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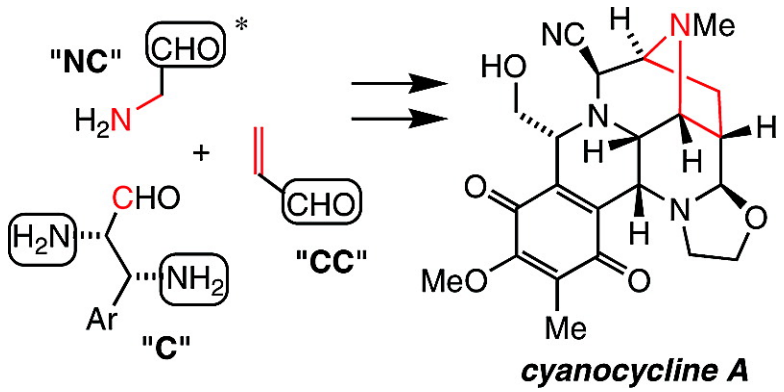


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# An Efficient Synthetic Approach to Cyanocycline A and Bioxalomycin β2 via [C+NC+CC] Coupling

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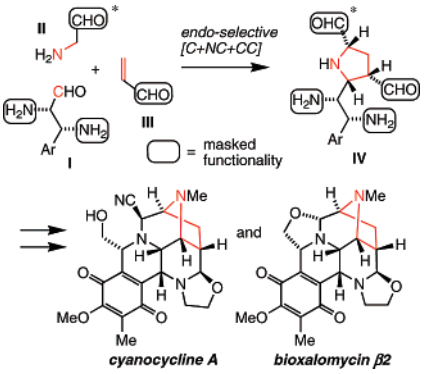
The exploitation of natural products for the treatment of disease is often limited by availability, placing the onus on the synthetic chemist to devise efficient and flexible approaches to specific target families. Our group recently disclosed a set of stereocomplementary metal-catalyzed multicomponent reactions for the synthesis of highly functionalized pyrrolidines, which we termed [C+NC+CC] coupling reactions.[1] Herein, we illustrate how this powerful reaction technology simplifies the synthesis of both the cyanocyclines[2] and bioxalomycins[3] (Scheme 1). We are interested in developing efficient syntheses of these natural products and structurally related analogues because of their potential as "privileged" small molecule scaffolds for protein interrogation and drug development.[4] Previous efforts[5] include two asymmetric syntheses of cyanocycline A from the laboratories of Evans (35 linear steps)[5c] and Fukuyama (32 linear steps).[5d] The [C+NC+CC] reaction provides rapid access to a key pyrrolidine intermediate (structure **IV**) that is converted to the target using established chemistry, reducing the total number of steps by one-third.

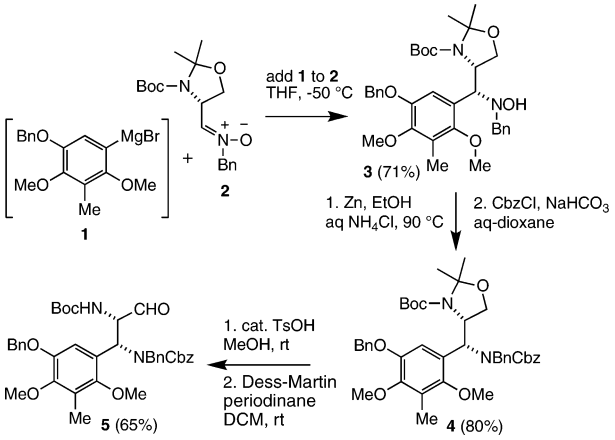
In our approach to the these natural products, the first order of business involved construction of a suitably functionalized 2,3-diamino aldehyde corresponding to **I** that incorporates an aromatic precursor of the targets' quinoid A-ring. Synthesis of the aldehyde **5** (Scheme 2) begins with a stereoselective reaction of Grignard reagent **1**[6] and the serinal-derived nitrone **2** to give the syn disposed hydroxylamine **3**, exclusively. The stereochemical outcome of this addition reaction was anticipated on the basis of the precedent provided by Merino and co-workers.[7] Reduction of the hydroxylamine functionality with zinc followed by N-protection with CbzCl produced the differentially protected diamine **4**. Mildly acidic methanolysis of the oxazolidine ring released the primary alcohol, which was oxidized by the Dess−Martin reagent to give the required aldehyde **5** (=**I**) in 42% overall yield from **2**.

The key [C+NC+CC] coupling reaction (Scheme 3) was effected by combining aldehyde **5** and L-glycylsultam **6** ($X^L$ = Oppolzer's L-camphorsultam)[8] in methyl acrylate (solvent) with 10 mol % AgOAc at room temperature. This reaction produced the desired pyrrolidine **7** in 74% yield. Because of the hindered urethane functionality present in this molecule, the relative configurations of the newly created pyrrolidine stereocenters could not be determined using standard NMR techniques. However, the endo-si product was expected on the basis of our earlier [3+2] cycloaddition studies and the proposed pre-TS model (shown in inset). This stereochemical assignment was supported by a subsequent NOE study on a more rigid synthetic intermediate (compound **12**) and confirmed by the successful conclusion of the synthesis. Compound **7** represents the most ambitious application of our asymmetric [C+NC+CC] coupling technology to date and essentially solves the cyanocycline/bioxalomycin synthesis problem.

