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Studies towards the total synthesis of hygrocins A and B

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ABSTRACT

The western segment of hygrocins A–B has been synthesized through the coupling of a chiral *C5–C13* synthon with the sterically demanding hexasubstituted naphthalenic core. The *C5–C13* chiral fragment has been assembled via a stereoselective Johnson orthoester rearrangement of an optically pure allylic alcohol derived from D-glucose. Our studies lay the platform for the determination of the absolute configuration of the unassigned *C8*-stereocenter of the title compounds in addition to the completion of the total synthesis of the unique ansamacrolides hygrocins A and B.

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Ansamycins, the predominant class of 3-amino-5-hydroxy benzoic acid (AHBA) derived natural products, display extensive biological and pharmaceutical activities, and are used as antibiotics, anticancer agents and enzyme inhibitors.[1] They are characterized by a macrocyclic lactam structure (Fig. 1), in which an aliphatic ansa chain forms a bridge between two non-adjacent positions of the chromophore.[2] Ansamycins are classified into two types on the basis of the structural features of the aromatic core[3]: (1) naphthalenic ansamycins (e.g. rifamycins,[4] naphthomycins,[5] streptovaricin,[6] etc.) that exhibit antimicrobial activities (2) benzenic ansamycins (geldanamycin,[7] herbimycin,[8] etc.) that possess anti-cancer activities.

The AHBA-derived secondary metabolites are mostly produced by *Actinomycetes* and continue to fascinate both basic and applied research scientists alike, by virtue of their complex biosynthetic and biochemical pathways as well as by their pharmacological potential.[9] Recently isolated hygrocins A (**1**) and B (**2**), unique naphthalenic ansamycins, isolated by Cai et al., from the fermentation broth of *Streptomyces hygroscopicus,* have been shown to possess anti-bacterial activity, although weaker compared to rifamycins.[10] Hygrocins A and B (**1** and **2**) feature an unusual ansabridge which is a hybrid of macrolide and macrolactam. Hygrocins resemble divergolides A–D (**9**, **10**, **4** and **5**) isolated from *Streptomyces* sp. HKI0576, an endophyte of the mangrove tree *Bruguiera gymnorrhiza.*[11] During their original isolation studies Cai et al., have noticed the conversion of hygrocin A (**1**) to compound **3** which has close resemblance with divergolide D (**5**) in its aromatic core and differs only in its side chain at *C12* and in its bridge size. Due to this close similarity, we expected divergolide C (**4**) to have similarity with hygrocin B (**2**), hence, revisited the isolation details of Hertweck et al., and concluded that indeed divergolide C has also been isolated at the oxidation states of the aminonaphthoquinone of hygrocin B as shown in structure **4**.[12] This revision allows invoking of the polyketide biosynthetic precursor **6** for hygrocins similar to **7** that was proposed by Hertweck et al., for the divergolides, which is thought to be derived from the ABHA-PKS pathway via a Baeyer–Villigerase disruption that allowed the formation of macrolide with optional acylmigration.[5,13] This putative biosynthesis proposal finds support from the instability of hygrocin A and its conversion into **3**, a new 1, 2-addition product which could potentially be called as "hygrocin D". By extending the mapping exercise,[14] it is also conceivable that polyketide shunt could have produced other hygrocins containing oxa-aromatic cores such as **11** and **12** akin to divergolides A and B (**9** and **10**) that would possibly be isolated in future. In the light of the above discussion and the similarities in structures and biosynthesis, the unassigned stereochemistry of *C8* (*C14* as per Cai's numbering) is presumed to be (***R***) by extrapolation to the *C8* configuration of the related centre in the divergolide family, whose stereochemistry in turn has been secured through the crystal structure of **9**.

