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Synthesis of complete carbon framework of baulamycin A

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ABSTRACT

The total carbon framework with all chiral carbons of proposed structure of baulamycin A is synthesized using Evans' aldol and Grubbs' cross-metathesis as key reactions. This strategy enables one to access all the isomers of this natural product.

The burgeoning research to identify chemicals from nature with potential antibiotic properties has led to many drugs and leads.[1] However rapid resistance developed by the pathogens is alarming. The low levels of interest in this area by pharmaceutical industries need to be balanced by aggressive approach from academic environment. While pharmaceutical industry has focussed its resources in enhancing the activity of existing pharmacophores, the academic institutions have embarked on identifying new mechanistic pathways to control the pathogen growth. Some such studies revealed that both Gram-positive and Gram-negative bacteria acquire iron utilizing virulence associated siderophores which are essential for bacterial survival.[2] The biosynthetic enzyme of siderophores has been targeted with small membered molecules to generate leads in antibiotics drug discovery.[3] (Fig. 1).

Recently, baulamycins A (**1a**) and B (**1b**) were isolated from *Streptomyces tempisquensis* and structures were established using extensive chromatographic techniques.[4] While baulamycin A exhibited *in vitro* bioactivities against NIS (nonribosomal peptide synthetase independent siderophore) and SbnE (synthetase siderophore staphylo bath biosynthesis protein) at IC_{50} 4.8 μM, baulamycin B exhibited IC_{50} 19 μM. Both compounds showed good activity against NIS synthetase *Bacillus anthracis* siderophore biosynthesis protein of (AsbA) also. The baulamycins A and B differ by only one methyl group at the terminus. The structural features contains seven asymmetric carbons including three hydroxyl groups, three methyl groups and one isobutyl group, dihydroxy phenyl ring and ethyl or methyl ketone at the end. The anti-bacterial properties of baulamycin A (**1a**) especially towards SbnE and AsbA prompted us to take up the total synthesis of this natural product. Disappointingly, while the work was at fag end, Goswami et al. reported the total synthesis of proposed structure of baulamycin A and two other isomers whose data did not match with the reported data.[5] While both syntheses of ours and Goswami et al. relied on Evans' chemistry, we employed Grubbs' metathesis (*vide supra*), whereas Goswami et al. used Wittig olefination to build the framework. Herein we report a strategy which allows installation of all carbon frame work with flexibility to stereodivergence.

The retrosynthetic scheme was designed with a purpose, that will enable one to introduce structural and strereochemical diversity with minimal synthetic interventions. Extensive asymmetric and substrate controlled aldol reactions (for C_4-C_5, C_{12}-C_{13}, $C_{1'}$-C_{14}) and stereoselective reduction (C_{11}) were utilised to install all stereocentres whereas C_9-C_{10} stitching was achieved through Grubbs' cross-metathesis reaction. The two key fragments envisaged are aryl unit **3** embedded with four chiral carbons (styrene unit to support cross metathesis as a type-II olefin to avoid any anticipated self-metathesis) and lipophilic methyl rich olefin unit **4**. The aryl unit **3** in turn was conceived from Evans' aldol reaction between aldehyde **6** and amide **7** and Mukaiyama aldol reaction with silyl enol ether **5**. Similarly, the liphophic intermediate **4** can be obtained from commercially available Roche ester **8** via Evans methylation and aldol reaction with 3-pentanone (Fig. 2).

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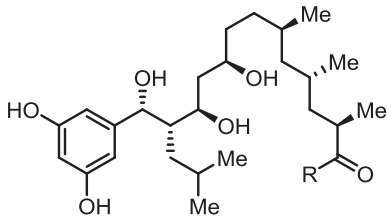


R = Et; Baulamycin A; **1a**
R = Me; Baulamycin B; **1b**

Fig. 1. Proposed structure of baulamycin A & B.