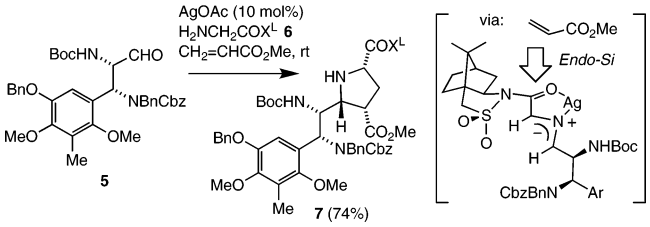
***Scheme 1.*** Key Elements of the Synthetic Strategy




***Scheme 2.*** Synthesis of Aldehyde **5**




***Scheme 3.*** Key [C+NC+CC] Coupling Reaction




The synthetic end game (Scheme 4) begins with Pd-catalyzed hydrogenolysis of **7** to give a phenolic lactam. This multistep operation effected concomitant removal of the benzyl ether and Cbz groups, followed by δ-lactam formation. At this point, Cbz protection of the pyrrolidine amine and removal of the Boc group led to the phenolic amine **8**, which was subjected to a Pictet−Spengler reaction with benzyloxyacetaldehyde to produce the tetrahydroisoquinoline **9** in 75% overall yield. The (9*R*) stereochemistry was tentatively assigned on the basis of Fukuyama's precedent and confirmed later by correlation with cyanocycline A.

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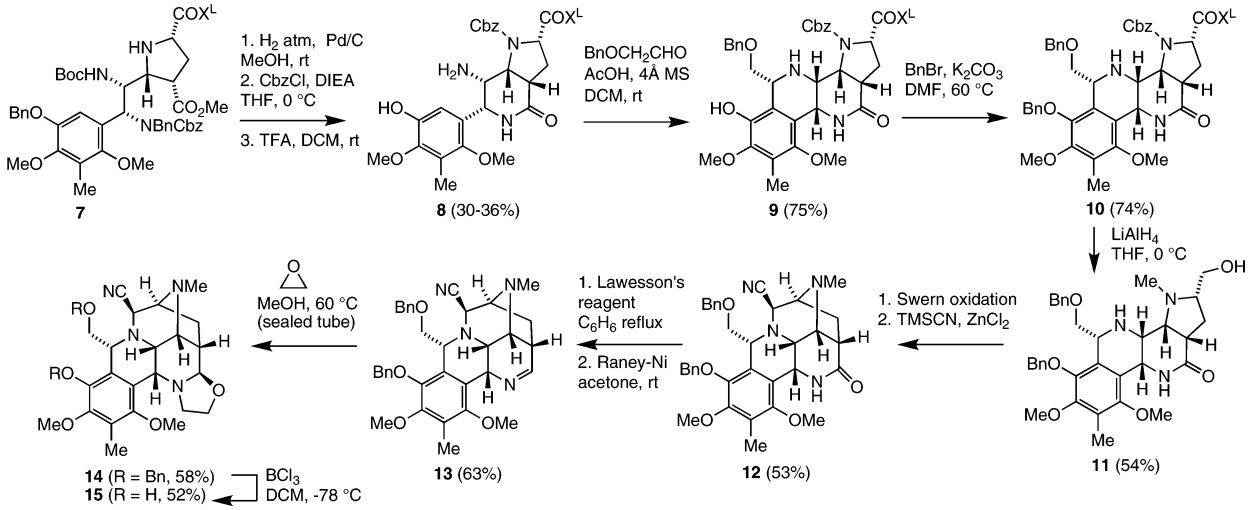
***Scheme 4.*** The Cyanocycline A/Bioxalomycin $\beta$2 Endgame




Reprotection of the free phenol gave **10**, which was reduced with $LiAlH_4$ to give the primary alcohol **11** in 54% yield. This reaction not only released the chiral auxiliary but also converted the urethane moiety to the required N-methyl group.[9] Swern oxidation and aminonitrile formation afforded compound **12**, which was amenable to NOESY experiments to confirm its structure (Supporting Information). The F-oxazolidine was introduced using methodology developed by Pelletier that proceeds via stable imine **13**.[10] Finally, **14** was deprotected with $BCl_3$ (hydrogenolysis was ineffective) to give diol **15**. This compound corresponded to an advanced intermediate that Fukuyama had converted to cyanocycline A (reference 5, parts b and d). Since cyanocycline A is convertable to bioxalomycin $\beta$2 through the agency of $Ag^I$ (references 5e and 2), attainment of **15** constitutes an efficient formal synthesis of this natural product as well.

Our formal synthesis of cyanocycline A proceeded in 22 linear steps from 2,6-dimethoxytoluene (19 steps from the commercially available serinal precursor of **2**). This represents the most efficient synthetic approach yet to these complex natural products. The successful application of our [C+NC+CC] coupling technology to the cyanocycline/bioxalomycin problem augers well for the synthesis of other members of this natural product family (dnacins, for example) as well as structurally related unnatural products. Improved access to this natural product family will enable their biological and biochemical evaluation with an eye on discovering previously unrecognized protein targets.[11]

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**Supporting Information Available:** Experimental details and characterization data for compounds **2** through **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Compound **12** has been found to inhibit cell migration, like DX-52-1, and has target overlap with DX-52-1 but has far greater selectivity for one target over another: Fenteany, G. Personal communication. This finding supports our hypothesis that this natural product family—now readily accessible using the strategy disclosed herein—will be useful for protein interrogation and drug development.

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