**A Common Precursor Approach to Structurally Diverse Natural Products: The Synthesis of the Core Structure of (±)-Clausenamide and the Total Synthesis of (±)-Hyalodendrin**

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**Abstract:** Structurally diverse natural products from unrelated sources typically require the development of individual synthetic routes. In a novel approach, we have shown that the epidithiodiketopiperazine derived natural product (±)-hyalodendrin and the core structure of the unrelated pyrrolidine derived natural product clausenamide can be synthesised from a common synthetic precursor in good yield by simple variation of the reaction conditions.

Structurally unrelated natural products typically require the development of individual synthetic routes to access their core structures due to their lack of chemical similarity. The epidithiodiketopiperazines (ETPs) as exemplified by chetomin **1**, gliotoxin **2**, hyalodendrin **3** and pyrrolidine-based alkaloids such as erythratin **4** and clausenamide **5** are such a case in point, due to their clear and obvious structural differences.[1-4] The ETPs as a family of compound are distinguished by the fact that they all contain a diketopiperazine core bridged by two or more sulfur atoms.[1-2] This family of secondary fungal metabolites displays potent biological activity ranging from the nanomolar anticancer activity associated with chetomin **1**,[1-4] through to the antibacterial and antiviral activity of gliotoxin **2**.[1] The fact that they are able to inhibit protein/ protein interactions has made the ETPs attractive targets as well as the ability of gliotoxin **2** to inhibit farnesyl transferase and the antifungal activity of hyalodendrin **3**.[1-7] All members of this class of compound exhibit potent and differing biological activity, which is related to the structural features around the central disulfide bridged core.[1] Clausenamide **5**, is a small five-membered heterocycle containing four contiguous stereocentres, which was isolated from *clausenia lanseum* as a racemic mixture of the (+)- and (-)- enantiomers. The (-)- enantiomer is responsible for the powerful nootropic effects and is currently undergoing clinical trials for the treatment of Alzheimer’s disease.[8] A number of the stereoisomers of clausenamide exhibit differing nootropic effects to a greater or lesser degree depending on their discreet stereo-arrangement.[8]

There have been a number of methods reported in the literature to access the core structure of hyalodendrin **3** and the ETPs, with most efforts directed towards the synthesis of the diketopiperazine ring prior to incorporation of sulfur.[1-7,9-20] One of the key challenges with this approach is the regioselective requirement for both sulfur atoms to be on the same face of the diketopiperazine ring in order to access the ETP core, as well as the challenge associated with the poor solubility of diketopiperazines in general.[1] Notable synthetic endeavours involve work by Kishi, Fukuyama, Movassaghi, Williams and others, which have led to the synthesis of the natural products.[17-20] As a result of its potent biological activity, clausenamide **5** has also attracted significant synthetic attention over a number of years due to its potential to treat neurological disorders and the synthetic challenge associated with its four contiguous stereocentres.[21-32]



***Figure 1.*** The epidithiodiketopiperazines as exemplified by chetomin **1**, gliotoxin **2**, hyalodendrin **3** and natural products containing a pyrrolidine core such as erythratin **3** and clausenamide **5**.

As a result of the structural complexities and potent biological activities of both the ETPs and pyrrolidine alkaloids we were interested in the development of separate novel methodology to access both classes of compound. However, we were also attracted to the development of synthetic routes which would be amenable to the synthesis of small molecular libraries to access related structural analogues for biological evaluation for each class of compound. With this in mind, we had previously developed a route to the ETP core **8**, which involved formation of the diketopiperazine ring **7** via a multicomponent reaction between a diacetoxyamide **6** with 4-methoxybenzylmercaptan and a range of amines, but were interested in the development of new methodology that would generate more highly substituted analogues in a single transformation from simple amino acids (Scheme 1).[33-34]



