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Stereoselective synthesis of a tricyclic guanidinium model of cylindrospermopsin

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Abstract

An 11-step enantioselective synthesis of the A-ring of cylindrospermopsin is described using an intramolecular conjugate addition as the key step to forming the piperidine ring. Further elaboration generates a tricyclic guanidine via a sequential double displacement strategy as a model for the cylindrospermopsin guanidinium core.

Keywords: cylindrospermopsin; guanidines; piperidines.

In 1979, drinking water contaminated with cyanobacteria caused a hepatoenteritis outbreak in Australia.[1] The causative toxin, cylindrospermopsin (**1**), was first isolated by Moore[2a] in 1992 from the cyanobacterium *Cylindrosperopsis raciborskii* and was later found in *Umezakia natans*[2b] and *Aphanizomenon ovalisporum* (Scheme 1).[2c] Cylindrospermopsin is toxic to cultured rat hepatocytes and is thought to inhibit reduced glutathione synthesis.[3] Architecturally, cylindrospermopsin is a compact zwitterionic molecule composed of a tricyclic guanidinium portion and uracil section. Currently, two groups have published synthetic approaches to this complex natural product,[4] including Snider and Xie's[4a] very concise synthesis of the hydroxymethyluracil fragment attached to a model of the AB-bicyclic guandinium system. The dense functionality and multiple stereocenters make the synthesis of cylindrospermopsin a very challenging prospect.

Our approach to cylindrospermopsin relies on forming the hydroxymethyl unit via a C-6 uracil anion[5] addition into the appropriately protected aldehyde **2** (Scheme 2). Guanylation of piperidine **3** and double displacement of the appropriate alcohols would yield the tricyclic guanidine core. The stereochemistry of the acyclic amine **4** should give rise to a single diastereomer upon intramolecular conjugate addition. Here

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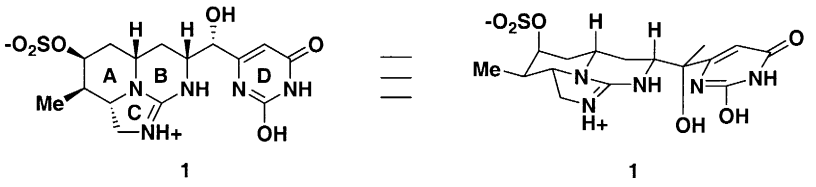
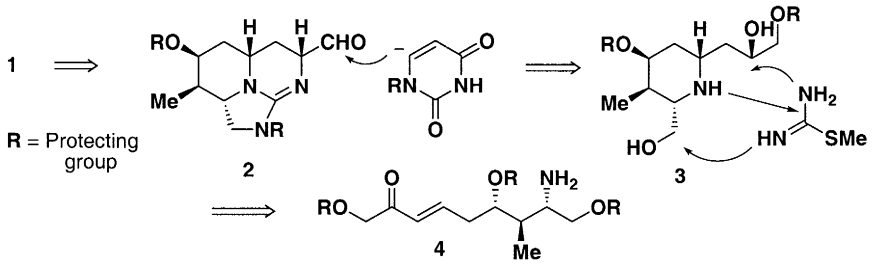


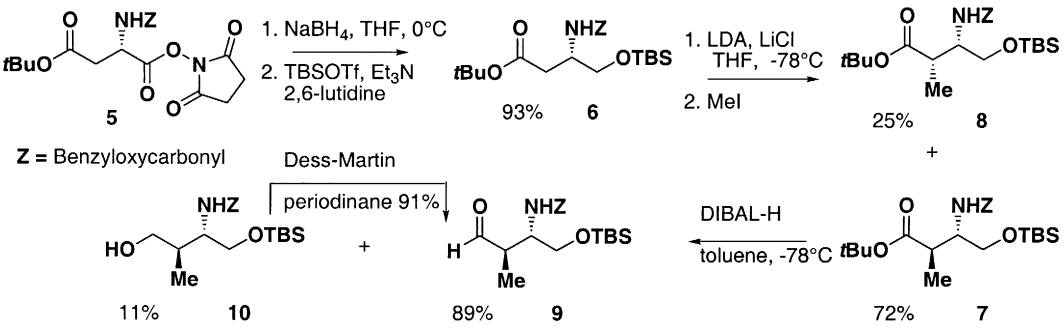
Scheme 1.

we report the stereoselective synthesis of the protected tricyclic guanidine **27** as a model demonstrating the feasibility of our synthetic design towards cylindrospermopsin.



Scheme 2.

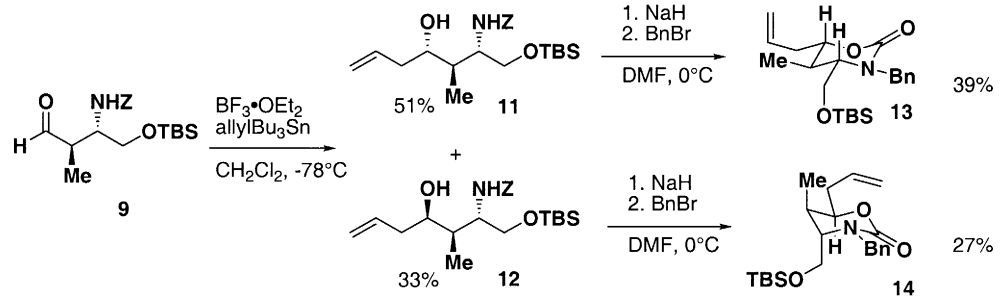
Sodium borohydride reduction of the commercially available activated aspartic acid derivative **5** followed by TBS protection of the resulting primary alcohol gave **6** in 93% yield (Scheme 3). Modifying conditions developed by Seebach[6] for similar aspartic acid analogs, formation of the dianion of **6** at −78°C using 2 equiv. of LDA followed by addition of iodomethane generated a 3:1 ratio of diastereomers **7** and **8** in 97% yield. At this point **7** was assigned the *anti*-configuration based on the precedent by Seebach.[6b] DIBAL-H reduction of the *t*-butyl ester **7** created aldehyde **9** in 89% yield, and the primary alcohol **10** in 11% yield which was easily oxidized to **9** using Dess–Martin periodinane (Scheme 3).[7]



Scheme 3.

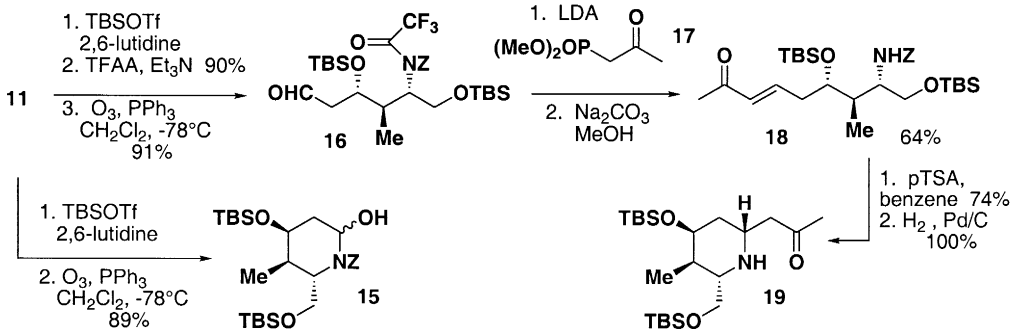
Diastereoselective allylation of aldehyde **9** in an *anti*-Felkin–Anh fashion created the last of the three contiguous stereocenters contained in the piperidine A-ring of cylindrospermopsin (Scheme 4). The Brown allylboration reaction using (−)-isopinocamphorborane auxiliary[8] gave the best diastereomeric ratio (2:1) of **11** to **12** in an acceptable 70% yield. However, we did find that treating a solution of aldehyde **9** and 2 equiv. of allyltributyltin in CH_2Cl_2 at −78°C with 1 equiv. of BF_3OEt_2 gave superior yields of 84% but with diminished diastereoselectivity (1.5:1 of **11**:**12**). Generation of the corresponding cyclic carbamates **13** and **14** helped us to determine the absolute stereochemisty of **11** and **12**. 2D NOESY experiments indicated that the cyclic carbamates **13** and **14** had the stereochemistries and conformations

as drawn.[9] These data confirm the expected diastereoselectivity for the methylation of **6** and prove the absolute stereochemistry of alcohols **11** and **12**.



Scheme 4.

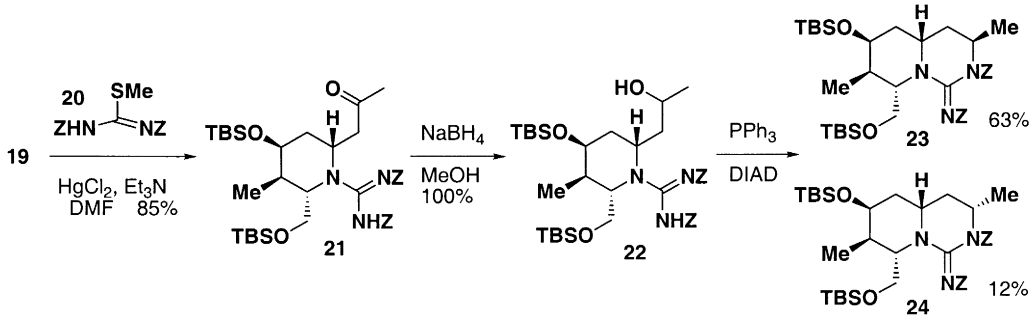
Protection of alcohol **11** with TBSOTf and 2,6-lutidine was quantitative. Ozonolysis of the terminal alkene resulted in a mixture of cyclic hemiaminals **15** (Scheme 5). In order to avoid this undesired cyclization the carbamate nitrogen of the bis-TBS diol was protected using TFAA and Et_3N in 90% yield. Subsequent ozonolysis generated aldehyde **16** in 91% yield. Reacting **16** with 2.5 equiv. of freshly prepared phosphonate ylide generated from **17** in THF followed by methanolic sodium carbonate work-up gave the α,β-unsaturated methyl ketone **18** in 64% yield along with hemiaminals **15** in 27% yield. As predicted, treating **18** with a catalytic amount of *p*TSOH in refluxing benzene gave one diastereomer of the corresponding *Z*-protected piperidine in 74% yield. Subsequent hydrogenation generated piperidine **19** in quantitative yield (Scheme 5).



Scheme 5.

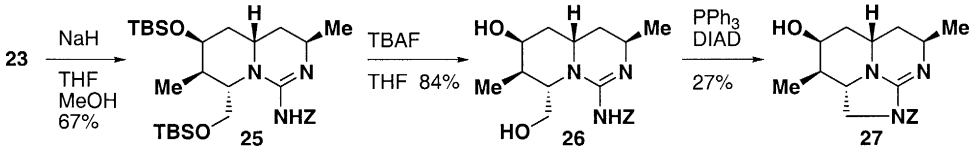
2D NOESY experiments confirmed that the relative and absolute stereochemisty of **19** corresponds to the stereochemistry of the A-ring of cylindrospermopsin.[9] Treatment of **19** with bis-*Z*-methylthiopseudourea **20**,[10] $HgCl_2$ and Et_3N in DMF guanylates the hindered piperidine nitrogen generating **21** in 85% yield, along with a small amount of ring-opened product (Scheme 6). The first of the two envisioned S_N2 displacements requires the alcohol with appropriate stereochemistry resulting from reduction of the methyl ketone. As a model study, treatment of **21** under non-asymmetric conditions using sodium borohydride quantitatively reduced the methyl ketone into an inseparable mixture of alcohols **22** that exists in roughly a 5:1 ratio by NMR. Subjecting the mixture **22** to Mitsunobu conditions generated the guanidine bicycles **23** and **24** in 75% combined yield (Scheme 6).[11] 2D NOESY experiments on the minor bicycle **24** confirm the equatorial conformation of the methyl group in the newly formed B-ring.[9]

Due to the small amount of **24** formed, bicyclic guanidine **23** was chosen to test conditions for tricycle formation. Sodium hydride in a THF:methanol (1:1) solution selectively deprotected one of the *Z*-groups to generate **25** in 67% yield (Scheme 7).[12] Treatment of the monoprotected guanidine with TBAF solution



Scheme 6.

in THF removed both TBS groups to give **26** in 84% yield. Cyclization using Mitsunobu conditions successfully generated the protected guanidine tricycle **27** as the only isolated product in 27% yield.



Scheme 7.

We have shown the utility of our synthetic plan towards cylindrospermopsin by synthesizing the bicyclic guanidine **24**, which possesses the relative and absolute stereochemistry of the natural product. Construction of the natural product would require the appropriately protected α-hydroxyphosphonate in place of **17** to generate aldehyde **2** following the same route. Finally, the synthesis of tricycle **27** demonstrates the feasability of a double displacement strategy to install the tricyclic guanidinium core of cylindrospermopsin.

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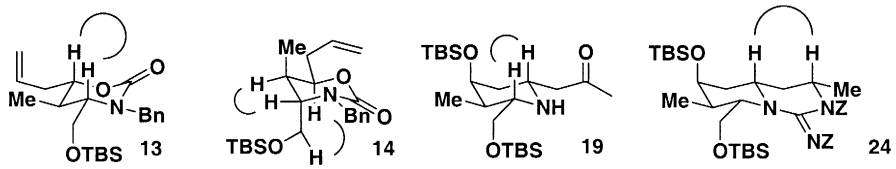

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