ORGANIC LETTERS

2011
Vol. 13, No. 15
3924–3927

Synthesis of the Carboline Disaccharide Domain of Shishijimicin A

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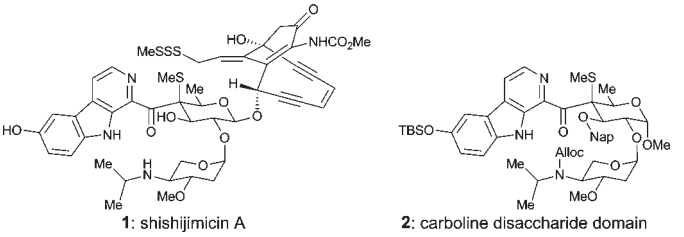
Received May 27, 2011

ABSTRACT



1: shishijimicin A **2**: carboline disaccharide domain

A synthetic route to the carboline disaccharide domain (2) of shishijimicin A (1) has been developed. The convergent synthesis relies on a novel application of the Reetz–Müller-Starke reaction to form the central, sulfur-bearing quaternary carbon center and addition of the carboline structural motif as a dianion to a disaccharide aldehyde fragment.

The enediyne class of natural products has captured the imagination of chemists, biologists and clinicians because of their novel molecular architectures, potent biological properties, and medical potential. Thus, investigations of members of this family of compounds led to important advances in fundamental science and practical applications in cancer chemotherapy.[1]

Isolated from the thin encrusting orange ascidian *Didemnum proliferum*, shishijimicin A (**1**, Figure 1) has joined its siblings (B and C)[2] and namenamicin[3] as the only members of the enediyne class that originate from marine sources. All three shishijimicins carry the same enediyne core as the one found in namenamicin and calicheamicin γ_1^I (known as calicheamicinone).[4] What sets the shishijimicins apart from all other enediynes, however, is their unique carboline structural motif. Indeed, β-carboline is known to intercalate into double-stranded DNA,[5] and a number of β-carbolines have been shown to cleave DNA under photoirradiation conditions.[6] Shishijimicin A (**1**) is the most potent of the shishijimicin family, exhibiting IC_{50} values of 2.0, 1.8, and 0.47 pM cytotoxicities against 3Y1, HeLa, and P388 cell lines, respectively.[2] In light of these observations and the extreme scarcity of shishijimicin A, its total synthesis and that of its carboline disaccharide domain are deemed important. In this letter, we report the

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10.1021/ol201444t
Published on Web 06/28/2011

chemical synthesis of the carboline disaccharide domain **2** of shishijimicin A, whose features include a Reetz–Müller-Starke reaction to install the tetrasubstituted, sulfur-bearing carbon center and a carboline dianion-aldehyde coupling.

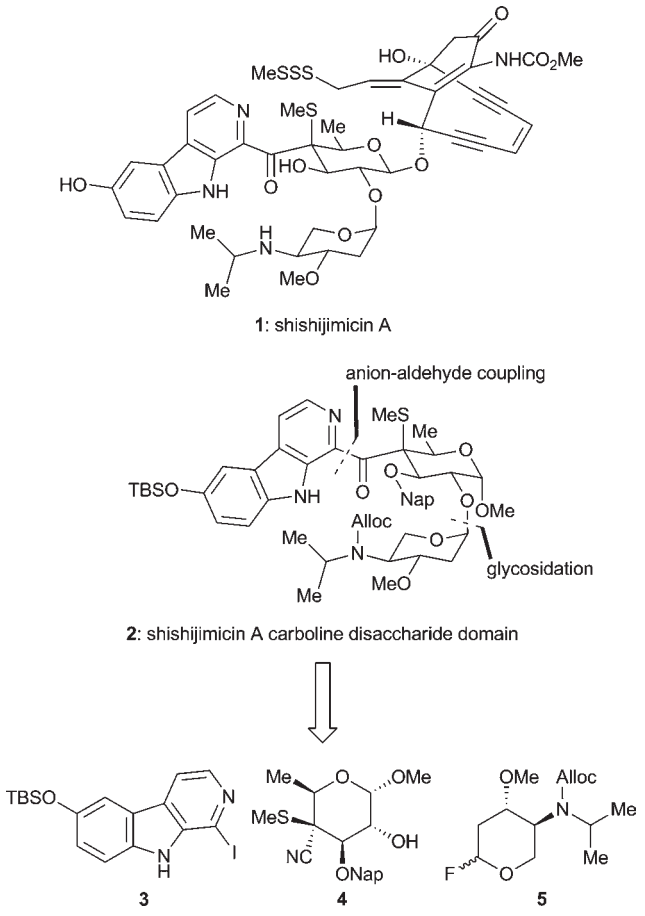
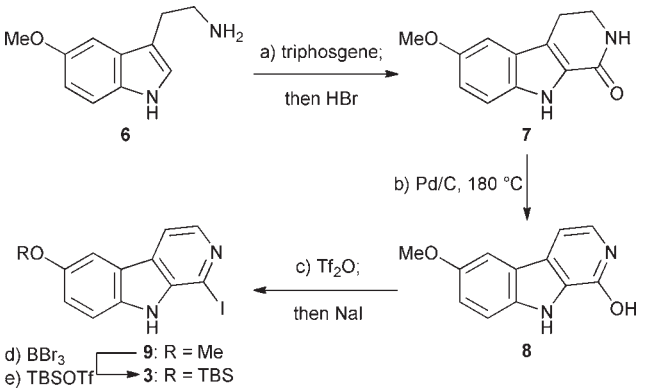


