversity of observed biological activities. For example, the enantiomers of hyalodendrin 2 are naturally occurring and have been isolated from different fungal sources, and they exhibit enantiomer-specific antimicrobial and antiviral/antibacterial

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Experimental procedures; characterization data; NMR spectra (PDF)

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activities.[4] Similarly, the annulated ETPs dehydrogliotoxin **3**[5] and glionitrin **4**[6] constitute antipodal forms and differ only in arene decoration. The former exhibits antibacterial activity, whereas the latter is antibiotic/antitumor active. Chetomin **5**, a rare heterodimeric indole containing two different ETP core units, has attracted significant interest as a chemotherapeutic agent.[7] It is a potent *in vitro* and *in vivo* inhibitor of hypoxia inducible factor 1α (HIF-1α), a transcription factor that is essential to the growth of solid tumors.[3g,8] Non-natural ETPs have also attracted significant attention.[9] Overman and co-workers have developed NT-1721 (**6**), a candidate ETP with potent activity against acute myeloid leukemia.[9a,b] Finally, Matile and co-workers have employed the unique properties of ETPs for strain-promoted intracellular probe delivery (e.g., **7**).[10] This occurs with such extraordinary cellular uptake efficiencies that endosomal capture is avoided, leading to ETPs being harnessed as "unstoppable" transporters for thiol-mediated cellular uptake. Overall, it is clear that with such unique reactivity and properties ETPs will continue to serve as target compounds for therapeutic development and as design scaffolds for chemical biology applications. However, bespoke ETP synthesis continues to present significant synthetic challenges, which restrict their widespread potential to address biological problems. In order to remedy this, we herein report an experimentally straightforward, concise, and modular protocol for the preparation of ETPs.

The synthesis of ETPs **9** typically involves the elaboration of preassembled diketopiperazines **8** via electrophilic (S^+) or nucleophilic (S^-) incorporation (Figure 1b).[11] However, achieving site selectivity, functional group tolerance, and necessary *syn* stereoselectivity using such strategies can be challenging. Furthermore, the assembly of DKPs comprising different amino acids, as well as the preparation of bespoke amino acids themselves, can be challenging and requires significant synthetic investment.[12] Triketopiperazines[13] (TKPs) are rigid scaffolds that possess only one enolizable site. This removes the issue of site-selective enolization that complicates diketopiperazine (DKP) elaboration and should permit straightforward alkylation via the derived enolate **11** (Figure 1c). In addition, site-selective nucleophilic carbonyl addition is possible due dipole minimization of the 1,4-configured bis-amide motif, which confers disparate carbonyl electrophilicities to the vicinal dicarbonyl motif within the TKP (see **11**).[14] Tertiary alcohols resulting from nucleophile addition would serve as precursors to electrophilic *N*-acyliminium ions, which can be trapped by pendant sulfur nucleophiles to forge the challenging transannular disulfide.[15] We expected that successful exploitation of this bifunctional reactivity within a common S-substituted TKP (**10**) would result in the straightforward preparation of both natural and non-natural *N,N′*-dimethyl ETPs (**12**). Herein, we report the successful realization of this goal in which a single TKP precursor can be elaborated via chemoselective functionalization events.

