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Synthesis of an Advanced Intermediate en Route to the Mitomycin Natural Products

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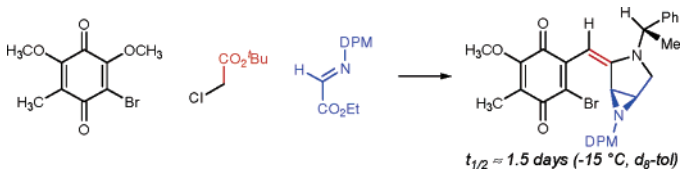
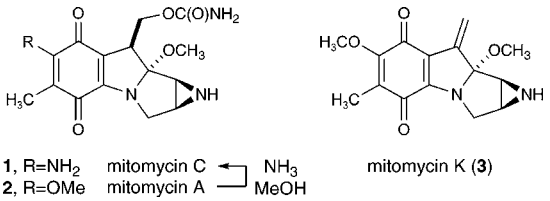
ABSTRACT



An advanced intermediate in our planned synthesis of mitomycin C has been acquired in nine steps from *tert*-butyl glyoxylate. The aziridinyl pyrrolidine and quinone subunits are coupled regioselectively to arrive at an enamine that is prepared for C10 homologation.

The mitomycin natural products have attracted the attention of medicinal and synthetic chemists for nearly a half century.[1,2] This interest results from several factors, including the continued clinical use of mitomycin C (**1**) for treatment of various forms of cancer. The unique pyrroloquinone backbone presents a high degree and density of oxidation, and this functional group array is the source of mitomycin C's unique ability to cross-link DNA.[3] Consequently, a substantial challenge for chemical synthesis is presented. Indeed, there have been many reports detailing synthetic efforts toward this class of natural products, and although interest has not waned with the passing of time, only two total syntheses of the title compound[4] and two syntheses of another member of the class, mitomycin K (**3**),[5] have been logged.



A successful synthesis, particularly one amenable to derivative formation, might further improve the therapeutic profile for this natural product class,[6] and rejuvenate efforts to use contemporary biochemical techniques to similarly improve efficacy.

To achieve a high degree of convergency, our retrosynthesis disconnects the aziridinopyrrolidine and quinone across the central dihydropyrrole ring (Figure 1). On the basis of our previous studies of regioselective enamine additions to

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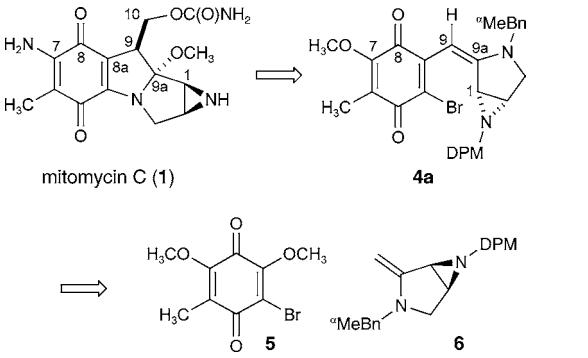


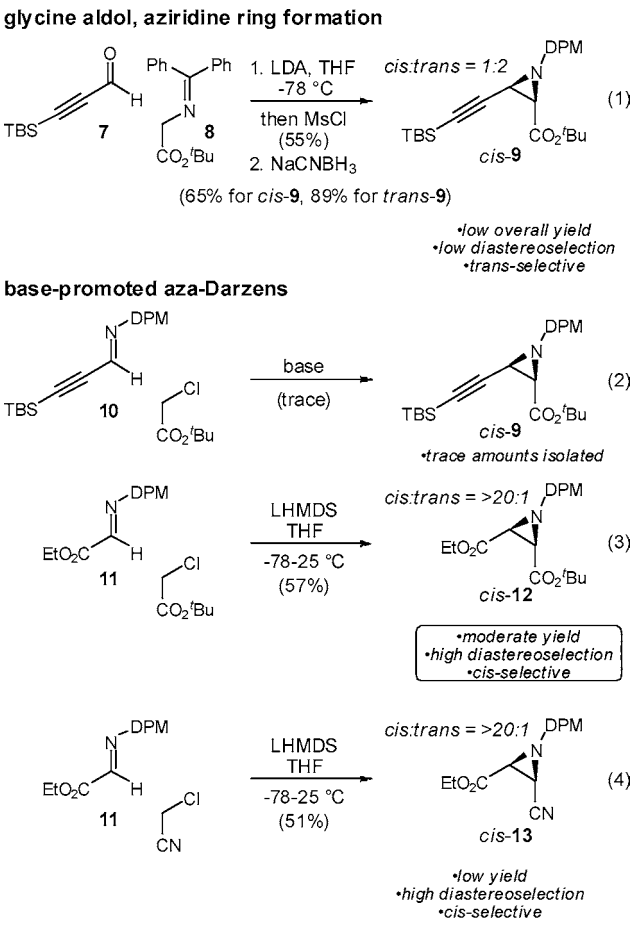
Figure 1. Retrosynthesis of mitomycin C (DPM = diphenyl methyl).