Thus, commercially available dimethoxybenzaldehyde **6** and oxazolidinone **7** under the influence of $TiCl_4$, NMP and DIPEA in CH_2Cl_2 at 0 °C furnished compound **9** in 68% yield with excellent stereocontrol.[6] The resulting *sec*-alcohol functionality in **9** was protected as silyl ether **10** with TBSOTf and 2,6-lutidine in CH_2Cl_2 in 88% yield. Reductive removal of Evans auxiliary was accomplished with $LiBH_4$ in EtOH to generate alcohol **11** in 90% yield. Swern oxidation of alcohol **11** yielded aldehyde which underwent a smooth Mukaiyama aldol reaction[7] with silyl ether **5** in presence of Lewis acid catalysis to yield enone **12** as a mixture of diastereomers (*dr* = 85:15) separated by simple column chromatography in 75% yield. The *syn*-selective reduction[8] of major isomer **12** with Et_2-BOMe and sodium borohydride at −78 °C gave *syn*-diol **13** along with its inseparable minor isomer (*dr* = 91:9) in 90% yield which were separated in the next step. Mixture of both diastereomers were subjected to 2,2-dimethoxypropane/ PPTS to afford acetonide **3** in 92% yield (Scheme 1).

The (*R*)-Roche's ester was converted to **14** following literature procedure.[9] Reduction of α,β-unsaturated ester[10] **14** using $NiCl_2$/$NaBH_4$ furnished silyl ether **15** with excellent yield. Hydrolysis of ester **15** to acid **16** followed by coupling with chiral auxiliary **17** under PivCl/Et_3N conditions provided Evans amide **18** which on alkylation with LiHMDS and MeI at −78 °C provided **19** in 92% yield with excellent diastereoselectivity.[11] The reductive cleavage of auxiliary in **19** with $LiBH_4$ furnished alcohol **20** in 83% yield. Oxidation of alcohol **20** followed by reaction with the Ti^{IV} enolate of pentan-3-one afforded two aldol products **21a** (72%) and **21b** (15%).[12] Both isomers were separated by simple column chromatography and major isomer was assigned as anti-Felkin product **21a** based on literature precedence (Scheme 2).[13] Deoxygenation of the secondary alcohol **21a** using two-step Barton-McCombie protocol[14] furnished ketone **22** in 76% yield which on subsequent desilylation gave alcohol **23** in good yield. Homologation with methylene group was achieved via oxidation of alcohol to aldehyde followed by Wittig olefination with methyltriphenylphosphonium bromide and *n*-BuLi base in decent yield to furnish the second cross-metathesis partner **4** (Scheme 3).

The stitching of two olefin partners **3** and **4** was achieved using Grubbs' 2nd generation catalyst without any self-dimerization to achieve **23** in 54% yield (Scheme 4).[15]

Conversion of **2** to Baulamycin A (**1a**) is expressed to occur via deprotection of the protecting groups. At this point, the publication by Goswami et al. appeared in print which has reported that the structure assigned to baulamycin A (**1a**) did not match with the synthetic compound. As we have also targeted the proposed structure the synthetic efforts were terminated at this stage.