***Scheme 1*.** Synthesis of the ETP core **8** via concomitmant formation of the diketopiperazine ring.

We reasoned that extending this methodology to a suitable dehydroamino acid acylal **11** would allow us to generate a more substituted ETP core **10** via analogous methodology. Reaction of the enamide with a protected thiol and further elaboration would therefore provide a facile route to (±)-hyalodendrin **3**. However, in our retrosynthetic analysis it was evident that there were two possible conformers of the open chain precursor, namely **11a** and **11b**. To access the ETP core, clearly the diacetate needs to be adjacent to the ester group for cyclisation. However, in conformer **11a** where the enamine is adjacent to the diacetate, we were intrigued by the possibility that under Lewis acid mediated intramolecular acylal cyclisation (IAC) conditions, the internal enamine could cyclise onto the diacetate to generate the pyrrolidinone core **9** of clausenamide **5** (Scheme 2).[8]



***Scheme 2*.** Disconnection of clausenamide **5** and hyalodendrin **3** to a common precursor **11**.

As such, the precursor **11a/b** is an ideal intermediate to access both the core structures of two distinct natural product classes and is unique in this manner. Herein, we now wish to report on our novel approach towards both the core structure of clausenamide **5** and the total synthesis of (±)-hyalodendrin **3**.

To investigate our hypothesis, and generate cyclisation precursor **11** that was required for both classes of compound, *N-*Boc protected phenylalanine methyl ester **12** was first alkylated with methyl iodide under basic conditions to give the *N*-methyl derivative. Subsequent deprotection under acidic conditions using TFA gave *N-*methylphenylalanine methyl ester **13** in 79% yield over two steps. (Scheme 3).[35-36]

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***Scheme 3*.** Formation of the cyclisation precursor **11**.

The conversion to the dehydroamino acid **14**, involved a three-step one-pot strategy, where *N-*chlorination, followed by elimination and subsequent tautomerisation would give rise to the required dehydroamino acid **14**. We initially attempted to follow the methodology of Lewin who had investigated imine/ enamine tautomerisation of dehydrophenylalanine via *N*-chlorination with *N*-chlorosuccinimide, but it proved unsuitable for our *N-*methyl derivative **13**.[37] We therefore switched to the use of the more soluble chlorinating agent *tert*-butylhypochlorite which gave *tert*-butanol as a by-product to avoid the intermediate filtration step. Use of this modified protocol enabled facile elimination with DABCO to generate the dehydroamino acid **14**. However, **14** proved unstable and rapidly decomposed on standing and was therefore rapidly reacted with diacetoxyacetyl chloride **15** under Schotten-Baumann conditions to give the cyclisation precursor **11** in 70% yield as a 7:3 mixture of amide rotamers over two steps.[38]

With the obtention of the cyclisation precursor **11**, we next turned our attention towards the formation of the two potential natural product classes. We first elected to explore cyclisation to the core structure of clausenamide **5**.[8] On reaction of the precursor **11** with tin tetrachloride as Lewis acid in dichloromethane as solvent, we were pleased to obtain the cyclised product **9** albeit in a low yield of 32% (Scheme 4).



***Scheme 4*.** Cyclisation to give the core structure **9** of clausenamide **5**.

Following successful cyclisation and demonstration that the reaction was indeed feasible, we attempted to optimise the reaction yield with a range of Lewis acids, alteration of reaction time and solvent as shown below to obtain the core structure of clausenamide **5** (Table 1).

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|  | **Table 1.** Exploration of a range of Lewis acids and conditions for the formation of the core structure of clausenamide **5**.  |
| Entry  | Lewis acid | Solvent | Timeh | Temperature ºC | Yield(%) |
| 1 | SnCl4 | DCM | 2 | 40 | 32 |
| 2 | AlCl3 | DCM | 2 | 40 | 21 |
| 3 | TiCl4 | DCM | 2 | 40 | 47 |
| 4 | FeCl3 | DCM | 2 | 40 | 43 |
| 5 | InCl3 | DCM | 2 | 40 | 60 |
| 6 | Zn(OTf)2 | DCM | 2 | 40 | 66 |
| 7 | BF3.OEt2 | DCM | 2 | 40 | 70 |
| 8 | BF3.OEt2 | DCM | 12 | 60 | 58 |
| 8 | BF3.OEt2 | 1,2-DCE | 6 | 60 | 62 |
| 9 | BF3.OEt2 | Neat | 24 | ambient | 72 |
|  |  |