methoxy quinones,[7] we expected the coupling of enamine **6** with quinone **7** to be regioselective for methoxy substitution at the bromomethoxy olefin.[8] Construction of enamine **6** could arise from a cyclization of an amino alkyne via formal alkyne hydroamination. Convergency could again be served if an aziridine ring-forming reaction could be used that would also form the aziridine carbon−carbon bond. Hence, we began our studies by investigating the traditional methods for aziridine construction by carbon−carbon bond formation.[9]

Scheme 1 lists several general lines of investigation toward this end. On the basis of the work of O'Donnell[10] and Miller,[11] we anticipated that glycinyl Schiff base **8** might engage propargyl aldehyde **7** in an aldol reaction. The resulting β-hydroxy ester could be converted to the corresponding mesylate. In order to avoid competitive cyclization to the corresponding oxazoline,[12] in situ trapping with mesyl chloride was necessary. Reductive amination then provided the desired aziridine in good overall yield. Unfortunately, the initial addition was minimally diastereoselective and favored the undesired *trans*-isomer.

The Darzens reaction[13] using an azomethine electrophile provided a more direct route to the aziridine because it avoided the necessity to activate the hydroxy imine intermediate in eq 1 and reduce the imine functionality.[14] The reaction of propargyl imine **10** under these conditions provided only trace amounts of aziridine, much less the

Scheme 1. Approaches to the Synthesis of *cis*-Aziridine Precursors to **6**



desired *cis*-**9**. By activating the imine electrophile without resorting to a more robust protecting group at nitrogen, we examined the diphenylmethyl amine Schiff base of ethyl glyoxylate (**11**). Combination of the reactants at low temperature, followed by slow warming to room temperature, resulted in modest yields of the desired aziridine. Of greater significance is the high *cis*-diastereoselection observed in this transformation, a prerequisite for eventual formation of the aziridinopyrrolidine. Substitution of chloroacetonitrile for *tert*-butyl chloroacetate was also effective and *cis*-selective but provided a greater amount of competing nitrile homocoupling.

Conversion of the *cis*-aziridinosuccinate **12** to enamine precursor **16** (Scheme 2) began with selective saponification of the ethyl ester using aqueous sodium hydroxide in ethanol (97%). Straightforward coupling of the carboxylic acid with commercial (*S*)-α-methyl benzylamine (98% ee) was achieved in 74% yield using DCC/HOBT to furnish diastereomeric *cis*-aziridines **14a**/**b**. Selective reduction of *tert*-butyl ester **14** provided the corresponding aldehydes in good yield as judged by spectroscopic analysis of the crude reaction mixture. Careful chromatographic separation at this stage provided the diastereomeric *cis*-aziridines in pure form, but at the expense of chemical yield due to their instability. Subsequent alkynylation of the less polar aldehyde was

