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Synthetic studies toward the mitomycins: construction of the tetracyclic core via a reductive aminocyclization reaction

Daniel A. Gubler [a], Robert M. Williams [a,b,*]

[a] Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA
[b] University of Colorado Cancer Center, Aurora, CO 80045, USA

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ABSTRACT

The tetracyclic core of the mitomycin family of natural products has been formed in one step from an acyclic precursor via a reductive aminocyclization reaction. Additionally, the eight-membered benzazocine can be prepared without the need for prior activation of the aniline. Construction of a mitomycin K analogue lacking the C9a methoxy moiety is also reported herein.

The mitomycin family of natural products (Fig. 1) have been of interest to the scientific community since their isolation over 50 years ago.[1] Members of this family exhibit potent activity against a variety of cancer cell lines, and were found to be particularly active against solid tumors.[2] The mode of action of these compounds arises from their ability to form interstrand DNA–DNA[3] as well as DNA–protein[4] covalent cross-links. Mitomycin C (Fig. 1) has been widely used clinically for over 40 years, and is still routinely employed today.[5]

These molecules present a significant synthetic challenge due to their densely functionalized nature, chemical lability as well as the difficulty in maintaining the vulnerable structural elements (i.e., aziridine, quinone, and exo-methylene) as the synthesis unfolds. Despite the numerous reported synthetic efforts toward the mitomycins, only Kishi[6], Fukuyama[7], Danishefsky[8], and Jimenez[9] have been successful in completing total syntheses. It is important to note that all the syntheses mentioned above delivered racemic products and there exists no enantioselective total synthesis of any of the mitomycins reported to date.

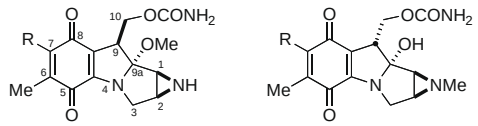
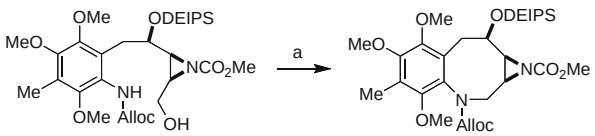


Figure 1. The mitomycin family of natural products.

Our research program has been focused on the development of an asymmetric total synthesis of the mitomycins which was a natural out-growth of our recently completed asymmetric total synthesis of (+)-FR900482.[10] These efforts are fueled in part by our interest in both the biosynthesis and mode of action of these compounds.[11] Herein we report efficient formation of the tetracyclic core of the mitomycins via a reductive aminocyclization reaction.

Previously, we reported the synthesis of benzazocines with the mitomycin substitution on the aromatic ring via an intramolecular Mitsunobu cyclization reaction.[12] We reported that prior activation of the aniline as the corresponding sulfonamide or carbamate was requisite for Mitsunobu cyclization to occur (Scheme 1). Through this method, benzazocines and benzazocanes containing all the key elements of the mitomycins were efficiently obtained. However, conversion of these benzazocanes to the natural products proved to be difficult.

As part of our continuing efforts to access this family of natural products, a new strategy was developed. This strategy employed the use of benzyl ethers as protecting groups on the arene ring, as well as installation of the exocyclic methylene prior to cyclization (Scheme 2). The synthesis commenced by coupling of nitro



Scheme 1. Reagents and conditions: (a) $(CH_3)_2NCON{=}NCON(CH_3)_2$ (1.5 equiv), PBu_3 (1.8 equiv), toluene, rt, 6 h; 85%.

* Corresponding author. Tel.: +1 970 491 6747; fax: +1 970 491 3944.
E-mail address: rmw@lamar.colostate.edu (R.M. Williams).

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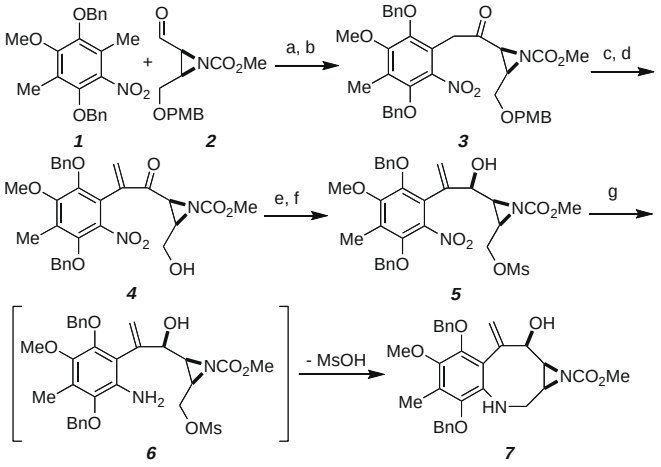
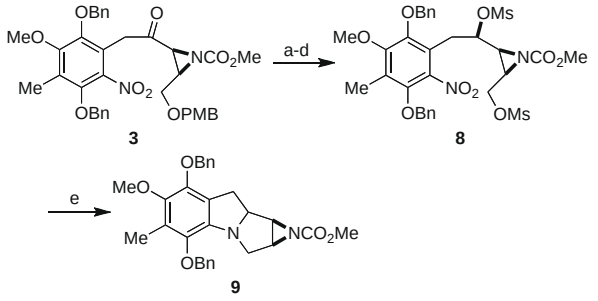