We began our investigations into the use of TKPs as useful synthetic intermediates by targeting the simplest of the ETPs, (±)-hyalodendrin **2** (Scheme 1).[16] This naturally occurring phenylalanine–serine-derived ETP exhibits enantiomer-specific antimicrobial and antiviral/antibacterial activity. Beginning with *N,N′*-dimethyl triketopiperazine **13**, which was readily prepared in two steps from sarcosine methyl ester,[17] we sought to install a suitably protected thiol, which would later serve as an anchor for transannular disulfide assembly. Treatment of **13** with LiHMDS followed by trapping of the resulting enolate with Clive's silyl ether protected sulfenating reagent[18] efficiently provided *S*-substituted TKP **14** in excellent yield on **5** g scale. A second enolization with LiHMDS was then performed, and the resulting *S*-substituted enolate was trapped with benzyl bromide to provide the fully substituted carbon **15** that constitutes the phenylalanine subunit of hyalodendrin **2**. Due to the limited solubility of the intermediate lithium enolate, the addition of DMPU to this second enolate alkylation was necessary to ensure consistently high yields. The next step involved installation of the crucial disulfide. Deprotection with a range of fluoride sources (TBAF, KHF_2, HF, HF·pyr, CsF) was efficient; however, the instability of resulting thiol precluded efficient stepwise reaction with tritylsulfenyl chloride and resulted in mixtures of **16** and the corresponding desulfenylated product.[19] Fortunately, this could be overcome by trapping the thiolate *in situ*; dropwise addition of TBAF to a solution of **15** and tritylsulfenyl chloride (TrSCl) in THF resulted in rapid and clean conversion to trityl-protected disulfide **16**. Next, and in line with our synthetic design we required site selective addition of an appropriate nucleophile to the vicinal dicarbonyl moiety. After significant experimentation we established that treatment with methylmagnesium bromide gave tertiary alcohols **17** exclusively as an inconsequential 1:1 mixture of diastereomers. Organocopper and organozinc nucleophiles were ineffective whereas organolithium regents resulted a myriad of products presumably due to the highly oxophilicity of Li^+. Thereafter, dehydration upon treatment of this mixture with a stoichiometric quantity of *p*-toluenesulfonic acid afforded a 3:1 mixture of both the desired dehydrated product 18 and the corresponding bridged disulfide product.[20] However, employment of substoichiometric quantities of *p*-toluenesulfonic acid effectively suppressed disulfide formation and reliably provided the alkene 18 in 58% (over two steps). Upjohn dihydroxylation followed by treatment of the resulting diols **19** (dr 1:1) with $BF_3{\cdot}OEt_2$ delivered (±)-hyalodendrin (2) in 70% yield via the putative *N*-acyliminium ion **20**.[21] In order to ensure efficient epidisulfide formation, purification of the intermediate diols **19** was necessary; direct exposure of the crude diols to $BF_3{\cdot}OEt_2$ resulted in drastically lower conversion. Attempts to replace $BF_3{\cdot}OEt_2$ with $Hf(OTf)_4$,[22a] milder Lewis acid, were unsuccessful and resulted in no reaction.

Our synthesis of (±)-hyalodendrin 2 establishes the utility of bifunctional S-substituted triketopiperazine **14**, and we next sought to exploit this in an operationally straightforward and modular synthesis of a focused library of ETP analogues of general structure **22** (Scheme 2). Starting from **14**, diversification via a modular three-step alkylation/disulfide formation/Grignard addition–ring closure sequence provided a range of ETP analogues in useful yield on preparative scale. First, a range of electrophiles was explored for the initial alkylation of the lithium enolate derived from **14** (step A, substituents in red). Benzyl derivatives bearing substitution at the *ortho*, *meta*, and *para* positions (**23**–**26**) were well tolerated, with both electron deficient (**24**) and electron rich (**25**) and halogenated (**23**, **26**) providing similar levels of efficiency. Disubstituted benzylic (**28**), *π*-extended naphthylic (**27**), and *N*-heterocyclic (**29**) electrophiles could also be employed, albeit in more modest yield.

Allylic and propargylic halides are also effective electrophiles (**30** and **31**) and provide potential handles for further functionalization within the context of broader SAR studies.

These differentially alkylated TKPs were then converted to the corresponding ETPs via trityl disulfide formation, followed by site-selective nucleophilic addition of methylmagnesium bromide and hafnium(IV) triflate-mediated ring closure using a modification of Movassaghi's protocol.[22] The use of milder and more functional group tolerant $Hf(OTf)_4$, where the number of equivalents of could be reduced from 10 to 1.5 equiv is noteworthy. During our hyalodendrin synthesis (cf. Scheme 2 **19** → **2**) this Lewis acid was ineffective for the conversion of 1,2-diols **19**; however, it functions effectively here in the rapid and chemoselective activation of lone tertiary alcohols.

