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Journal:	*ChemComm*
Manuscript ID:	CC-COM-12-2014-009904.R1
Article Type:	Communication
Date Submitted by the Author:	28-Jan-2015

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A Concise Route to Highly-Functionalized Azetidine Precursor: Enantioselective Synthesis of Penaresidin B

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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An efficient and high-yielding synthesis of penaresidin B is disclosed herein. The concise 8-steps synthesis of azetidine aldehyde was devised by incorporating our novel strategy for the ready access to 3-amino-2,3-dideoxysugars *via* regio- and stereoselective tandem hydroamination/glycosylation of glycal as the key step.

Azetidines constitute an important class of azaheterocycles that have been widely used in drug design as well as in the synthesis of natural products and pharmacologically active compounds.[1,2] In addition, they also serve as versatile building blocks for other types of nitrogen-containing compounds with potential biological properties.[3] However, azetidine alkaloids structurally related to phytosphingosines are rare, only three biologically active sphingosine-like compounds derived from marine organisms have been isolated to date (Figure 1). Penaresidin A (**1**) and Penaresidin B (**2**), which exhibited potent actomyosin ATPase-activating activity when tested as an inseparable mixture, were isolated from an Okinawan marine sponge Penaressp. by Kobayashi *et* al.[4] The

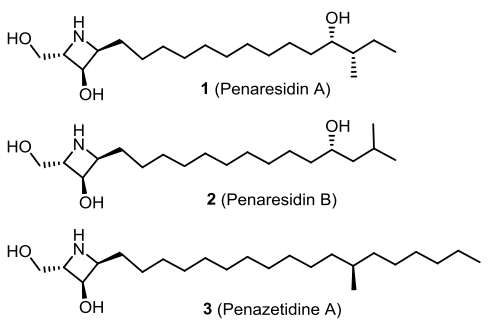
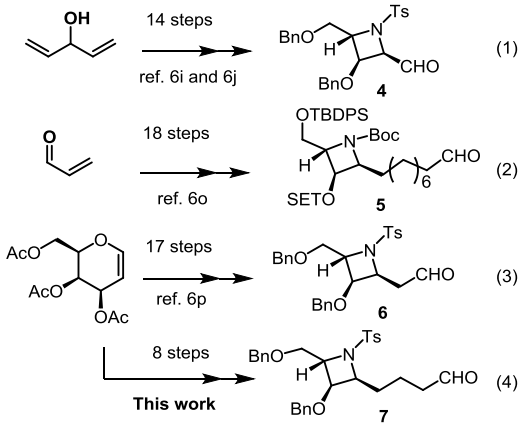


Figure 1 Structures of azetidine alkaloids

related compound Penazetidine A (**3**), which showed specific rat brain protein kinase C inhibitory activity, was isolated from the Pacific sponge Penaressollasi by Crews and co-workers.[5]

Interestingly, despite their rare occurrence in nature, azetidine alkaloids have captured tremendous interest of many synthetic chemists due to their significant biological activity and unique structure. To date, several syntheses of such alkaloid compounds have been reported.[6] Current synthetic strategies rely on the construction of a highly functionalized azetidine skeleton with the requisite stereogenic centers. For example, Lin and co-workers reported the enantioselective synthesis of Penaresidin A *via* a 14-step construction of a highly functionalized azetidine aldehyde **4** starting from divinylcarbinol, using Sharpless asymmetric epoxidation and Sharpless asymmetric hydroxylation reactions as key steps (Scheme 1, eqn (1)).[6i, 6j] In addition, Raghavan and co-workers recently developed an alternative approach which comprises of an 18-steps construction of the azetidine subunit **5** of Penaresidin A through stereoselective addition of the lithio anion of (R)-methyl *p*-tolylsulfoxide to an unsaturated sulfinylimine (Scheme 1, eqn (2)).[6o] Another multistep strategy that consists of a 17-steps construction of the azetidine subunit **6** of Penaresidin A, which started from D-galactal and involved Sharpless asymmetric epoxidation, regioselective ring-opening of epoxide and azetidine formation *via* S_N2 reaction, was most recently accomplished by Reddy's group (Scheme 1, eqn (3)).[6p] Although results from most reports are encouraging, poor stereoselectivities, low yields and lengthy synthetic steps present major impediments for the reported strategies to be widely applied. Hence, a short and straight forward synthetic route to azetidine with contiguous stereogenic centers in enantiomerically pure form has remained a great and significant challenge for the chemical community.