Figure 1. Structures of shishijimicin A (**1**), carboline disaccharide domain **2**, and retrosynthetic analysis of **2**.

Retrosynthetic rupture of the targeted disaccharide fragment **2** as shown in Figure 1 revealed carboline derivative **3**, methylthio sugar **4**, and *N*-alloc aminoglycosyl fluoride **5** as the required building blocks.

Scheme 1 summarizes the developed expedient route to carboline derivative **3** starting with 5-methoxytryptamine **6**. Thus, **6** was sequentially treated with triphosgene (60–70 °C) and 30% HBr in glacial acetic acid (100 °C) to afford the dihydrocarboline **7** in 72% overall yield. The fully aromatized carboline **8** was obtained from the latter compound through oxidation in the presence of 10% Pd/C in refluxing cumene (68% yield). Previous studies[7] with carboline dianions employed bromide derivatives; however, in this case, the bromide was obtained in rather low yield (i.e., <40%), prompting us to target the corresponding iodide derivative, which was also expected to undergo a smoother halogen-metal exchange at the step of the anion-aldehyde coupling. Toward this end, and capitalizing on the reactivity of the hydroxypyridine moiety of compound **8**, we transformed the latter, first to its triflate (Tf_2O, pyridine) and then to its iodide in the same pot by iodide displacement (NaI, TfOH) in 61% overall yield.[8] Exchange of protecting group within the so-obtained iodo-β-carboline **9** (BBr_3, demethylation; TBSOTf, silylation) led to the desired carboline block **3** in 55% overall yield.

Scheme 1. Synthesis of Iodo-β-carboline **3**



With the carboline coupling partner in hand, our attention turned to the synthesis of the central unit of the molecule, namely the methylthio sugar **4**. Our successful construction of this intermediate commenced with differentially protected glycoside **10**[9] and proceeded as shown in Scheme 2. Cleavage of the benzylidene group under acidic conditions (TsOH) liberated the 1,3-diol system **11** (80% yield), whose tosylation (TsCl, Et_3N, DMAP cat.) furnished monotosylate **12** in 89% yield. Subsequent reduction of the tosylate **12** with $LiAlH_4$ led smoothly to 6-deoxymethylpyranoside **13** in 94% yield. The remaining hydroxyl group within **13** was then oxidized with NMO in the presence of TPAP (cat.), yielding ketone **14** (84% yield). Aiming for the eventual installment of the quaternary center bearing the methylthio and nitrile groups in the growing molecule, ketone **14** was treated with TMSSMe and TMSOTf in CH_2Cl_2 at −78 → 0 °C to furnish dithioketal **15** in 94% yield. Careful monitoring of the temperature for this reaction was important, as warming above 0 °C resulted in the formation of a byproduct in which the anomeric methoxy group was replaced with a methylthio substituent.