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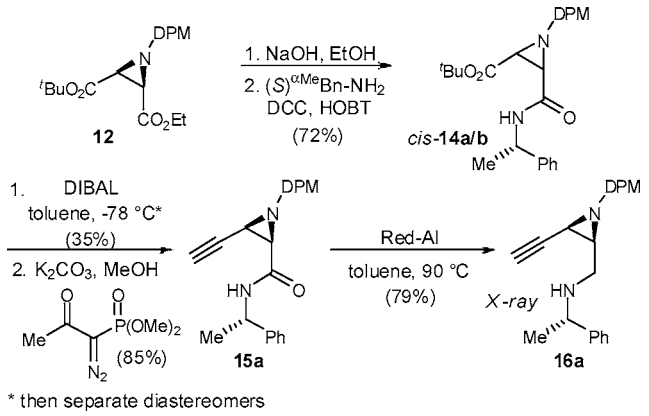
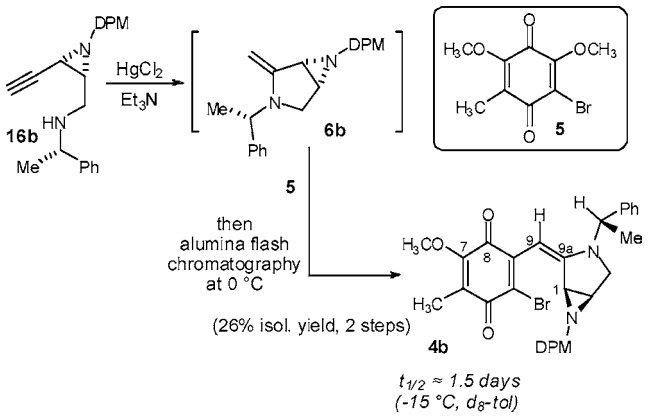
Scheme 2. Synthesis of Alkynyl Amine **16**



effected using the Gilbert−Seyferth phosphonate reagent.[15] In this manner, the terminal alkyne was produced in 85% yield from the intermediate aldehyde. Red-Al reduction of the amide was similarly effective, and alkynyl amine **16a** was obtained in 79% yield. Upon standing for 1 week, this amine crystallized and single crystals could be obtained by slow evaporation from dichloromethane. X-ray crystallographic analysis enabled assignment of the stereochemistry depicted in Scheme 2.

An aminomercuration/coupling sequence was next evaluated with quinone **5** (Scheme 3). Enamine **6b** was generated

Scheme 3. Formation of the Key Enamine Intermediate and Subsequent Alkylation to the Mitomycin Backbone



in situ by treatment of alkynylamine **16b**[16] with Hg(II),[17] and this solution was added to quinone **5**. The resulting deep blue solution was concentrated at 0 °C. Analysis of this crude reaction mixture by ^{1}H NMR suggested selective and efficient production of a coupled product (see Supporting Information for details). However, successful purification of the putative enamine required cold column chromatography (ice water cooling). Using the bright color of the conjugated system as an indicator during this process, a product was isolated and kept at low temperature during NMR analysis. Notwithstanding, the material decomposed slowly with an approximate half-life of 1.5 days at −15 °C. The reactivity of this intermediate, manifested as instability during purification, is a feature we anticipated and desired as part of our synthesis strategy; notwithstanding, we sought to fully characterize it by spectroscopic means.

Immediate recognition of several features suggested its identity to be **4b**. The aminobenzyl methine proton resonances are readily differentiated by chemical shift. The methine of the enamine is consistently deshielded to 4−5 ppm. The corresponding aziridine DPM-methine is further upfield at 3−4 ppm. HMBC, HMQC, and COSY experiments allowed assignment of all proton and carbon resonances. The coupling regiochemistry was identified by $^3J_{CH}$ between the enamine proton resonance (H9) and the quinone carbonyl carbon (C8) nearest the methoxy substituent. The latter was assigned indirectly by identification of the companion quinone carbonyl (C5) for which a $^3J_{CH}$ cross-peak could be observed from the quinone ring methyl subsituent. Consistent with our earlier observation, the methoxy group is preferentially substituted despite the electronic counter-influence of the distal methoxy. This behavior is consistent with rate-limiting addition in this nucleophilic vinylogous acyl substitution. The geometry of the newly formed enamine olefin was assigned by analogy to similar reactions we have investigated, all of which provide the (*E*)-olefin stereoisomer.[7]

In summary, we have arrived at an advanced intermediate (**4**) in our approach to the synthesis of the antitumor agent mitomycin C. This is accomplished in only nine steps from ethyl glyoxylate. The next significant step is homologation to install the C10 hydroxymethyl; the enamine character of **4** and the steric influence of the aziridine are perfectly suited to this task. Details on this front will be the subject of future reports.

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Supporting Information Available: Preparative information and analytical data for all new compounds, as well as data in CIF format for the structural determination of **16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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