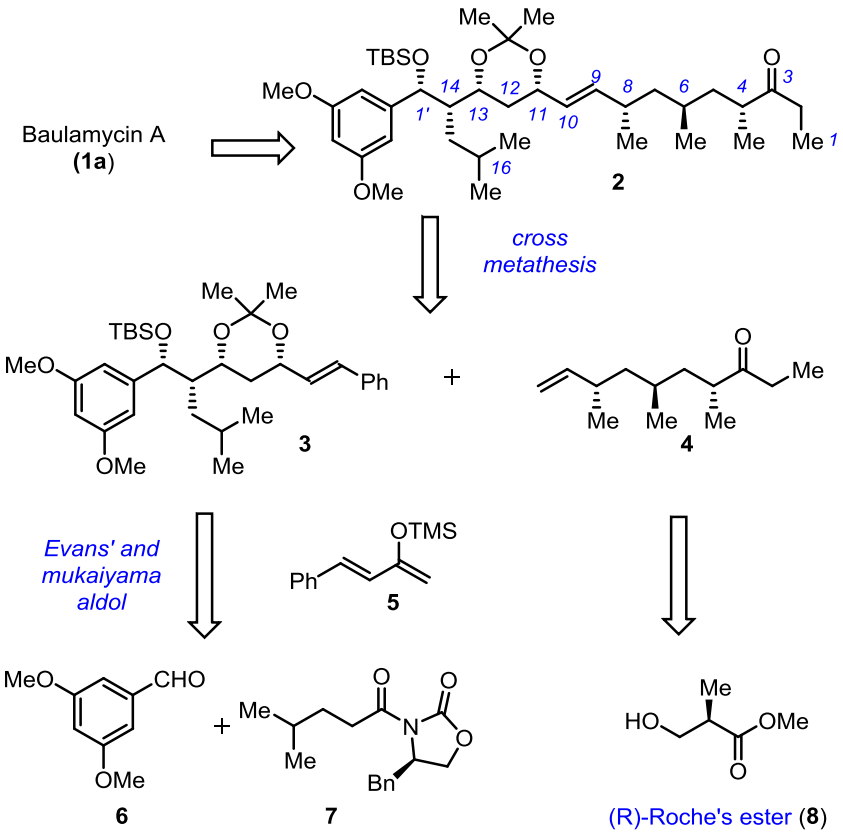
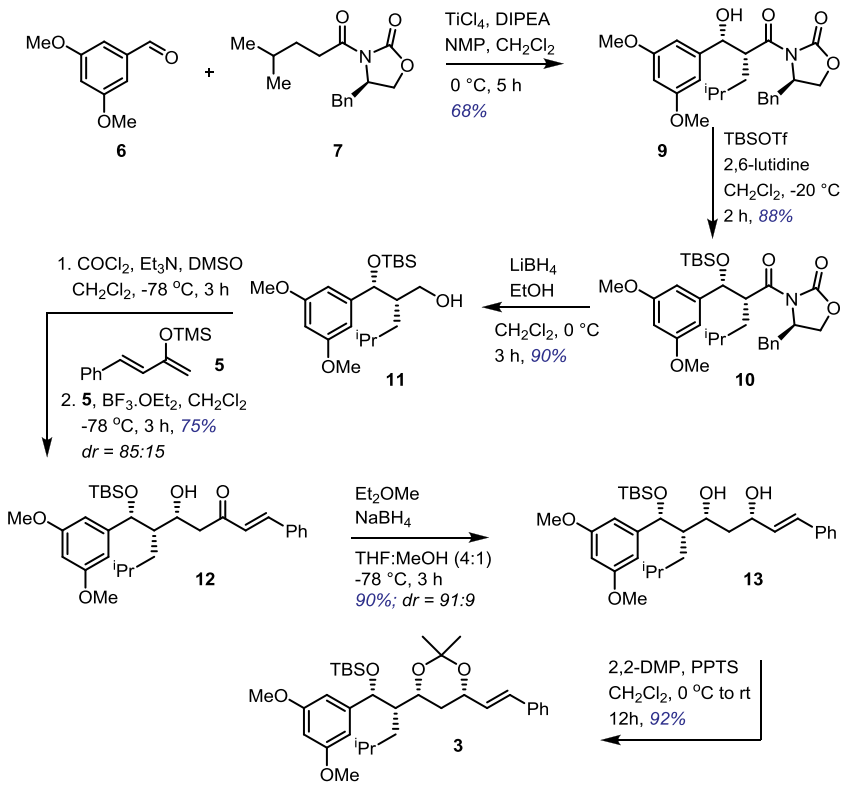
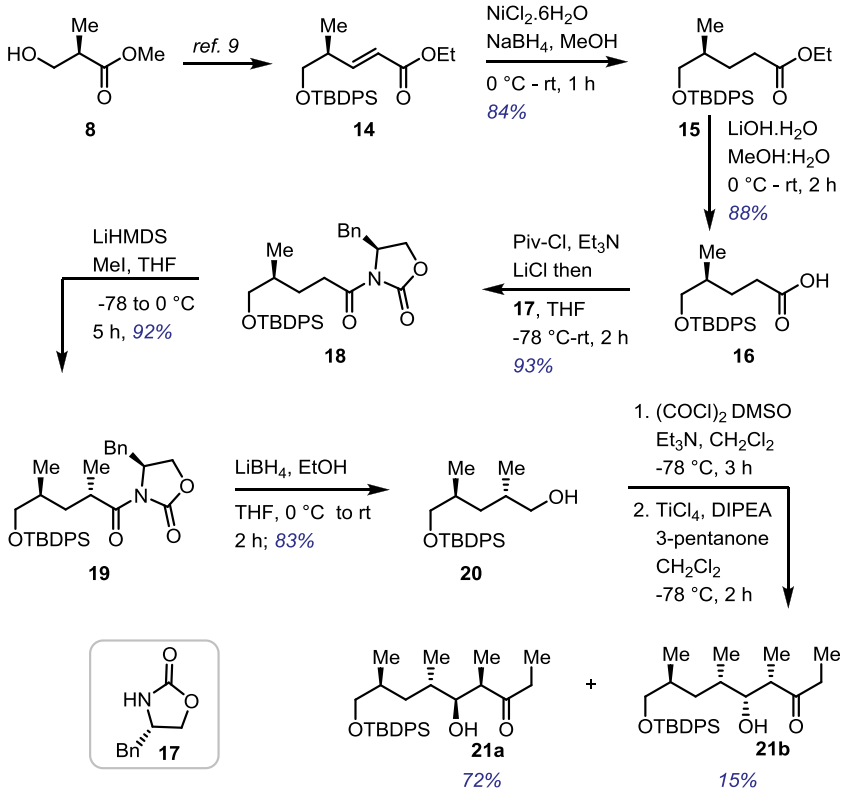