With an aim to refine the synthetic route, we formulated a novel strategy which incorporates our reported method for ready access to 3-amino-2,3-dideoxysugars *via* the regio- and stereoselective tandem



Scheme 1 Strategies for construction of azetidine core in synthesis of azetidine alkaloids

hydroamination/glycosylation of glycal as shown in Figure 2.[7] By extension of the synthetic utility of this protocol and its application in the total synthesis of natural products, we aim to demonstrate the efficient synthesis of azetidine from 3,4,6-tri-*O*-acetyl-D-galactal *via* a linear sequence consisting of only 8 steps. Penaresidin B is envisioned as the ideal target molecule for this demonstration (Scheme 1, eqn (4)). Towards the end, the manner by which the above mentioned general strategy could be exploited to accomplish the shortest synthesis of azetidine alkaloids using commercially available and inexpensive compounds, will be discussed.

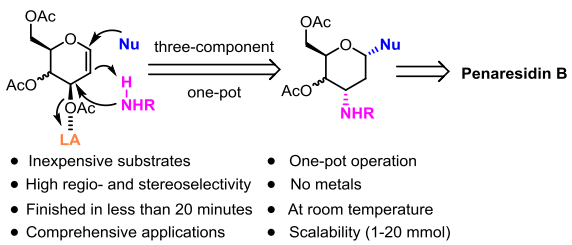
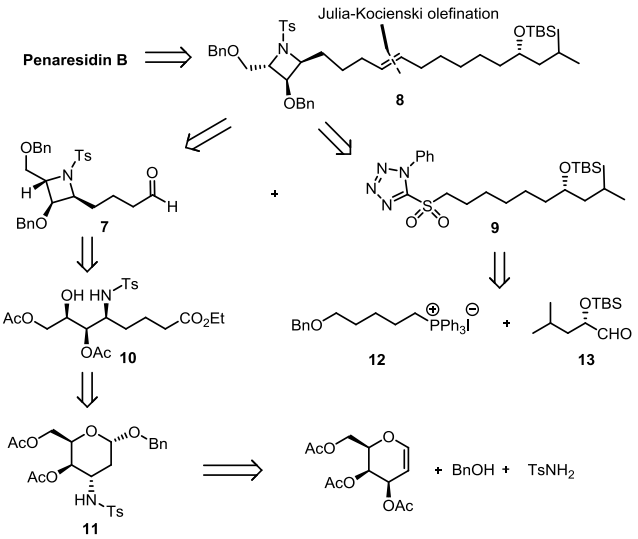


Figure 2 Our strategy for synthesis of penaresidin B *via* 3-amino-2,3-dideoxysugars

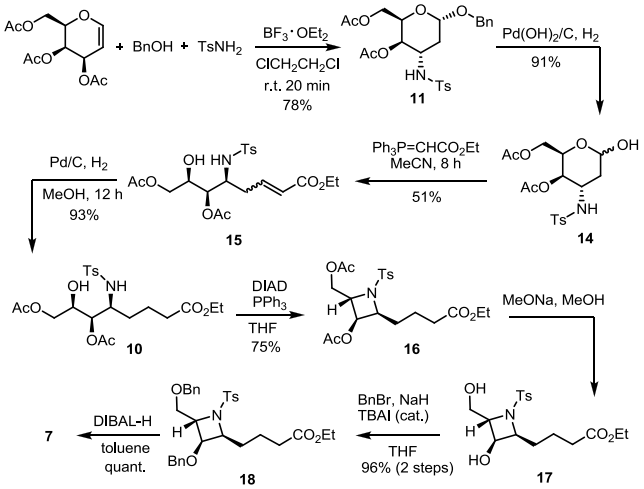
As azetidine alkaloids share similar core structure and differ mainly along their long alkyl chains, we developed a strategy that focused on increasing structural and library diversity in a more efficient manner and hence pave way for potential azetidine analogues to be synthesized for biological studies. Our retrosynthetic analysis of Penaresidin B is depicted in Scheme 2. We proposed that our target molecule can be obtained from intermediate **8** which in turn could be formed *via* Julia–Kocienski olefination between azetidine aldehyde **7** and sulfone **9**. The sulfone moiety **9** could be prepared through Wittig reaction of **12** with aldehyde **13**, while the azetidine core **7**, which can also be regarded as an advanced intermediate for the synthesis of other azetidine alkaloids, presumably can be constructed from the ester **10** using intramolecular Mitsunobu cyclization. Ester **10** could in turn be derived from 3-amino-2,3-dideoxygalactoside **11** by Wittig reaction following removal of benzyl group. Finally, the 3-amino-2,3-dideoxygalactoside **11** could be accessed by regio- and stereoselective tandem hydroamination/glycosylation of D-galactal in a one–pot manner.