As seen above, the cyclisation yield varied widely depending on the Lewis acid that was used. However, changing to the use of boron trifluoride led to an increase in the yield to 62% when 1,2-dichlorethane was used as solvent and the reaction heated at 60 ºC. Further optimisation of the reaction conditions via simple use of neat BF3 at ambient temperature led to an increase in the reaction yield to 72% with a concomitant reduction in unwanted side products. Mechanistically, our proposed reaction cyclisation involves initial activation of the diacetate with BF3 to generate the oxonium ion **17** which reacts with the internal nucleophilic enamide to give the pyrrolidine core **18**. Further BF3 mediated elimination of acetate followed by addition of water on work up and hydride rearrangement led to the core structure **9** of clausenamide **5** (Scheme 5).



***Scheme 5*.** Proposed mechanism for formation of the core structure **9** of clausenamide **5**.

Following the successful synthesis of the core structure **9** of clausenamide **5** from the diacetate cyclisation precursor **11**, we attempted to explore whether we would be able to access the natural product (±)-hyalodendrin **3** from the same cyclisation precursor **11**. As such, **11** was reacted with a solution of methylamine in THF and *para*-methoxylbenzylmercaptan **23** with DMAP as a catalyst in acetonitrile for 16 hours, followed by purification to give the ETP cyclised product **10** in 46% yield as a 2:1 mixture of *cis-* and *trans*-isomers.[34] The low yield in this reaction was attributed to the volatility of methylamine which we had also encountered with methylamine in our previous synthetic approaches to the ETP core.[33] With the obtention of the dehydroamino acid containing monothiodiketopiperazine **10**, we next explored the incorporation of a second sulfur atom required for the synthesis of the ETP core. Accordingly, reaction with *para*-methoxylbenzylmercaptan **23** in dichloromethane with HBr as an acid catalyst led to efficient formation of the protected disulfide **24** in 73% yield as a 2:1 mixture of *cis*- and *trans*-isomers. Introduction of the CH2OH group was mediated by simple reaction with MOMCl which gave the fully protected hyalodendrin precursor **25** as the all *cis*-isomer in 76% yield (Scheme 6).



***Scheme 6*.** Formation of the natural product (±)-hyalodendrin **3**.

The conversion of a mixture of the *cis*/ *trans*-mixture of **24** to the single protected product **25** was facilitated by deprotonation with LHMDS to give a planar intermediate. Alkylation using MOMCl occurred on the same side of the ring as the benzyl group on the opposite side of both protected thiols presumably due to steric effects of the bulky thiol protecting groups. Finally, triple deprotection using three equivalents of boron tribromide unmasked both thiol groups and the OH of the methyl protected alcohol to give the intermediate dithiol **26**, which was oxidized to (±)-hyalodendrin **3** in good yield (55%) using iodine as oxidant. Comparison with the published data for hyalodendrin **3** was in good agreement, confirming that we had indeed synthesised the natural product.[18]

In summary, we have developed a unique novel approach to two distinct and structurally separate natural product classes starting from a single precursor based on a phenylalanine derivative and in good yield for both product classes. Further studies into the total synthesis of clausenamide **5** and examination of its biological activity will be reported in due course.

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**Keywords:** clausenamide• Natural Products • hyalodendrin • cyclisation • electrophilic cyclisation

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| Structurally unrelated natural products often require individual synthetic routes. In our approach, the epidithiodiketopiperazine natural product (±)-hyalodendrin and the core structure of the unrelated pyrrolidine derived natural product clausenamide were synthesised from a common precursor by simple variation of the reaction conditions. |  | Blanka R. Szulc, B. C. Sil, A. Ruiz and Stephen T. Hilton\*Page No. – Page No.A Common Precursor Approach to Structurally Diverse Natural Products: The Synthesis of the Core Structure of (±)-Clausenamide and the Total Synthesis of (±)-Hyalodendrin |