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Construction of the A-ring of cylindrospermopsin via an intramolecular oxazinone-*N*-oxide dipolar cycloaddition

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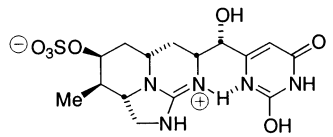
Abstract—The efficient synthesis of an A-ring synthon for the marine hepatatoxin cylindrospermopsin has been achieved. The key step features an intramolecular oxazinone *N*-oxide/alkene dipolar cycloaddition resulting in the establishment of the three contiguous stereogenic centers in the A-ring from one pre-existing stereogenic center in a single step.

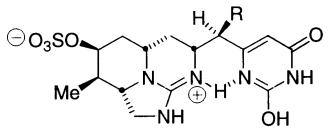
Cylindrospermopsin (**1**) was first isolated in 1992, from the marine cyanobacterium *Cylindrospermopsis raciborskii*.[1a] Following the initial discovery of **1** it has also been isolated from *Aphanizomenon* ovalisporum[1b] and *Umezikia natans*.[1c] The family has recently been expanded with the isolation of 7-*epi*-cylindrospermopsin (**2**)[2a] and deoxycylindrospermopsin (**3**).[2b] These compounds have exhibited hepatotoxic activity ($LD_{50}=0.5$–0.2 mg/kg in mice for **1**) and are partially responsible for the acute toxicity of algae blooms.[3] Much effort has been dedicated to the detection of these toxins in water supplies as outbreaks of both human and animal hepatoenteritis have become a serious problem.[4a] Cylindrospermopsin, along with mycrocrystin heptapeptides, have been implicated in the death of at least 50 people in Cararu, Brazil who consumed contaminated drinking water.[4b] Although the exact mode of action has not been elucidated for these compounds, it has been shown that cultured rat hepatocytes experience an inhibition of glutathione synthesis prior to cell death.[3,5]



1, cylindrospermopsin

In addition to cylindrospermopsin's intriguing biological activity, the incorporation of six stereogenic centers, the zwitterionic guanidinium and sulfate units, and a densely functionalized tricyclic core have made these molecules attractive synthetic targets. A racemic total synthesis of **1** has recently been accomplished[6] and several synthetic strategies have appeared in the literature.[7] We envisioned that the three contiguous stereogenic centers of the 4-hydroxypiperidine moiety in the A-ring of **1** could be set in a single intramolecular cycloaddition reaction.

The intramolecular 1,3-dipolar cycloaddition (1,3-DC) of nitrones has become a powerful tool to access architecturally complex heterocycles.[8] Nonetheless, the use of functionalized nitrone precursors, in particular α-alkoxycarbonylnitrones, has found little application in the synthesis of natural products.[9] This is in part due to poor stereoselectivity arising from nitrone *E*/*Z* isomerization in acyclic systems. The ability of the 1,3-DC reaction to set three contiguous stereogenic centers, with the possibility of post cycloaddition manipulation of the carbonyl functionality, makes α-alkoxycarbonylnitrones functionally rich synthons for heterocyclic ring construction. The development of geometrically (*E*/*Z*) constrained nitrones, from chiral 1,4-oxazin-2-ones



2, R = OH
3, R = H

(oxazinone *N*-oxides), have shown excellent regio- and diastereoselectivity in intermolecular 1,3-DC reactions, but have remained unexplored in an intramolecular fashion.[10]

The synthesis of the requisite oxazinone *N*-oxide **10**, began with the esterification of (±)-3-buten-2-ol (**4**) with *N*-*t*-Boc-Gly to afford the allylic ester **5** (Scheme 1).[11]

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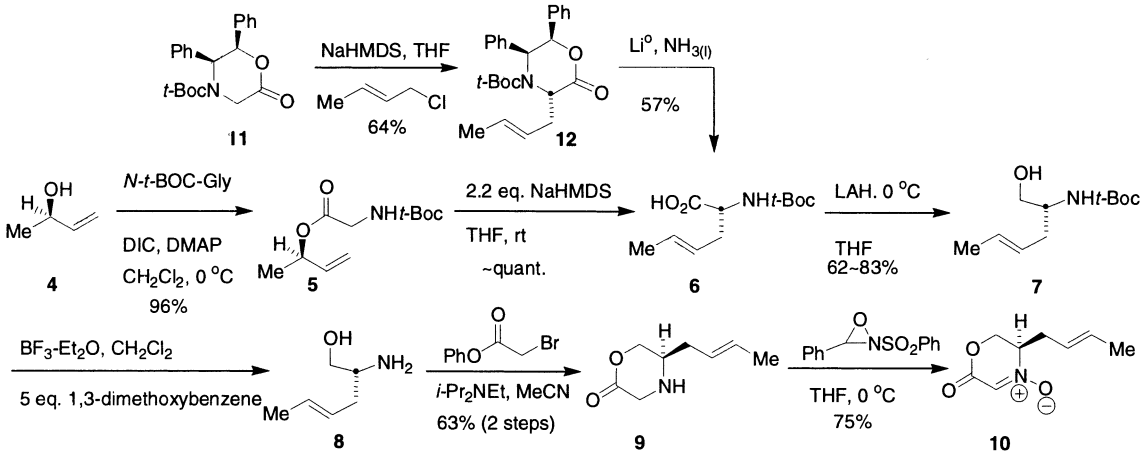


Scheme 1.