Attracted by the unique structural features and impressive bioactivities of these novel ansamacrolides, we initiated a research program to obtain the structural analogues of these novel ansamacrolides in biomimetic and non-biomimetic fashions to explore

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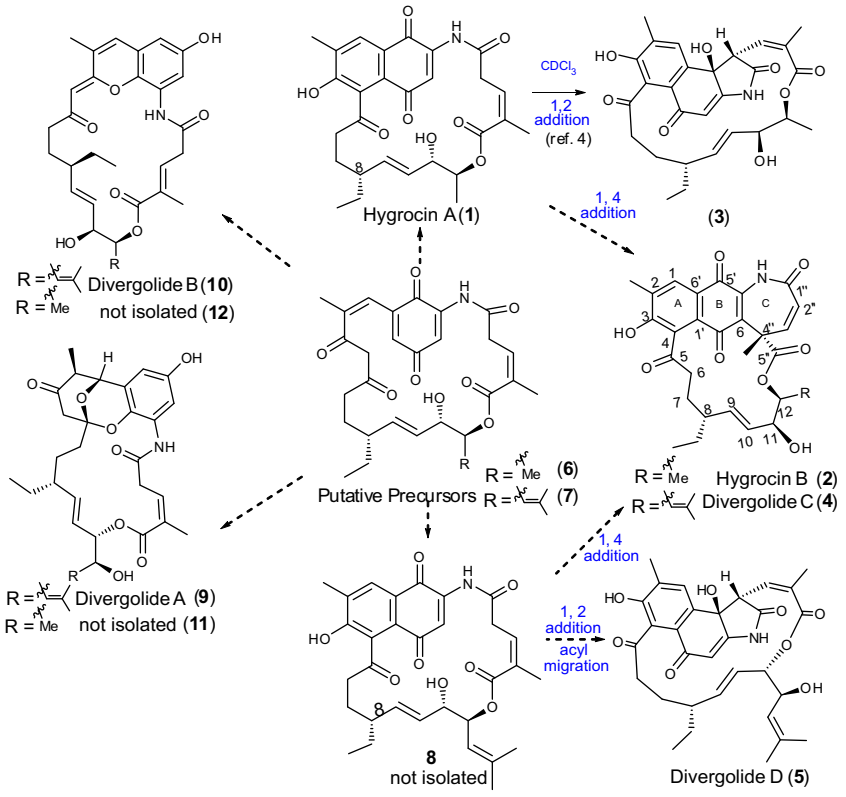
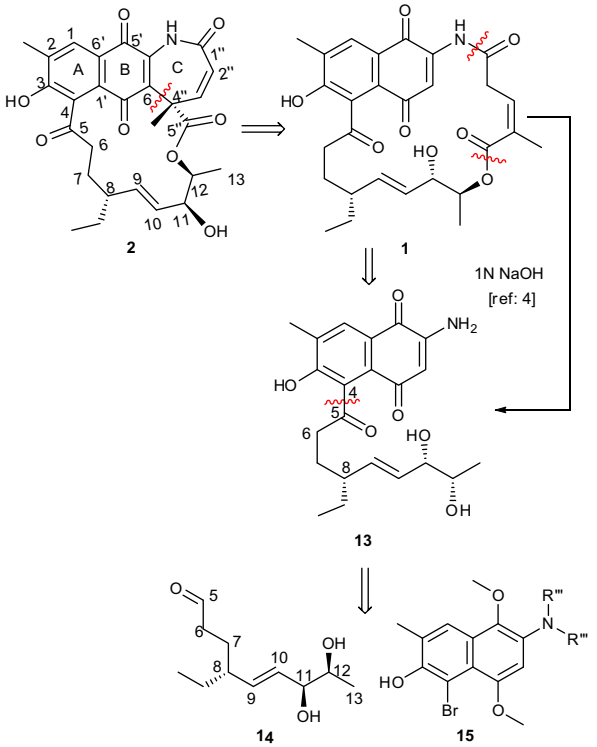


