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Stereoselective synthesis of complex polycyclic aziridines: use of the Brønsted acid-catalyzed aza-Darzens reaction to prepare an orthogonally protected mitomycin C intermediate with maximal convergency†

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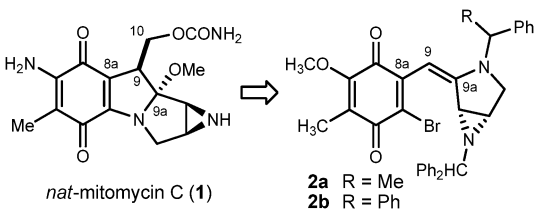
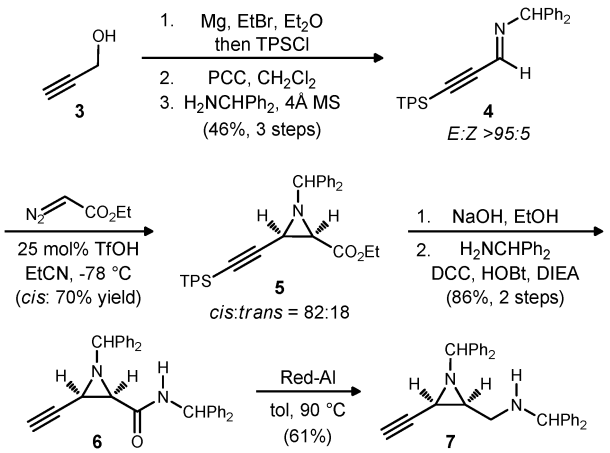
A concise synthesis of a highly functionalized intermediate lacking only C10 of the mitomycin backbone is described. The key to this development is the Brønsted acid-catalyzed aza-Darzens reaction used to forge the *cis*-aziridine. Additionally an oxidative ketalization fortuitously occurs during the quinone–enamine coupling step, leading to an orthogonally protected hydroquinone.

The mitomycins are a family of potent antibacterial and anticancer agents that have sustained broad interest since their isolation in the late 1950s due to their biological activity and the synthetic challenge they offer.[1] Mitomycin C (**1**) has been shown to crosslink DNA and has been clinically used to treat cancer for several decades.[2] The challenge of mitomycin chemical synthesis is largely due to the compact array of reactive functionalities, and reflected by only two total syntheses of *rac*-mitomycin C and two total syntheses of *rac*-mitomycin K.[3–5] It could be argued that the length of these preparations (28 steps or more for **1**) has limited the further development of the mitomycins as powerful therapeutics.[6]



We have outlined a strategy to convergently access the mitomycins using a regioselective enamine–quinone coupling to prepare bromoquinone **2a**.[7] The reactivity of this intermediate was reflected by the use of cold column chromatography to purify enamine **2a** and its tendency to decompose during spectroscopic analysis. As a result of our desire to incorporate new reactions into this sequence to further streamline access to advanced intermediates, we considered the ostensibly less desirable strategy in which both nitrogens bear identical protecting groups (**2b**). In this report, we detail our finding that protecting group differentiation can be achieved during preparation of **2b** by a selective hydride transfer that reduces the quinone, and then protects it *via* ketalization. Furthermore, the *cis*-aziridine precursor to **2b** is readily prepared using a diastereoselective, Brønsted acid-catalyzed aza-Darzens reaction.[8,9]

Enamine **2a** was prepared using a base-promoted aza-Darzens reaction of α-bromo ethyl acetate with the aldimine derived from *tert*-butyl glyoxal.[7] The esters were then chemoselectively refunctionalized to alkyne and aminomethyl substituents of the central *cis*-aziridine. As an alternative, we investigated whether a Brønsted acid-catalyzed aza-Darzens reaction[10] might produce the alkyne-substituted aziridine more immediately. The imine substrate (**4**) for this was prepared in three steps without purification from commercially available propargyl alcohol (**3**) (Scheme 1). Alkyne protection of



Scheme 1 Preparation of an alkynyl amine using the Brønsted acid-catalyzed aza-Darzens reaction.