To complete the construction of the central carbon center bearing the required methylthio and nitrile groups,

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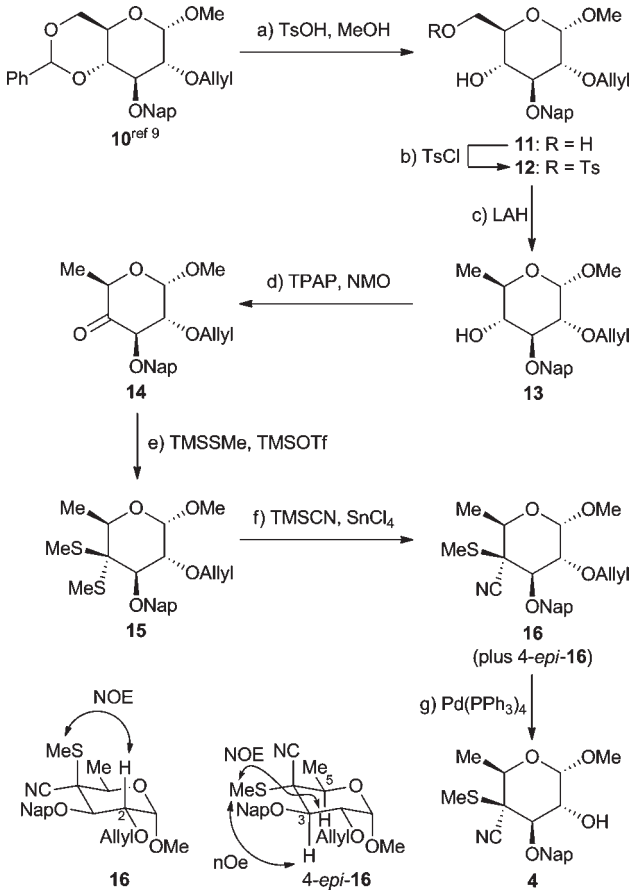
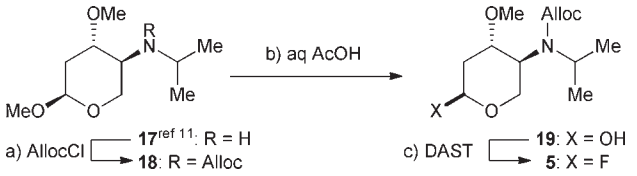
Scheme 2. Synthesis of Thiosugar **4**



we called upon the Reetz–Müller-Starke reaction.[10] This method had been successful previously on dithioketals but not demonstrated on carbohydrates such as **15**, where the anomeric methoxy group may lead to complications. Despite these fears, we were pleased to observe that, under the conditions originally reported by Reetz and Müller-Starke (i.e., TMSCN, $SnCl_4$, CH_2Cl_2, 0 °C), dithioketal **15** reacted to afford the expected methylthio nitrile **16** as a ca. 2:1 diastereomeric mixture and in 75% combined yield. The structures of the chromatographically separated isomers **16** (major, desired) and 4-*epi*-**16** (minor, undesired) were assigned by ^{1}H NMR spectroscopic analysis. Specifically, the desired isomer **16** exhibited a diagnostic NOE between the methylthio group protons and the C-2 proton, whereas the undesired epimer did not (see chair structures **16** and 4-*epi*-**16** in Scheme 2). In support of the stereochemical assignment of 4-*epi*-**16** were the NOE's exhibited between its methylthio group protons and those at C-3 and C-5. All that remained to generate the targeted fragment **4** was the deallylation of intermediate **16**, a reaction that proceeded smoothly, and in 77% yield, in the presence of $Pd(PPh_3)_4$.

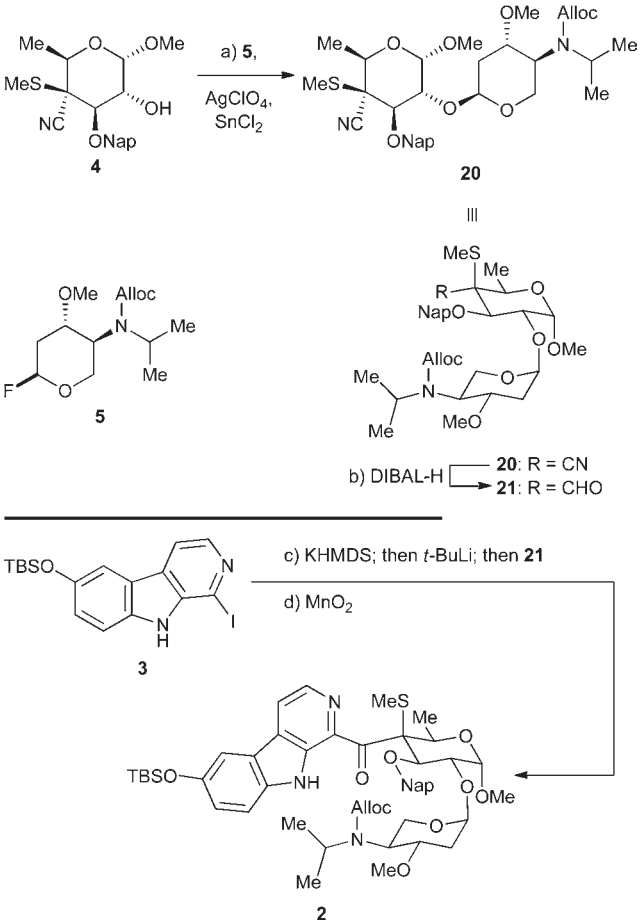
(10) Reetz, M. T.; Müller-Starke, H. *Tetrahedron Lett.* **1984**, *25*, 3301–3304.