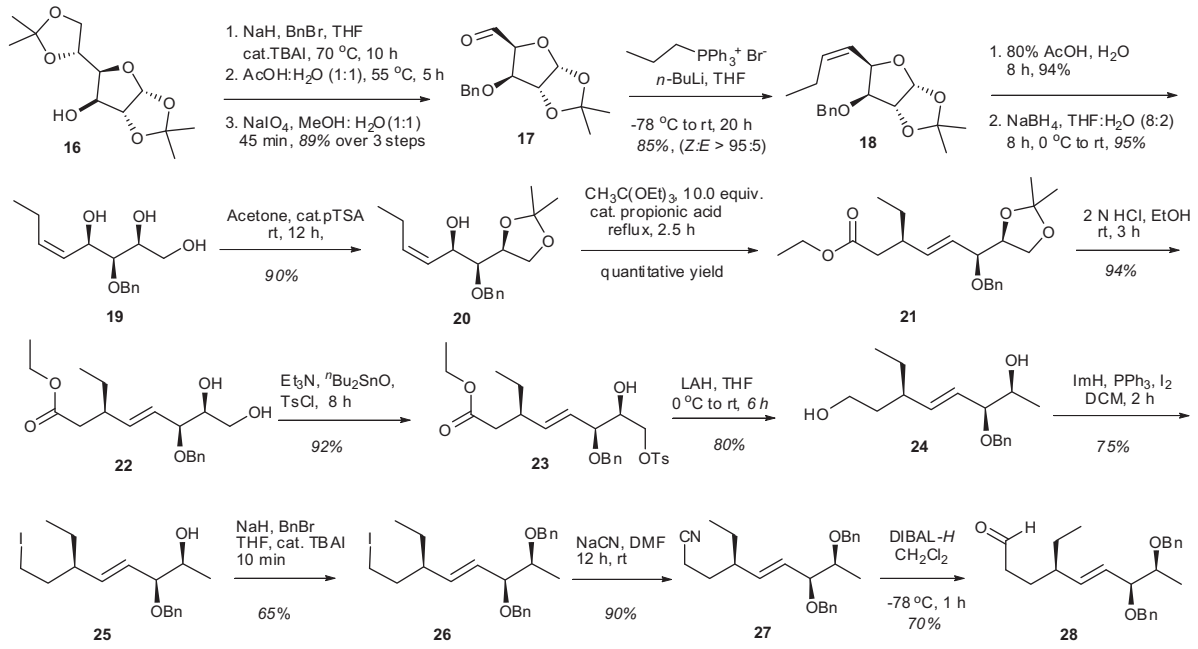
Figure 1. Novel ansamacrolides: Hygrocins and divergolides and their biosynthetic relations.

their biomedicinal potential further.[15] As can be seen from our retrosynthetic analysis of hygrocins A (**1**) and B (**2**) shown in Scheme 1, we proposed to assemble the hygrocin A in a non-biomimetic fashion and planned to rely on its intrinsic biomimetic transformation to hygrocin B via 1,4-addition. Disconnection of the macrolide **1** either at the lactam (*C1″–N*) or lactone (*C11/12–OH* and *C5″*) sites offers either the macrolactamization or macrolactonization as strategies to assemble the macrocyclic skeleton from the western fragment **13** and 2-methyl-2-propenedioic acid. Our fragment based disconnection of western segment **13** at *C4–C5* identified two synthons, namely chiral fragment **14** and the aromatic core **15**. We initially focused our efforts on the synthesis of the chiral (*C5–C13*) fragment **14** and we intended to develop a scalable and cost effective stereoselective route that allows orthogonal protection of the *C11* and *C12* hydroxyl groups while accommodating different substituents at *C12* and amenable for installation of different functionalities on *C5* suitable for coupling.[16] Keeping the above criteria and our resources in focus, the stereochemistry of the target molecules was planned to be obtained via the chiral pool synthesis through stereoselective Johnson orthoester variant of the Claisen rearrangement, whose synthetic utility is well appreciated by the synthetic community due to its predictable high diastereoselectivity.[17]