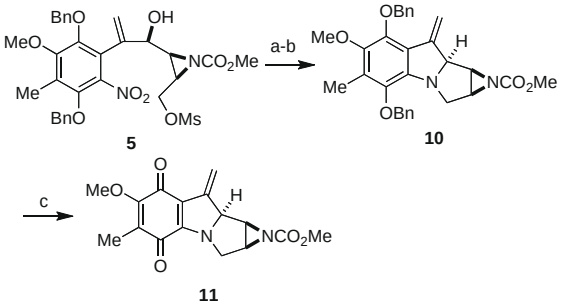
Scheme 2. Reagents and conditions: (a) 1 (2.0 equiv), 2 (1.0 equiv), $ZnCl_2$ (1.5 equiv), NaHMDS (2.0 equiv), DMF, −45 °C, 2 h, 85%; (b) Dess–Martin (1.6 equiv), CH_2Cl_2, rt, 2 h, 98%; (c) formalin (112 equiv), LiOH (0.4 equiv), THF/water (20:3), rt, 20 h, 99%; (d) DDQ (1.3 equiv), CH_2Cl_2/water (95:5), rt, 2 h, 92%; (e) MsCl (1.3 equiv), Et_3N (3.0 equiv), 0 °C, 30 min, 85%; (f) $CeCl_3{\cdot}7H_2O$ (5.0 equiv), $NaBH_4$ (3.0 equiv), 0 °C, 30 min, 92%; (g) Zn dust (5.0 equiv), NH_4Cl (10.0 equiv), acetone/water (4:1), rt, 3 h, 99%.

arene **1**[13] and aziridine aldehyde **2**[14], followed by oxidation of the resultant alcohol (obtained as a 2:1 mixture of diastereomers *R*:*S*) to ketone **3**. Methylenation and removal of the PMB ether with DDQ proceeded in excellent yield over two steps to provide primary alcohol **4**. Conversion of alcohol **4** to the corresponding mesylate and reduction of the ketone under Luche conditions gave secondary alcohol **5** in high yield as a single diastereomer. Reduction of the nitro group using zinc dust did not provide the expected aniline **6**, but rather gave benzazocine **7**[15] in near quantitative yield as the product of a reductive aminocyclization reaction. To the best of our knowledge, this is the first example of a cyclization reaction in this family of compounds which proceeds without the need for prior activation of the aniline.

Having found an efficient method for formation of benzazocine **7**, we were interested in examining the utility and scope of this transformation. Specifically, we investigated the possibility of forming the tetracyclic core of the mitomycins in one step from an acyclic precursor via this newly discovered reductive aminocyclization reaction. Accordingly, ketone **3** was transformed to bis-mesylate **8** in four straightforward steps consisting of PMB ether removal, mesylation, reduction of the ketone, and a second mesylation (Scheme 3). Treatment of bis-mesylate **8** under identical nitro reduction conditions furnished tetracyclic indoline **9** in 53% yield. Attempted conversion of indoline **9** to the mitomycins is now in progress.



Scheme 3. Reagents and conditions: (a) DDQ (1.3 equiv), CH_2Cl_2/water (95:5), rt, 2 h, 85%; (b) MsCl (1.5 equiv), Et_3N (3.0 equiv), 0 °C, 30 min, 53%; (c) $CeCl_3{\cdot}7H_2O$ (5.0 equiv), $NaBH_4$ (3.0 equiv), 0 °C, 30 min, 93%; (d) MsCl (1.5 equiv), Et_3N (3.0 equiv), 0 °C, 30 min, 75%; (e) Zn dust (5.0 equiv), NH_4Cl (10.0 equiv), acetone/water (4:1), rt, 3 h, 53%.



Scheme 4. Reagents and conditions: (a) MsCl (1.5 equiv), Et_3N (3.0 equiv), 0 °C, 30 min, 53%; (b) Zn dust (5.0 equiv), NH_4Cl (10.0 equiv), acetone/water (4:1), rt, 3 h, 55%; (c) 10% Pd/C (120 wt.%), Et_3N (6.0 equiv), EtOAc, H_2, rt, 30 min, then O_2, 50%.

With indoline **9** in hand, we decided to pursue the synthesis of mitomycin K using the same reaction, with prior installation of the C10 exocyclic olefin. Accordingly, mesylation of alcohol **5** under standard conditions provided the aminocyclization precursor bearing the exocyclic olefin (Scheme 4). Reductive aminocyclization conditions used previously did provide tetracycle **10** without any isomerization of the exocyclic olefin to the corresponding indole (mitosene) adduct.[16] Treatment of tetracycle **10** under hydrogenation conditions gave quinone **11** in moderate yield. Quinone **11** comprises the core skeleton of mitomycin K, lacking only the C9a methoxy group. Installation of the requisite methoxy moiety may be accomplished by an allylic C–H activation strategy, and efforts in this vein are in progress.

In summary, benzazocines were synthesized in high yield by use of a reductive aminocyclization reaction without the need for prior activation of the aniline. The tetracyclic core of the mitomycins was also accomplished in a single step from an acyclic precursor using this methodology. This strategy was used in formation of the tetracyclic indoline compound **9**, as well as the core structure of mitomycin K bearing an exocyclic olefin (i.e., **10**).

Acknowledgments

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Supplementary data

Complete experimental details and spectroscopic data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.004.

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