The dianion of **5**, generated by the addition of sodium bis(hexamethylsilyl)amide, smoothly underwent [3,3]-sigmatropic Claisen rearrangement to give the crotyl glycine derivative **6** in quantitative yield.[12]

The optically active *N*-*t*-Boc crotylglycine[13] derivative **6**, could alternatively be prepared by enolate alkylation of the commercially available oxazinone **11** affording **12** as a single stereoisomer in 64% yield.[14] Birch reduction of **12** afforded **6** in 57% yield and >99:1 er. Preliminary results have shown that rearrangement of the ester **5** derived from *R*-(−)-3-buten-2-ol proceeds in 91.5:8.5 er.

Reduction of **6** with lithium aluminum hydride generated the protected amino alcohol **7** in 62–83% yield.[15] Removal of the *t*-Boc group was effected by treatment with boron tifluoride etherate.[16] It should be noted that, the use of traditional Brønsted and Lewis acids led predominantly to urethane formation. Treatment of the free amino alcohol **8** with α-bromophenyl acetate in situ gave moderate yields of the oxazin-2-one **9**.[17]

Oxidation of the secondary amine (**9**) with Davis' oxaziridine led exclusively to the conjugated oxazinone-*N*-oxide **10** in 75% yield.[18] The dimerization of **9** to the corresponding diketopiperazine was rapid in polar solvents. Oxidation of the amine was therefore carried out immediately after isolation of **9**. The stability of nitrone **10** was surprising as no dimerization[9b] nor spontaneous cyclization was observed.

Exposure of the oxazinone-*N*-oxide **10** to elevated temperatures cleanly effected the 1,3-dipolar cycloaddition reaction to give the tricyclic isoxazolidine **13** in 78% isolated yield (Scheme 2). As expected from Oppolzer's work with intramolecular *N*-alkenylnitrone cycloadditions,[9b] the nitrone **10** added suprafacially to the alkene predominantly through the chair like *exo*-transition state $A^{\ddagger}$ to give **13**. Although the reaction produced **13** as a single diastereomer it was accompanied, as a 10:1 mixture, by the regioisomeric isoxazolidine **14** as evidenced by a quartet at 3.77 ppm (1H, $J=6.3$ Hz) in the

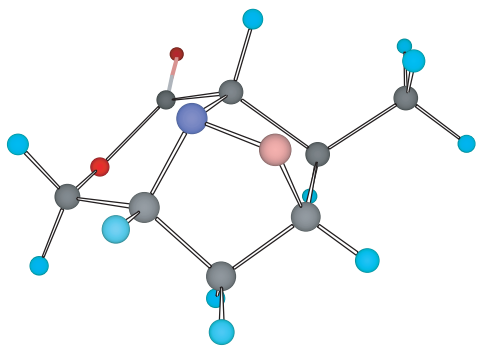
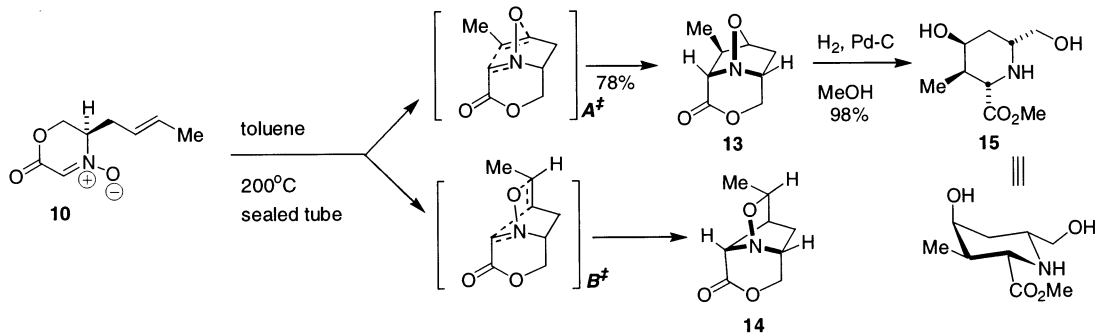


Figure 1. X-Ray structure for **13**.



Scheme 2.

^{1}H NMR spectrum for the alkoxy-methine proton. The stereochemistry of **13** was confirmed by single-crystal X-ray diffraction (Fig. 1). Presumably severe eclipsing interactions in the regioisomeric *exo*-transition state ***B***‡ disfavor the formation of the tricyclic ring system in **14**.

Hydrogenolysis of **13** in the presence of methanol led directly to the ester **15**. NO bond cleavage in **13** leads to a highly strained bicyclic system. The resulting 1,3-diaxial disposition of the lactone renders the ensuing *trans*-esterification a facile process.

In summary, we have found that the use of α-alkoxycarbonylnitrones to be an efficient and highly stereoselective route to the 4-hydroxy piperidine moiety in the A-ring of cylindrospermopsin. Current work in our laboratory is directed toward the enantioselective total synthesis of cylindrospermopsin utilizing this general approach.

Acknowledgements

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