Accordingly, our synthetic efforts commenced with the commercially available D-glucose diacetonide **16** to obtain the chiral (*C5–C13*) fragment with the requisite stereochemistry and functional groups, as shown in Scheme 2. Thus, D-glucose diacetonide **16** was converted to aldehyde **17** following the literature procedure.[18] Wittig olefination of aldehyde **17** with *n*-propylidenetriphenyl phosphorane (generated in situ from n-$C_3H_7PPh_3^+Br^-$ and *n*-BuLi) at −78 °C gave the *Z*-olefin **18**[19] with good (>95:5 *Z*:*E*) stereoselectivity. Deprotection of the secondary acetonide in **18** by treatment with 80% acetic acid under reflux conditions provided a 1:1 mixture of anomeric hemiacetals whose subsequent $NaBH_4$ reduction resulted in triol **19**. Triol **19** was converted to the 1,2-acetonide to give the enantiomerically pure allylic alcohol **20**. Gratifyingly, allylic alcohol **20** underwent smooth [3,3]-sigmatropic rearrangement at 130 °C with triethyl orthoacetate (10 equiv) in



Scheme 1. Retrosynthesis of Hygrocin A and B (**1** and **2**).



Scheme 2. Synthesis of chiral *C5–C13* fragment **28**.

the presence of catalytic propionic acid to provide ester **21** exclusively as a single diastereomer in quantitative yield.[20] Deprotection of the acetonide group of ester **21** in ethanolic 2 M HCl provided the diol **22**. The substrate **22** is ideal for divergent synthesis of the chiral fragments with various side chains at *C12* (e.g. *C12*-isobutenyl substitution for divergolides) by oxidation of the primary-OH to aldehyde, and Wittig olefination.[21] We planned the deoxygenation of the primary alcohol for installation of the *C12*-methyl substituent required for hygrocins A and B (**1** and **2**). Towards this direction, the primary hydroxyl group of **22** was selectively tosylated in the presence of $^{n}Bu_2SnO/NEt_3/TsCl$ to obtain the compound **23** in 92% yield. The stereochemical and structural conformation of **23** was secured through X-ray crystallography of the single crystals grown in dichloromethane (Fig. 2).

The concomitant reduction of the ester and tosylate functionalities of **23** with $LiAlH_4$ provided the diol **24**. The diol **24** was selectively converted to primary iodide **25** which in turn enabled the protection of the secondary hydroxyl group. It is pertinent to mention that this synthetic design allows for the orthogonal protection of the *C11* and *C12* hydroxyl groups that would allow selective deprotection at the later stages in the synthesis for esterification. For establishing the conditions for elaboration of the ansabridge, we decided to place another benzyl protection and proceed with elaboration of ansa bridge of hygrocins A–B. Thus, we converted the secondary hydroxyl group of **25** to benzyl ether **26** under NaH/BnBr conditions which was subsequently converted to nitrile **27** using NaCN/DMF. Reduction of **27** with DIBAL-*H* proceeded uneventfully resulting in the clean formation of aldehyde **28**.

Having constructed the chiral fragment **28** in an enantiopure form, we extended the chemistry established en route our efforts to divergolides for aromatic core.[8] Briefly, we had obtained the aromatic core **31** via well-established cycloaddition chemistry of modified Danishefsky's diene **29** with quinone **30**. Bromination of the cycloadduct under NBS conditions in dilute $CHCl_3$ solution provided the bromoquinone which was subsequently converted to naphthalenic bromide **32** by Luche reduction followed by methylation of the resulting bisphenol.[22]

After gaining access to both the synthons **28** and **32**, we began to investigate the critical *C4–C5* bond which is known to be