Scheme 2 Retrosynthetic analysis for a concise synthesis of penaresidin B

The proposed synthesis of the key fragment 7 starting from D-galactal is detailed in Scheme 3. In the initial step, a mixtureof 3,4,6-tri-*O*-acetyl-D-galactal, benzyl alcohol and *p*-toluenesulfonamide in DCE was subjected to treatment with 2.2 equiv of $BF_3{\cdot}OEt_2$ at room temperature under a nitrogen atmosphere for 20 min. This led to the formation of benzyl 3-*p*-toluenesulfonamido-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-galactopyranoside **11** in 78% yield with exclusive stereoselectivity. The exclusive formation of pure diastereomer allowed easy purification of the desired product by SiO_2 flash column chromatography. Chemical structure determination and stereochemical characterization of **11** was achieved by extensive and detailed 1D and 2D NMR studies.[8] The described protocol resulted in an efficient and stereoselective formation of 3-amino-2,3-dideoxygalactoside **11** with great reproducibility on a gram scale synthesis albeit in slightly lower yields. Sequentially, **11** was treated with $Pd(OH)_2/C$ under a hydrogen atmosphere to allow selective deprotection of the benzyl group and this was followed by Wittig olefination of the resulting aldehyde **14** to form unsaturated ester **15**. Notably, 2-deoxy-β-*C*-glycoside was obtained by intramolecular cyclization when the reaction time was prolonged. Successive treatment of **15** with 10% Pd/C under a hydrogen atmosphere resulted in the reduction of the C-C double bond to form ester **10** with overall 43% yield in three steps. Subsequent intramolecular Mitsunobu reaction in the presence of PPh_3/DIAD, which resulted in the conversion of ester **10** to the azetidine core **16**, proceeded smoothly with a 75% yield.[9] This step represents the key step in the present synthetic route as the core structure azetidine is assembled along with the requisite contiguous stereogenic centers. Removal of all the acetyl groups present in **16** followed by protection with benzyl groups resulted in the formation of compound **18,** a benzyl protected azetidine ester, with a yield of 96%. Chemical structure determination and stereochemical characterization of **16** and **18** were

established based on extensive and detailed 1D and 2D NMR studies, which showed a strong NOE correlation between the protons of C-3 and C-4; and between the protons of C-3 or C-4 and the protons of C-5; and between the proton of C-2 and the protons of C-6, no correlation for H-2/H-4 (Figure 3).[8] Compound **18** was then subjected to chemoselective reduction with DIBAL-H to afford azetidine aldehyde **7** in quantitative yield and was used directly in Julia–Kocienski olefination. Azetidine aldehyde **7** is of great significance for natural product synthesis as it comprises the core structure of several azetidine alkaloids.



Scheme 3 8-Step construction of the core azetidine aldehyde **7**

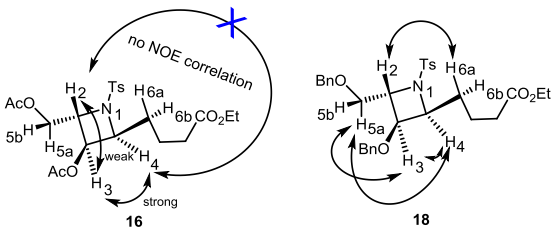
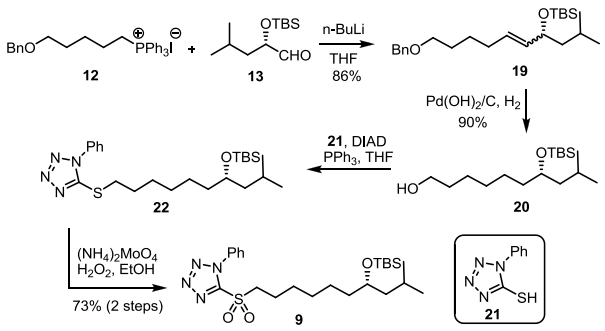