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† Electronic supplementary information (ESI) available: Complete experimental details and analytical data for all new compounds; X-ray data for **12**. CCDC 806065. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc05734g

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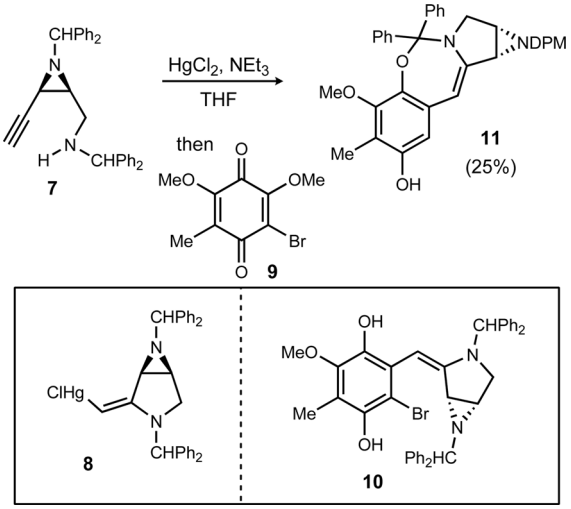
propargyl alcohol was followed by oxidation[11] and condensation of the resulting aldehyde with diphenyl methyl amine (DPM-NH_2) to afford imine **4** ($E:Z > 95:5$). The imine $E:Z$ ratio is dependent on the alkyne protecting group and ranges from 63 : 37 (trimethylsilyl) to exclusively *E* geometry (triphenylsilyl group, TPS). The Brønsted acid-catalyzed aza-Darzens reaction of **4** with ethyl diazoacetate provided *cis*-**5** in 70% isolated yield compared to 39–50% for the analogous TMS-imine. The ethyl ester was then saponified and coupled with diphenyl methyl amine to give amide **6**. Reduction of the amide to amine **7** readied this fragment for coupling.

Cyclization of alkynyl amine **7** with $HgCl_2$ leads to an intermediate enamine[12] (perhaps **8**) that is treated with quinone **9**.[13] Standard reductive workup with $NaBH_4$ was expected to give the hydroquinone of **2b** (**10**, Scheme 2). Although a colorless product was isolated from this mixture, its spectroscopic data was different in key areas from **2a** or its analogous hydroquinone, specifically in the downfield shift of both enamine and pyrrolidine-DPM methine protons by ~0.5 ppm. Assuming the formation of **10**, we treated this material with benzoyl chloride and triethylamine. A single phenolic hydroxyl group was acylated despite varying reaction conditions. Attempts to oxidatively cleave the pyrrolidine protecting group failed,[14] and resulted in oxidation of the hydroquinone and production of benzophenone (a DPM oxidation product).

Since the next planned synthesis step was to install C10, the enamine nucleophilicity was assessed using *N*-chlorosuccinimide. The chlorinated product was crystalline and an X-ray structure was obtained (Fig. 1). This revealed that the bromine on the hydroquinone ring had been replaced by a hydrogen and one hydroquinone hydroxyl group had formed a seven-membered ring with the pyrrolidine diphenylmethyl group. By retrospective analysis, the coupling reaction had resulted in an oxidative ketalization to form *N*,*O*-ketal **11**, thus explaining the observation that the coupling product could only be singly benzoylated.

This unusual transformation requires two reducing equivalents during the reaction. The oxidation of the pyrrolidine diphenylmethyl group suggested an intramolecular source of one equivalent of hydride. This would also explain why the α-methylbenzyl-protected pyrrolidine in **2a**, which is a poorer hydride donor, did not exhibit this behavior. The second reducing equivalent may be attributed to triethylamine, as variations that did not employ sodium borohydride still produced the mixed ketal.



Scheme 2 Formation of an *N*,*O*-ketal during the second convergent coupling.