We next explored the nucleophile scope by treating benzylated and trityl-protected disulfide TKP **15** with a range of Grignard reagents, prior to epidisulfide formation. Both alkyl and aryl Grignard reagents performed well within the reaction and in each case the corresponding ETP was obtained with useful efficiency. Addition of *i*-butylmagnesium bromide to the benzyl-substituted TKP **15** resulted exclusively in hydride delivery and gave the phenylalanine–glycine containing ETP **32**[11f] following ring closure, whereas the addition of methylmagnesium bromide afforded **33**,[11f] the deoxygenated serine–alanine analogue of hyalodendrin, via the two-step sequence. Acetal-protected and allyl Grignard reagents provided ETPs **34** and **35**, respectively, with functional handles for further manipulation. The nucleophilic addition of benzylmagnesium bromide was also successful and provided the C2-symmetric phenylalanine–phenylalanine-containing ETP **36**.[11c,d,f] Finally, aromatic nucleophiles with various substitution patterns and functionality were also effective and gave ETPs **37**–**40** in good yield. These are particularly noteworthy as they would otherwise require independent syntheses of 2-arylglycines prior to sulfide-bridged DKP assembly.

In conclusion, we have demonstrated the utility of bifunctional *S*-containing triketopiperazine **14** as a common building block for the modular and flexible synthesis of epidithiodiketopiperazines. (±)-Hyalodendrin, a prototypical ETP target, was prepared from the parent sarcosine-derived TKP 13 in only seven steps and 22% overall yield. Using the same synthetic strategy, **14** could be elaborated *via* enolate alkylation with a range of previously inaccessible non-natural ETP analogues of general structure **22**. Of particular significance is the fact that naturally occurring ETPs all derive from at least one aromatic amino acid; this strategy provides a straightforward means to divert from this as evidenced by the preparation of non-natural ETPs **30** and **31**. Efforts to render the challenging enolate benzylation (**14** to **15** or **21**) enantioselective[23,24] are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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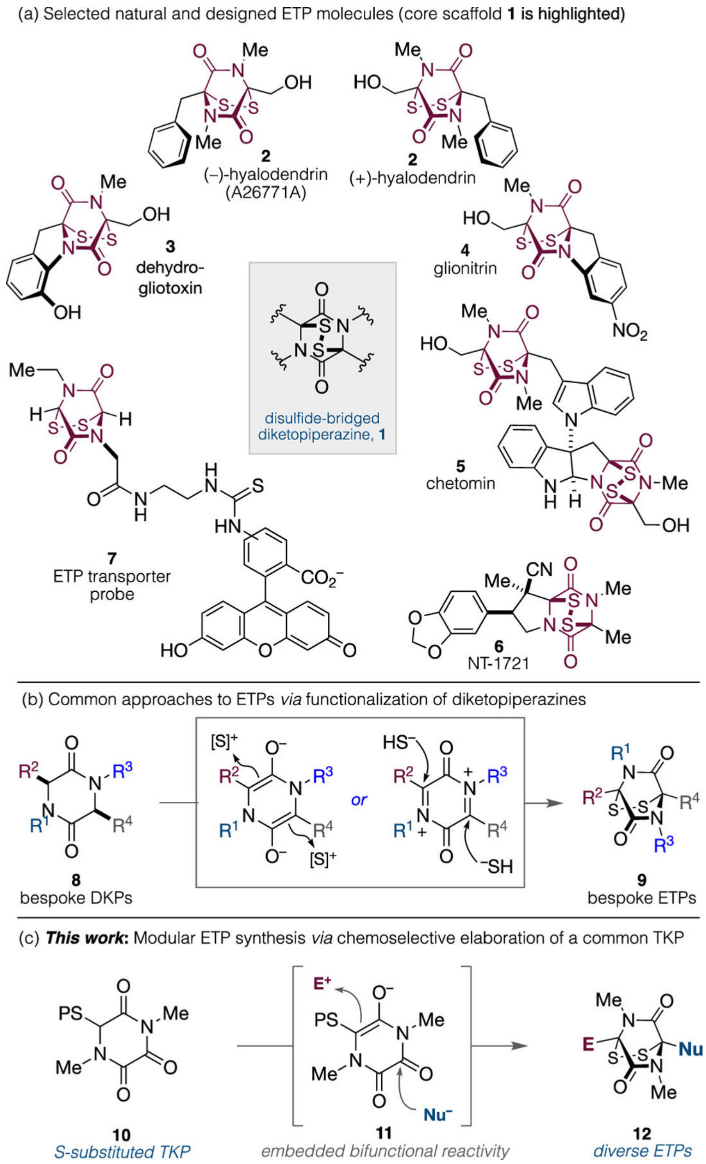
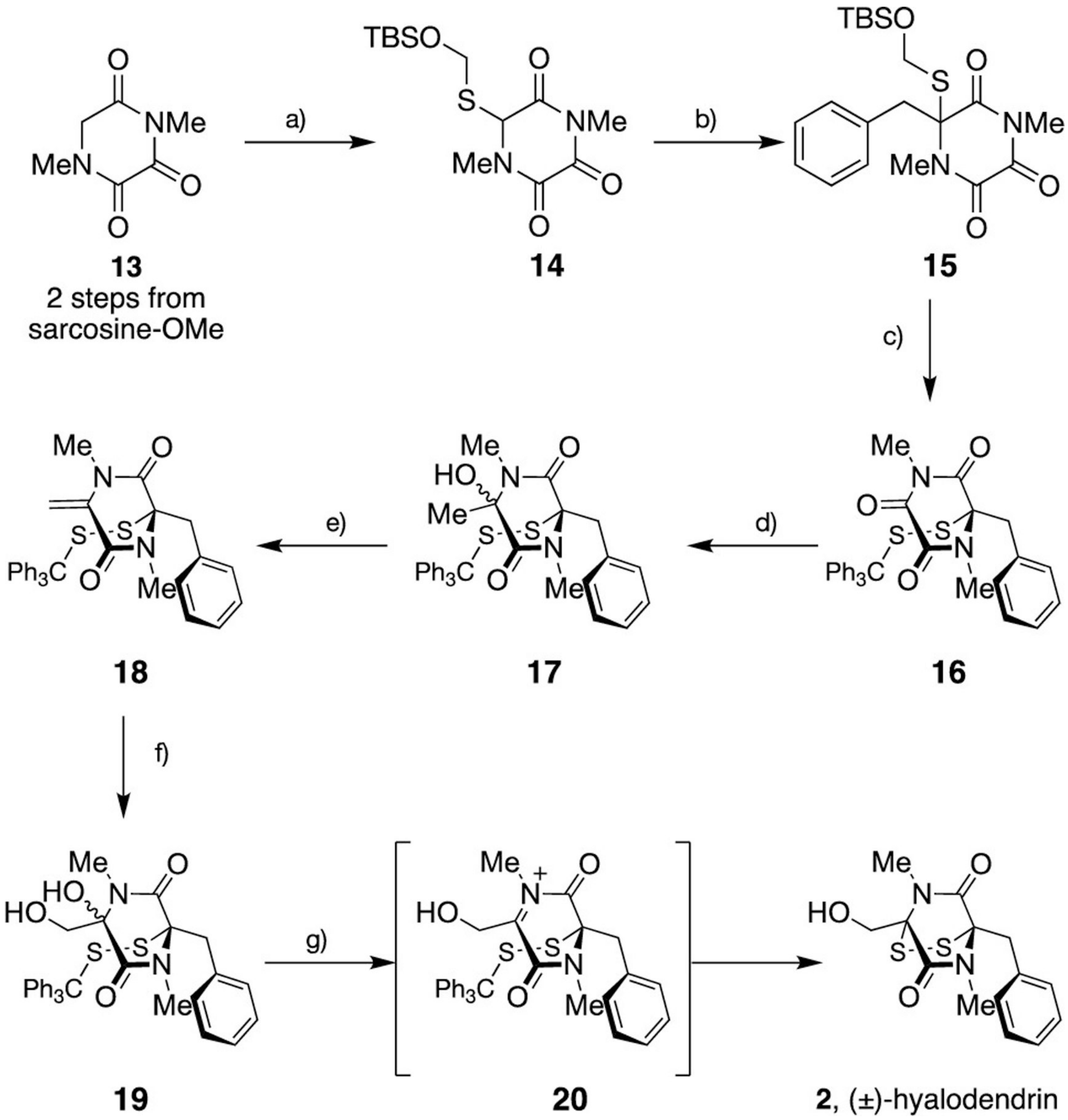