Scheme 3. Synthesis of Glycosyl Fluoride **5**



The preparation of the remaining carbohydrate unit, glycosyl fluoride **5**, was prepared from the known amino glycoside **17**,[11] as summarized in Scheme 3. The alloc group was chosen as a protecting group for the secondary amine moiety, instead of the Fmoc group employed in previous work,[12] due to the anticipated basic conditions of the carboline coupling. Thus, treatment of **17** with allyl chloroformate in the presence of K_2CO_3 and 18-crown-6 led to carbamate **18** (98% yield), whose exposure to AcOH/H_2O (5:1) at 95 °C liberated lactol **19** (70% yield; 90% based on recovered starting material). Finally, glycosyl fluoride **5** was formed from the latter compound through the action of DAST in 64% yield.

Scheme 4. Fragment Coupling and Completion of the Synthesis of Carboline Disaccharide **2**



With all three required fragments available, their coupling and elaboration to the targeted carboline disaccharide domain **2** became the next task. Scheme 4 summarizes the accomplishment of this goal. Coupling of carbohydrate fragment **4** with glycosyl donor **5** proceeded smoothly following the Mukaiyama protocol.[11a,13] Thus, in the presence of $AgClO_4$ and $SnCl_2$ under anhydrous conditions (4 Å MS), the mixture afforded, stereoselectively, disaccharide **20** in 85% yield (based on **4**). Direct addition of the dianion derived from carboline fragment **3** to disaccharide nitrile **20** gave a complex mixture of products, necessitating the intermediacy of aldehyde **21**. The latter was produced from **20** by DIBAL-H reduction (−78 °C, 88% yield). Reaction of this aldehyde with the dianion generated from iodocarboline derivative **3** by deprotonation (KHMDS, Et_2O, −20 °C), followed by halogen-metal exchange (*t*-BuLi, −78 °C), resulted in the formation of the corresponding coupling product as a mixture of diastereomeric alcohols (**2′**, *epi*-**2′**, not shown, *dr* ca. 1:1; 70% yield based on 50% recovered starting material **21**).[7a] This mixture was then oxidized with MnO_2 to afford the targeted ketone **2** in 74% yield.

The described chemistry provides a highly convergent entry to the carboline disaccharide domain **2** of shishijmicin A (**1**), paving the way for an eventual total synthesis of the natural product itself, and for binding and biological evaluation studies with the synthesized domain **2** and its derivatives. This synthesis demonstrated the application of the Reetz−Müller-Starke reaction[10] and of the carboline dianion coupling in complex situations.

Acknowledgment. Within The Scripps Research Institute, we thank Drs. D.-H. Huang and L. Pasternack for NMR spectroscopy assistance and Dr. G. Siuzdak for mass spectrometry assistance. Financial support for this work was provided by the National Institutes of Health (U.S.A.) (R01 CA100101) and the Skaggs Institute for Research, as well as predoctoral fellowships from the National Science Foundation and Skaggs−Oxford Scholarship program (both to J.L.K.), and postdoctoral fellowships from A*STAR (Singapore to W.T.) and the Alexander von Humboldt Foundation (Germany, to J.B.).

Note Added after ASAP Publication. The toc/abstract graphic and Figure 1 contained an error in the version published ASAP June 28, 2011, the correct version reposted June 30, 2011.

Supporting Information Available. Schemes with respective reagents and conditions, experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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