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A concise approach to the epidithiodiketopiperazine (ETP) core

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Abstract—A novel approach to the epidithiodiketopiperazine nucleus, incorporating two three-component reactions in a four-step synthetic sequence is reported.

The epidithiodiketopiperazine (ETP) core structure **1** is found in a large number of natural products, ranging from the simpler members such as hyalodendrin **2** through to highly complex derivatives such as the recently isolated MPC1001 **3** (Fig. 1).[1–3] The vast range of biological activities displayed by these compounds stems from the disulfide bridged diketopiperazine core structure **1**,[1] and the reactivity of the disulfide bond is essential for the observed activity in all members of this class of compound.[4,5]

Sub-groups of this class of compound such as the Leptosins and Scabrosins exhibit potent anticancer activity, whilst other members have been shown to display antibacterial, antiviral and antifungal activity.[1,6–11] However, the exact mechanism by which this class of compound operates has yet to be fully determined. As a consequence of their biological activity and of the structural diversity which surrounds the central ETP motif, a considerable number of synthetic efforts have been directed towards formation of the ETP core.[12–24] As part of an ongoing programme of research into this intriguing class of natural products,[25,26] it became evident that the existing synthetic methods towards the ETP core were hindered by strategies that involved incorporation of sulfur into a preformed diketopiperazine. We now report our initial results on a mild, convenient and rapid multi-component approach to this nucleus.

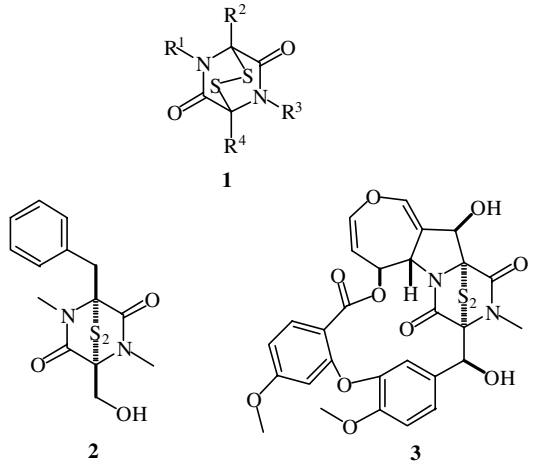

Figure 1.

We have recently described a synthetic approach towards monomercaptodiketopiperazines based on the elaboration of α-alkylthioglycine derivatives such as **4** which were in turn, simply prepared by a three-component reaction involving a glyoxalate ester, an amine and a mercaptan.[26] We were accordingly attracted to the possibility outlined in Scheme 1 whereby the addition of a two-carbon glyoxylic acid synthon would generate the acyclic aldehyde **5** or an equivalent which could then be used in a second three-component reaction to install a second sulfur atom, and hence on subsequent cyclisation provide a highly concise route to the ETP core **1** via the protected derivative **6**.

In the event, initial attempts at formation of the aldehyde **5** via a carbodiimide mediated reaction met with

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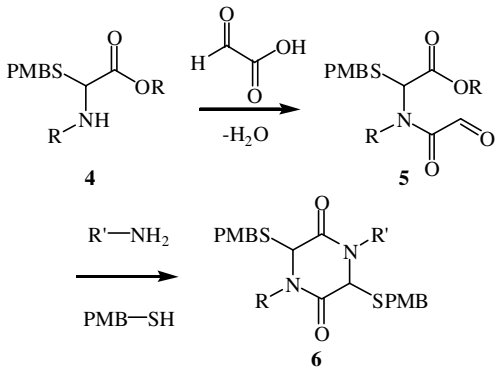


Scheme 1. Proposed three-component reaction.

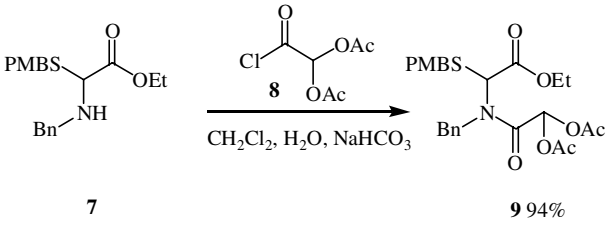
failure. We therefore elected to utilise the protected diacetoxyacetyl chloride **8** as a masked aldehyde source.[27] Gratifyingly reaction of **8**, with the α-alkylthioglycine three-component derivative **7** under Schotten–Baümann conditions led to the desired protected aldehyde **9** in 94% yield (Scheme 2).

