ORGANIC LETTERS

2007
Vol. 9, No. 26
5341−5344

Synthetic and Biosynthetic Studies on FR900482 and Mitomycin C: An Efficient and Stereoselective Hydroxymethylation of an Advanced Benzazocane Intermediate

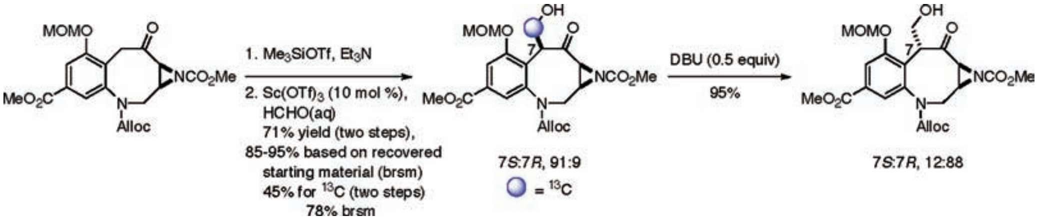
Hidenori Namiki,† Stephen Chamberland,† Daniel A. Gubler,† and Robert M. Williams*,†,‡

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523-1872, and University of Colorado Cancer Center, Aurora, Colorado 80045

rmw@lamar.colostate.edu

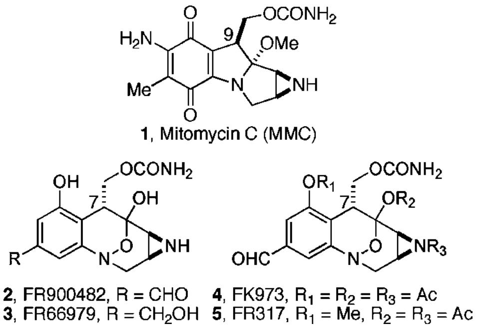
Received August 22, 2007

ABSTRACT



We report a simple, efficient, and stereoselective Mukaiyama aldol approach to install the key hydroxymethyl moiety into the benzazocane framework of FR900482. Synthetic investigations revealed that the reaction is highly dependent upon the electronics of the aromatic ring. This approach enabled the economical introduction of a [^{13}C] label to study the biosynthesis of these structurally and biogenetically related natural products. Epimerization of the initially formed *β*-hydroxy ketone may enable access to mitomycin C or FR900482 biosynthetic congeners.

FR900482 (**2**) and congeners FR66979 (**3**), FK973 (**4**), and FK317 (**5**) have enormous potential as anticancer agents (Figure 1).[1] These new prospective drugs are cytotoxic to tumors but do not appear to exhibit the deleterious side effects characteristic of the structurally related drug mitomycin C (MMC, **1**).[2] For example, myelosuppression and hemolytic uremic syndrome have plagued the broad clinical utility of MMC since 1974.[3] The allure of less toxic and more active chemotherapeutic agents has spawned numerous total and formal syntheses of FR900482 and its congeners.[4]



1, Mitomycin C (MMC)

2, FR900482, R = CHO
3, FR66979, R = CH_2OH
4, FK973, $R_1 = R_2 = R_3 = Ac$
5, FR317, $R_1 = Me$, $R_2 = R_3 = Ac$

Figure 1. Structures of mitomycin C, FR900482, and congeners.

In particular, we recently described a stereoselective, convergent total synthesis of FR900482 (**2**)[5] as well as an improved synthesis of the benzazocane core of both FR900482

---

† