Synthetic Studies on a Model of Cylindrospermopsin

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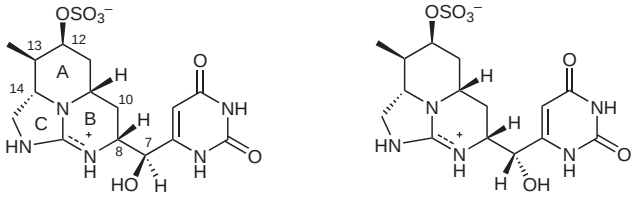
Abstract: A new strategy for the synthesis of cylindrospermopsin is described using an intramolecular Mannich reaction to form ring A. Guanylation of the piperidine nitrogen and reaction on an activated double bond generates ring B.

Key words: cylindrospermopsin, piperidines, intramolecular Mannich reaction

Cylindrospermopsin (**1**) has been isolated from different sources of cyanobacteria, predominantly *Cylindrospermopsis raciborskii*,[1] but also *Umezaki natans*[2] and *Aphanizomenon ovalisporum*.[3] This compound, together with its diastereoisomer **2**,[4] exhibits hepatotoxic activity when 7-deoxycylindrospermopsin (**3**) is devoid of biological activity (Figure1).[5]



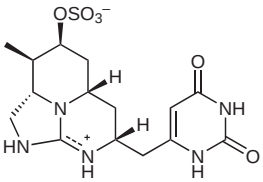
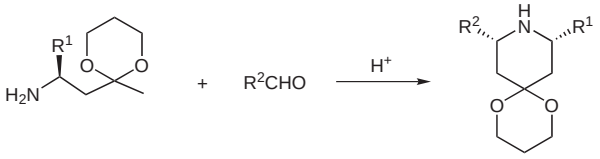


Figure 1

Due to the various functionalities in the molecules and their high toxicity, the synthesis of cylindrospermopsin alkaloids in both their racemic[6] and enantiomeric form[7] has been attempted. Part of our research involves the asymmetric synthesis of saturated N-heterocycles. We have studied a simple and efficient Mannich-type cyclization permitting rapid and highly stereoselective access to polysubstituted piperidine systems (Scheme 1), which have been validated through the enantioselective synthesis of various alkaloids.[8]



Scheme 1

We decided to extend our methodology to more challenging targets and focused on the cylindrospermopsin alkaloids. Our approach to cylindrospermopsin (**1**) is depicted in Scheme 2. Displacement of the primary alcohol derivatives in **4** would yield the tricyclic guanidine core. Synthesis of **4** relies on forming the hydroxy function via a stereoselective intramolecular opening of an appropriate epoxide by a guanylated piperidine.[9]

Therefore, a possible precursor of compound **4** could be **5**, which results from guanylation of the piperidine nitrogen and a stereospecific epoxidation of the double bond of **6**. Compound **6** could be obtained by stuctural transformations on tetrasubstituted piperidine **7**, generated by an intramolecular Mannich-type reaction,[8] with the ultimate starting point being the correct stereoisomer of amine **8**. We wish to report our strategy and preliminary results towards the stereoselective construction of the cylindrospermopsin framework.

In order to test the strategy, we chose to work on a simpler model starting from amine **8** and benzaldehyde. Synthesis of amine **8** was realized from commercial methyl-3-oxopentanoate (**9**, Scheme 3). Protection of the keto function of **9** with ethylene glycol, followed by reduction with lithium aluminum hydride furnished the alcohol **10**. Oxidation with manganese dioxide and subsequent Wittig–Horner olefination gave unsaturated ester **11**. Diastereoselective conjugate addition of *N*-benzyl-*N*-methylbenzylamine to **11** (de>95%) led, after deprotection of the amino group, to amine **8**, in a 27% overall yield (six steps).

Intramolecular Mannich reaction of **8** and benzaldehyde using our standard conditions cleanly afforded the expected piperidine **12** as a mixture of diastereoisomers (**12a**:**12b** = 3:2), which were isolated in 62% yield and separated by flash column chromatography (Scheme 4). We have previously demonstrated that the potential carbonyl functionality could be conveniently used to quantitatively epimerize a substituent in the α-position.[10] Furthermore, subsequent reduction of this carbonyl group with L-Selectride® gave the desired alcohol with an axial

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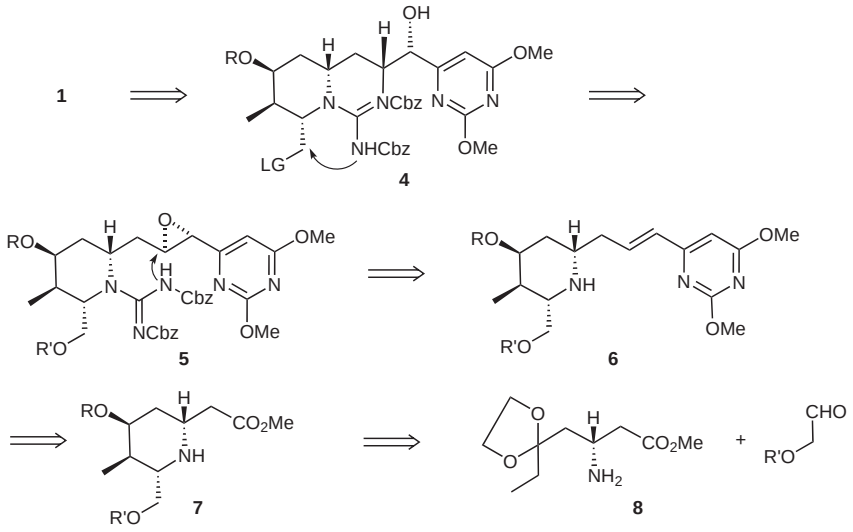
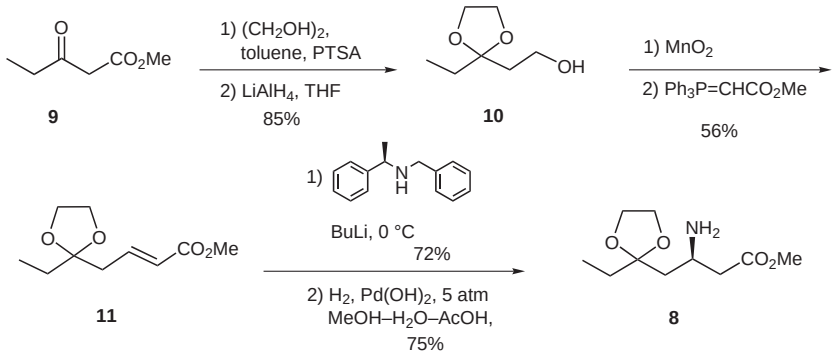


Scheme 2

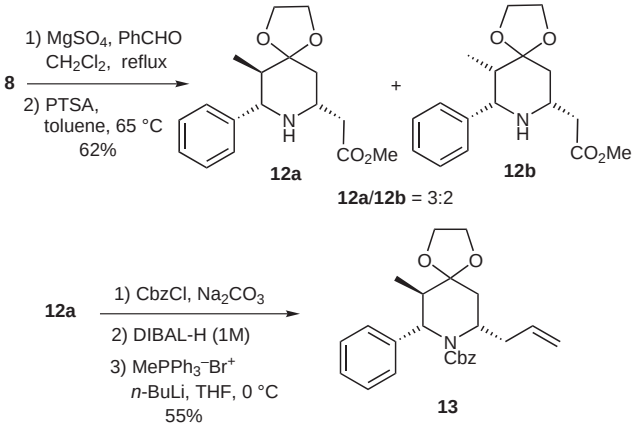


Scheme 3

configuration and excellent diastereoselectivity.[10] All the subsequent reactions were done on major isomer **12a**. Attempts to Boc-protect the amine functionality of the piperidine **12a** were unsuccessful. However, Cbz-protection and subsequent reduction of the N-protected piperidine with DIBAL-H led to the corresponding aldehyde, which could be used in the next step without purification. Wittig–Horner olefination, using methyl triphenylphosphonium bromide, gave piperidine **13** in an overall yield of 55% for three steps.

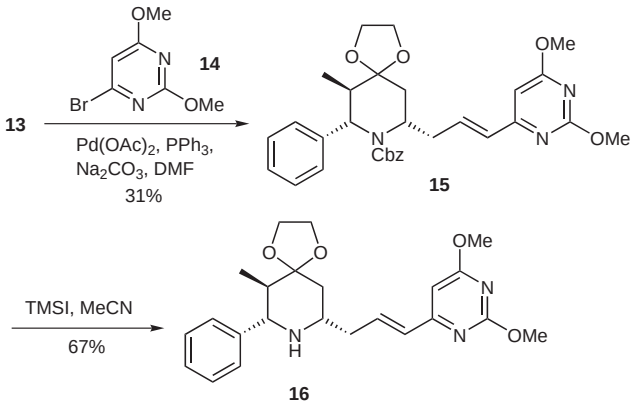
Heck cross-coupling[11] of **13** with 4-bromo-2,6-dimethoxypyrimidine (**14**)[12] led to piperidine **15**, albeit in poor yield. Modifying the conditions of this reaction (reagents, temperature and solvent) did not improve the yield. Convenient N-deprotection of the Cbz using TMSI in acetonitrile[13] gave the expected piperidine **16** in an overall yield of 67% (Scheme 5).

Treatment of **16** with bis(benzyloxycarbonyl)methylthiopseudourea **17**,[14] using mercury(II) chloride and triethylamine in *N*,*N*-dimethylformamide at 0 °C, conveniently guanylated the hindered piperidine nitrogen, which spontaneously cyclized to **18** during purification (flash chromatography) in an unoptimized 45% yield (Scheme 6).

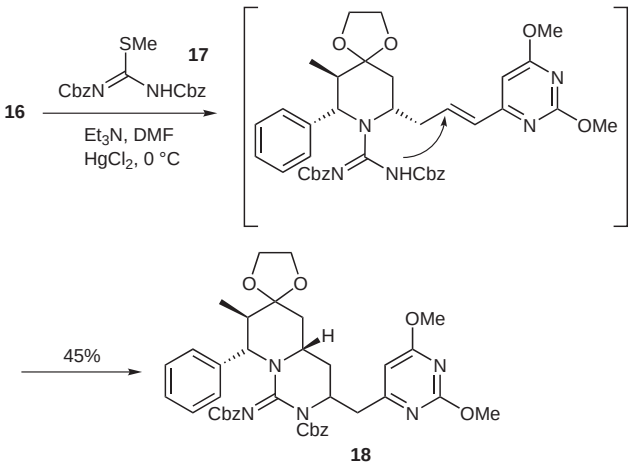


Scheme 4

In conclusion, we have developed a new approach to cylindrospermopsin alkaloids by efficiently synthesizing the A and B rings of their framework. We are now working on the synthesis of piperidine **7**, as well as the epoxidation step, which must be realized before guanylation of the piperidine nitrogen. This work is currently under investigation and will be reported shortly.



Scheme 5



Scheme 6

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