Subsequent attempts at deprotection of the geminal diacetate to the aldehyde under either acidic or basic conditions were unsuccessful and led to degradation of the starting material. In order to obviate the need for isolation of the aldehyde **5**, we then decided to attempt an in situ deprotection. Pleasingly, a control reaction of the diacetate **9** with 3 equiv of benzylamine in ethanol as solvent with a catalytic amount of trifluoroacetic acid (10 mol %) led to the diketopiperazine **10** in 55% yield as a mixture of diastereoisomers (Scheme 3).

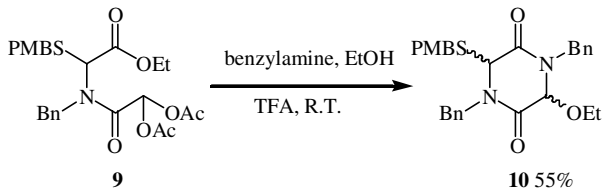
In light of this encouraging result we next attempted the crucial three-component reaction with *para*-methoxybenzylmercaptan as the nucleophile. Thus, reaction of the diacetate **9** with benzylamine (3 equiv) and *para*-methoxybenzylmercaptan (1.5 equiv) in acetonitrile in the presence of a catalytic amount of TFA at room temperature led to the protected epidithiodiketopiperazine precursor **11** as a 2:1 *cis:trans* mixture (Scheme 4).

Finally, through the simple expedient of heating the reaction at reflux for 16 h, the required *cis* isomer was obtained as the exclusive product in 64% yield. A potential pathway for equilibration may involve proton catalysed loss of the mercaptan to yield an acyliminium cation followed by readdition of the sulfur nucleophile. The intriguing thermodynamic preference for formation of the *cis* isomer is also supported by gas phase DFT calculations[28] for a single molecule using the B3LYP/6-31G(d) level of theory which revealed that this configuration is ~9 kJ mol^{-1} more stable than the alternative *trans* arrangement (Fig. 2).

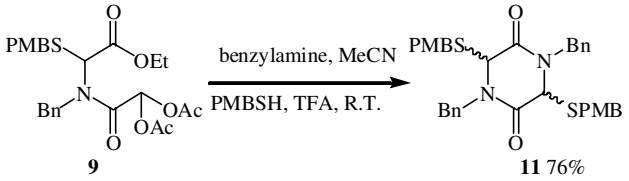
As indicated in Table 1, application of the optimised conditions with a number of amines provided a range of protected ETP core structures **12** in good yields (Fig. 3 and Table 1).



Scheme 2.



Scheme 3.



Scheme 4.

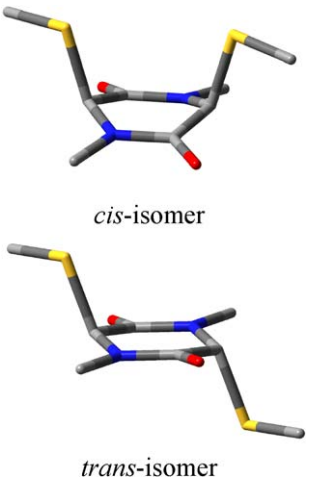
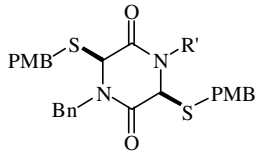


Figure 2.

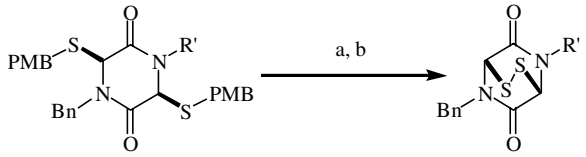
Table 1.

Entry	Amine R′	Yield (%)
1	Methylamine	33
2	Isopropylamine	85
3	*n*-Butylamine	65
4	*para*-Methoxybenzylamine	84
5	3,4-Dimethoxybenzylamine	76
6	3,4,5-Trimethoxybenzylamine	88
7	1-Naphthylmethylamine	58
8	3-Chlorobenzylamine	67



12

Figure 3.



12 **20**

Scheme 6. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C to R.T. then NH_4Cl (aq), (b) I_2 then $Na_2S_2O_3$.

With the exception of methylamine (entry 1), all of the amines which reacted with diacetate **9** gave good yields of the protected *cis*-ETP core structure. In the case of entry 1, the low yield arose from formation of a product in which the second sulfur atom was replaced by a hydroxyl group in 58% yield as a mixture of diastereoisomers.