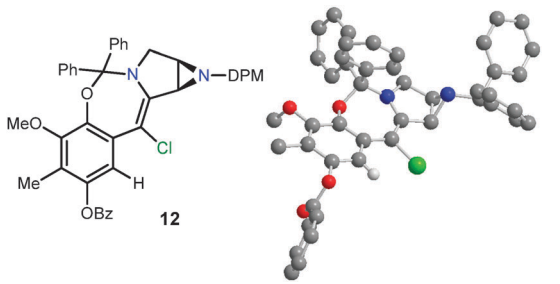
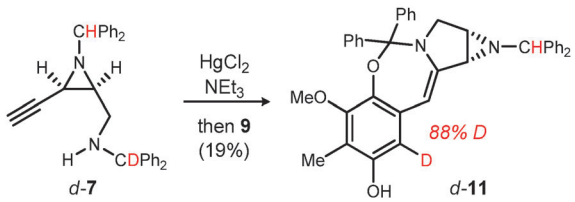
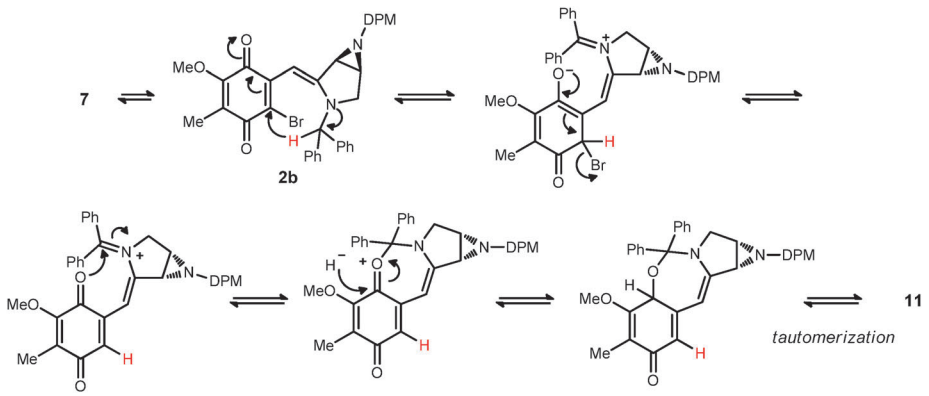


Fig. 1 X-ray crystal structure of **12**.



Scheme 3 Deuterium labeling experiment revealing selective transfer of deuterium from one diphenylmethyl group.



Scheme 4 Mechanistic proposal for the RedOx ketalization subsequent to coupling.

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Our hypothesis that the diphenylmethyl group delivered the hydride was investigated using a deuterium labeling experiment (Scheme 3). Deuterated alkynyl amine *d*-**7** was prepared and subjected to the standard reaction conditions. The coupled *N*,*O*-ketal showed an 88% deuterium incorporation at the hydroquinone C–H. This verifies that one of the two reducing equivalents results from the conserved transfer of the diphenylmethyl methine.[15]

The mechanism outlined in Scheme 4 for the formation of **11** is consistent with these observations. The initial aminomercuration of alkynyl amine **7** and subsequent enamine addition to quinone **9** would form coupled intermediate **2b**. An *E*/*Z* isomerization would bring the pyrrolidine in close proximity for the 1,6-hydride shift of the diphenylmethyl methine, resulting in elimination of the bromide and subsequent cyclization of the quinone oxygen onto the iminium ion. A second hydride addition and tautomerization would then give *N*,*O*-ketal **11**.

The cascade that ensues after coupling of the two halves of the mitomycin backbone was unexpected, but delivers an advanced intermediate containing all but one of the required carbons for mitomycin C. The oxidative ketalization provides differential protection of the hydroquinone hydroxyls while chemically differentiating the pyrrolidine and aziridine nitrogens. Equally important is the maintenance of enamine nucleophilicity, a feature that will be used to install the final carbon. Overall, convergency of approach and the Brønsted acid-catalyzed aza-Darzens reaction of propargyl imine **4** combine to deliver *N*,*O*-ketal **11** in 8 steps.

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