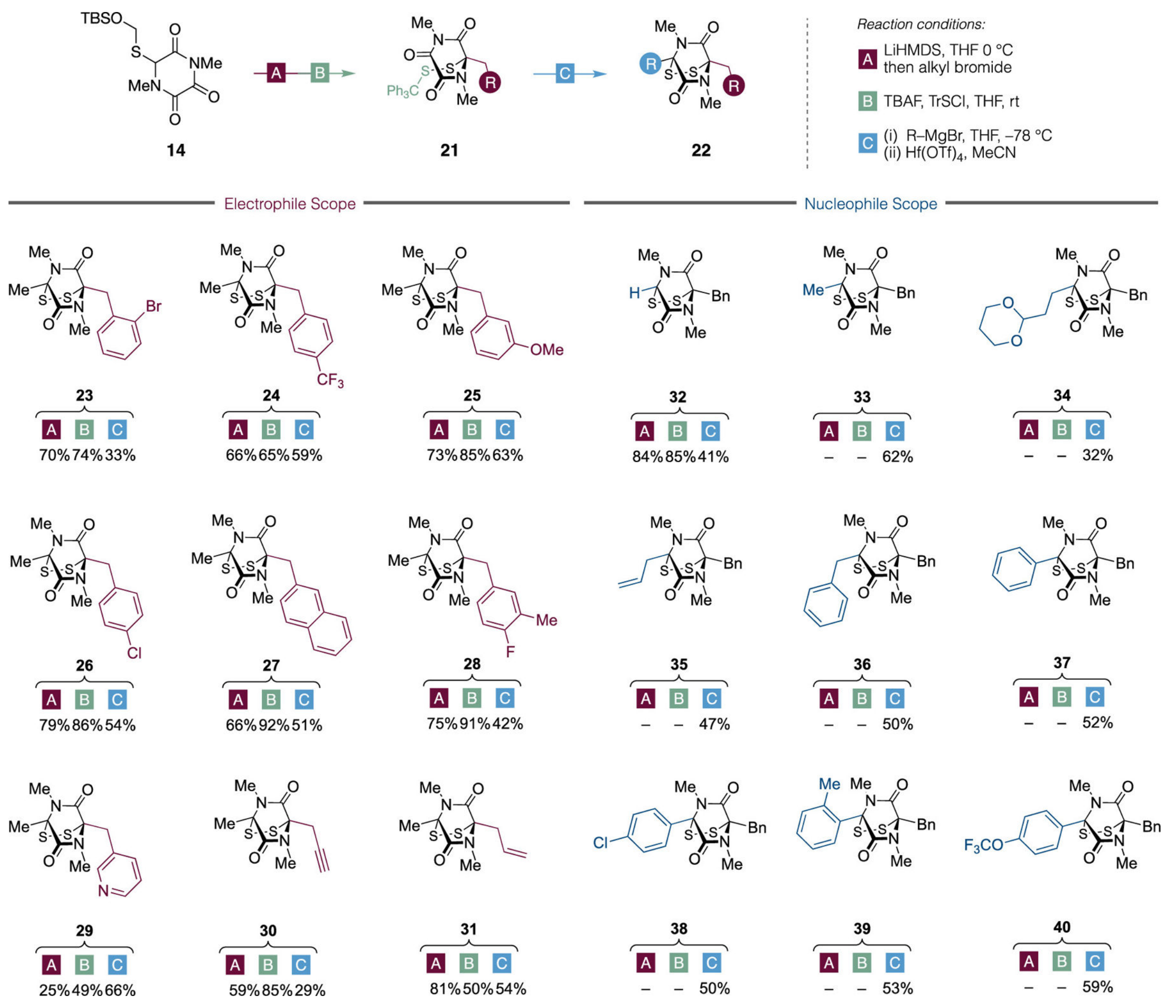
Figure 1.

(a) Selected natural and non-natural ETPs. (b) ETP synthesis from DKP derived from parent amino acids. (c) Modular ETP synthesis which exploits the bifunctional reactivity of triketopiperazines (TKPs).



Scheme 1. Synthesis of (±)-Hyalodendrin 2[a]

[a] Conditions: (a) LiHMDS, THF, −78 °C, *S*-[[(*tert*-butyldimethylsilyl)oxy]methyl] 4-methylbenzenesulfonothioate, 85%; (b) LiHMDS, THF, DMPU, 0 °C, BnBr, 84%; (c) TBAF, TrSCl, THF, 85%; (d) MeMgBr, THF, −78 °C; (e) PTSA, DCM, 58% (over two steps); (f) OsO_4, NMO, acetone/H_2O, 89%; (g) $BF_3{\cdot}OEt_2$, DCM, −78 °C to rt, 70%.



Scheme 2.

ETP Analogues Synthesized from Common TKP 14