From a mechanistic standpoint, as indicated in Scheme 5, a considerable number of acyclic cyclisation precursors and intermediates can be considered as evolving from the geminal diacetate moiety **9**, and these in turn do not necessarily require in situ liberation of the free aldehyde **18**. Thus intramolecular amide formation can occur either from an α-acetoxy amine **13** or from a hemithioaminal **16**, whilst an α-acetoxysulfide **15** could also be generated en route to a hemithioaminal. Possibly the isolation of the monomercapto–monohydroxy derivative from the reaction with methylamine could be considered as deriving from a more rapid cyclisation of an α-acetoxy amine **13** followed by reaction of the acetate **14** with methylamine to yield the monomercapto–monohydroxy derivative.

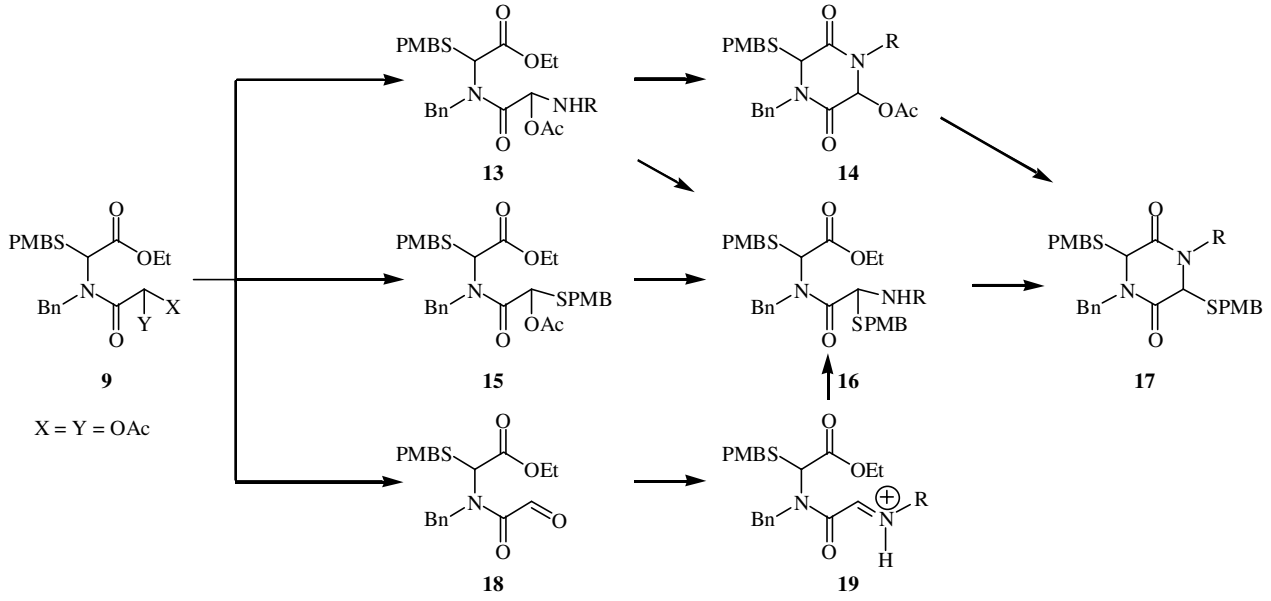
Efficient deprotection of the *cis para*-methoxybenzyl protected ETPs was then achieved by reaction with 2 equiv of boron tribromide in dichloromethane. Furthermore, addition of iodine to the work-up of the reaction led to a one-pot deprotection/oxidation sequence,

Table 2. Deprotection to give the ETP core

Entry	R′	Yield (%)
1	Methyl	65
2	Isopropyl	57
3	*n*-Butyl	81
4	Benzyl	85
5	*para*-Methoxybenzyl	48
6	3-Chlorobenzyl	64
7	1-Naphthylmethyl	85

which yielded the ETP core structure **20** in good yields (Scheme 6 and Table 2).

In summary, we have developed a mild, rapid, four-step synthesis of the epidithiodiketopiperazine core structure **1**, which is applicable to the synthesis of a small library of compounds. Moreover, the present protocol also allows for the possibility of trapping the *cis* dithiols with *para*-methoxybenzaldehyde to give the useful dithioacetal Kishi building block for carbon alkylation.[14,15] The synthetic route outlined above also overcomes the notorious solubility issues associated with formation of the diketopiperazine ring prior to incorporation of sulfur, often encountered in previous synthetic routes to this class of compound. Further studies are underway in order to explore the scope of this reaction.



Scheme 5.

Acknowledgements

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