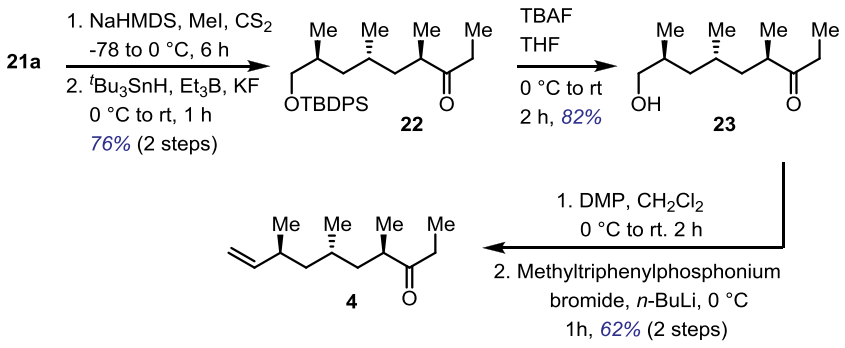
Fig. 2. Retrosynthetic analysis.



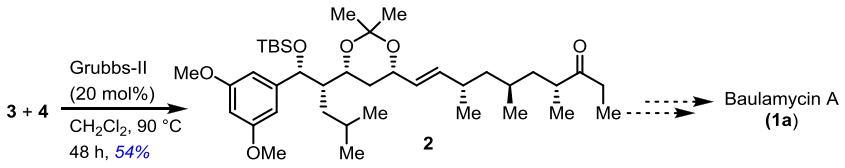
Scheme 1. Synthesis of intermediate **3**.



Scheme 2. Synthesis of the C1–C9 fragment.



Scheme 3. Synthesis of the C1—C10 fragment.



Scheme 4. Synthesis of advanced intermediate **2**.

Conclusions

In conclusion, a flexible protocol amenable for the preparation of all the isomers and analogues of baulamycin is carried out. Our route allows the synthesis of both advanced fragments in large scale. Based on Goswami et al. synthetic studies, the structure of the proposed baulamycin A is not correct and requires structural revision. Synthesis of other isomer is going on in our laboratory and the results of those studies will be published in due course.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.06.011.

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