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An Approach to the 3,8-Diazabicyclo[3.2.1]octane Moiety of Naphthyridinomycin and Quinocarcin via 1,3-Dipolar Cycloaddition of Photochemically Generated Azomethine Ylides.

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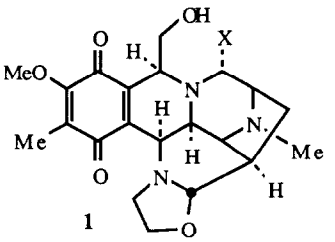
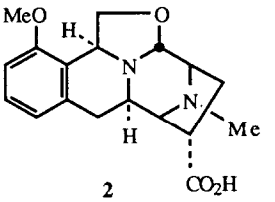
Summary: An attractive strategy for construction of the 3,8-diazabicyclo[3.2.1]octane moiety of targets **1** and **2** involving the 1,3-dipolar cycloaddition of photochemically generated azomethine ylides is presented.

Naphthyridinomycin (**1**) and quinocarcin (**2**) represent two families of bioactive alkaloids that hold promise as antineoplastic agents because of their ability to inhibit DNA synthesis.[1,2] The structural complexity associated with these substances makes them formidable targets for total synthesis and a number of efforts in this area have already been reported.[3-5] Still, a more general approach that would also permit a stereocontrolled and enantiospecific synthesis of both **1** and **2** remains to be developed.

With this in mind, we have focused on construction of the 3,8-diazabicyclo[3.2.1]octane skeleton **I** common to both target molecules. An attractive strategy here involves the 1,3-dipolar cycloaddition of a chiral azomethine ylide **II** (ie. R^1 is chiral) to a monosubstituted olefin **III**.[6] Should this addition to the prochiral ylide proceed diastereoselectively, then a truly asymmetric synthesis of both **1** and **2** (as well as their congeners) would be possible. A recent Letter by Joule and coworkers (ref. 5d) outlined a related approach based on 1,3-dipolar cycloadditions to (achiral) oxidopyraziniums and prompts us to report our preliminary results on the photochemical generation of azomethine ylides corresponding to **II** and their trapping with methyl acrylate to give systems such as **I**.

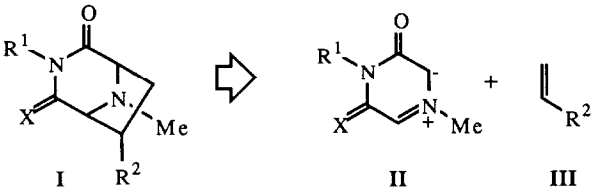


1

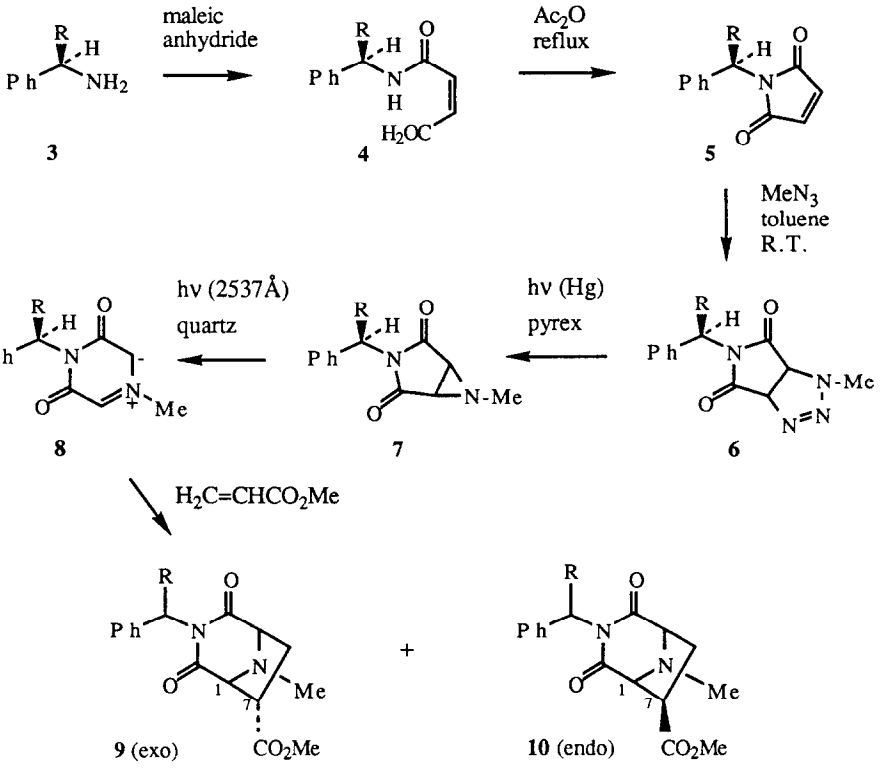


2

Strategy:



I II III



3 4 5 6 7 8

9 (exo) 10 (endo)

a: R = H, b: R = CO_2Me, c: R = CH_2OH, d: R = CH_2OAc

We began by preparing the known maleimide derivative **5a**, mp 68-69°C, in two steps from benzylamine (**3a**) via Ac_2O mediated dehydration of the half acid **4a**, mp 131-133°C.[7,8] Treatment of **5a** with a stock solution of methyl azide in toluene at ambient temperature resulted in the clean formation of triazoline **6a**, mp 142-143°C (73% yield).[9] Irradiation of the triazoline **6a** (0.04M in dioxane) using a medium pressure Hanovia Hg lamp and a pyrex filter led to extrusion of nitrogen and so produced the aziridine **7a**, mp 114-115°C (89% yield).[10] These photochemical conditions for aziridine formation were necessitated by our observation that thermolysis of **6a** resulted in formation of an isomeric enamine (not shown) in addition to the desired **7a**. Having secured an ample supply of aziridine **7a**, we were now set to examine the crucial 1,3-dipolar cycloaddition reaction. Thus photolysis of a (N_2-purged) dioxane solution of **7a** (0.2M) using a 2537Å Rayonet source and a quartz vessel resulted in the generation of azomethine ylide **8a** (via concerted disrotatory aziridine opening)[11] which was "trapped" with methyl acrylate (2 equiv.) to give a mixture of the *exo*-adduct **9a**, mp 69-70°C (59% yield) and an *endo*-adduct **10a** (12% yield). These compounds were easily separated by flash chromatography on silica gel. The stereochemistry of each of these cycloadducts was apparent from their respective ^1H NMR spectra with H-1 appearing as a singlet for the *exo*-product **9a** (H_1-C-C-H_7 = 90°) and a doublet (J = 7 Hz) for the *endo*-product **10a** (H_1-C-C-H_7 = 20°).

We next examined substrates **7b** and **7d** that would lead to the chiral azomethine ylides **8b** and **8d** required for an enantioselective synthesis of targets **1** and **2**. These aziridines were prepared in good overall yields (24-28%) from phenylglycine methyl ester (**3b**) and phenylglycinol (**3c**) using the general procedure outlined above. The Ac_2O mediated dehydration of **4c** was in this case accompanied by acetylation of the primary alcohol. It should also be noted that the triazolines **6b**, mp 159-160°C, and **6d**, mp 118-120°C, were each isolated as mixtures of diastereomers that resulted from nonselective cycloaddition of methyl azide to the chiral maleimides **5b**, mp 87-88°C, and **5d**. Photolysis of **7b** and **7d** produced azomethine ylides **8b** and **8d** which added to methyl acrylate smoothly to give mixtures of the cycloadducts in 62% and 45% yields respectively. In line with our results from the achiral "a-series", the *exo:endo* ratio remained approximately (5:1), as determined by ^1H NMR analysis. It was also apparent from the doubling of certain NMR signals that these cycloadditions had proceeded with little or no diastereoselectivity. This is not really surprising (recall **5b,d**→**6b,d**) since the lone chiral center in **8b** and **8d** is somewhat removed from the developing stereocenters and would constitute a rare example of 1,4-asymmetric induction. In any case, the viability of a 1,3-dipolar cycloaddition strategy for the enantioselective synthesis of quinocarcin (**2**) has been demonstrated and sets the stage for further work in this area. A solution to the problem of diastereoselectivity with chiral ylides such as **11** that also leads directly to the epimeric configuration at C-7 as required for naphthyridinomycin (**1**) will be reported in due course.[12]

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