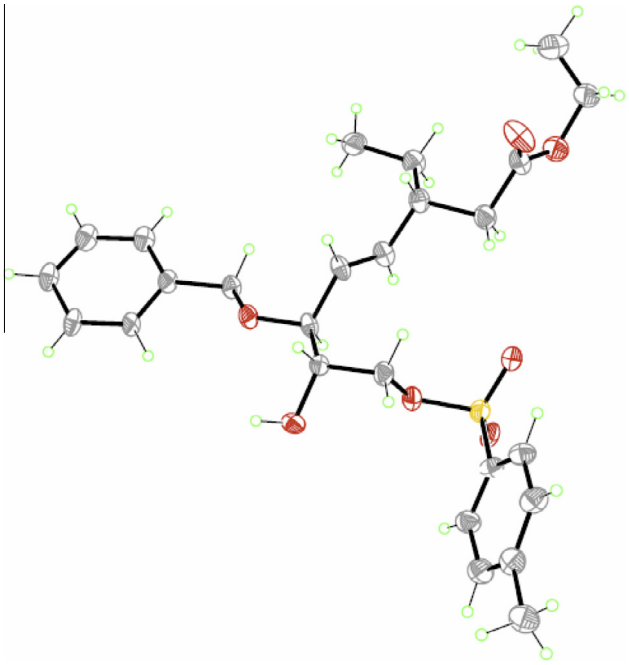
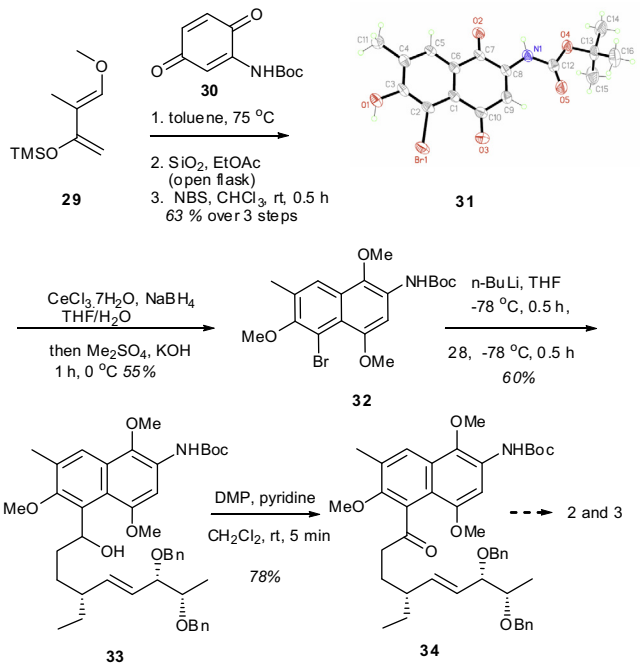


Figure 2. Solid state structure of compound **23**.

problematic in such sterically hindered systems.[23] Pleasingly, the coupling reaction of the lithiated naphthalenic core **32** with aliphatic chiral aldehyde **28** proceeded with moderate yield (60%, not optimized) to provide the alcohol **33** as a diastereomeric mixture, as shown in Scheme 3. Careful oxidation of **33** under DMP/pyridine conditions provided ketone **34** in good yield as a mixture of atropisomers in a 1:1 ratio, based on ^{1}H NMR analysis.[24] At this point, we decided to converge the synthesis with the fragment **13** that Cai et al., had obtained by hydrolysis of the natural hygrocin A (**1**) in order to confirm the stereochemical assignment of *C8* before we proceeded too far with the total synthesis. However, the attempts to effect the global deprotection of **34** to obtain **13** under



Scheme 3. Coupling of the **32** and **28** towards western segment.

Lewis acidic conditions proved not so clean warranting the change in the protection of the phenol of the A-ring for future studies towards the completion of the total synthesis of the targets under consideration.[25]

Conclusions

In summary, we have successfully synthesized the western segment of hygrocins A and B (**1** and **2**). The required variously functionalized and protected chiral fragments with the requisite stereochemistry of the targets i.e. *C8* (*R*), *C9* = *C10* (*E*), *C11* (*S*), *C12* (*S*) have been accessed via a chiron approach. The aromatic core obtained through cycloaddition chemistry has been utilized in establishing the coupling of chiral fragments through *C4–C5* bond formation as a viable approach for further studies towards completion of the total synthesis of hygrocins A–B. Our efforts thus far, would lay the platform for us to assign the stereochemical assignments of the hygrocins A–B especially to that of *C8* which had remained unassigned for nearly a decade since their isolation. Our efforts to develop a divergent synthesis of the chiral fragments for both the families i.e., divergolides and hygrocins and their structural analogues via ester **21**, and completion of the total synthesis of the targets is under progress and the results will be reported in due course.

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Supplementary data

Crystallographic data (excluding structure factors) for the structures **23** and **31** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 922930 and CCDC 922929, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk). Supplementary data (general experimental procedures, NMR spectra and X-ray crystal structural info) of this manuscript can be obtained free of charge.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.017.

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