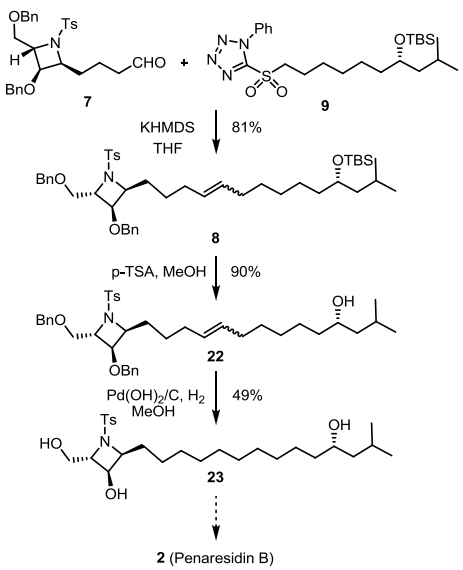
Figure 3 NOE correlations of compounds **16** and **18**

Next, we shift our focus onto the preparation of the desired sulfone **9**. Wittig olefination of two known fragments, stable ylide **12** (prepared from pentane-l,5-diol in 3 steps)[10] and aldehyde **13** (prepared from L-leucine in 4 steps)[11], in the presence of *n*-BuLi was first carried out to afford unsaturated ether **19** in 86% yield (Scheme 4). Treatment of **19** with $Pd(OH)_2/C$ under hydrogen atmosphere resulted in the reduction of the C-C double bond and removal of the benzyl group, which produced a 90% yield of alcohol **20** in one pot. Subsequently, alcohol **20** was converted into thioether **22** using 1-phenyl-1H-tetrazole-5-thiol **21** in the presence of PPh_3/DIAD. This was followed by oxidation of thioether **22** with molybdenum salt and hydrogen peroxide to give sulfone **9** with a 73% yield.[12] The above mentioned protocol produced an enantiopure sulfone with the required R-configuration efficiently and stereoselectively. Additionally, it allows great reproducibility on various scales.



Scheme 4 Preparation of sulfone **9** required for Julia-Kocienski olefination

With the azetidine aldehyde **7** and sulfone fragment **9** successfully prepared, we embarked on the construction of the C-C double bond *via* coupling of these two fragments. Assembly of the azetidine core structure with the sulfone chain constitutes the key step in this synthetic route. This was accomplished *via* Julia–Kocienski olefination, using KHMDS as a base at -78 °C to give olefin **8** in 81% yield.[13] Sequential desilylation of **8** with *p*-TSA in methanol furnished alcohol **22** in 90% yield (Scheme 5) which was later converted to Ts-protected Penaresidin B (**23**) in 49% yield by treatment with 10% Pd/C under hydrogen atmosphere. In fact, removal of the two Bn protecting groups at this point proved rather challenging, as most methods attempted either resulted in no reaction or caused incomplete decomposition of the starting material. To our delight, after numerous attempts, facile deprotection of the two benzyl groups could be achieved with 10% Pd/C under hydrogen atmosphere to afford the desired products, with moderate yield. Ts-protected Penaresidin B (**23**) could be deprotected to eventually give the Penaresidin B in one step.[6h,6j,6o,6q] In summary, starting from commercially available D-galactal, we have accomplished the formal synthesis of Penaresidin B in a linear sequence of 11 steps with an overall yield of 13%.



Scheme 5 Formal synthesis of penaresidin B (**2**)

Overall, we have developed a short, high-yielding synthetic approach for the formation of Penaresidin B. The eight-step

synthesis of azetidine aldehyde with contiguous stereogenic centers entailed our novel strategy for ready access to 3-amino-2,3-dideoxysugar *via* regio- and stereoselective tandem hydroamination/glycosylation of glycal as the key step. One-pot transformations have also been applied to decrease the number of isolated steps and increase the efficiency of the synthesis while the Julia-Kocienski olefination was employed to couple the azetidine and side chain subunits. As three-component reactions have been proven to be useful for large scale syntheses and applicable to various azetidines, scalable synthesis and efficient preparations of Penaresidins A, Penazetidine A and other azetidine alkaloids bearing different side chains can be anticipated. The potential success of this methodology in the creation of a library of azetidine alkaloids analogues will set the foundation for in-depth studies of structure activity relationships.

We gratefully acknowledge Nanyang Technological University (RG6/13) and the Ministry of Education, Singapore (MOE 2009-T2-1-030) for the financial support of this research.

Notes and references

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

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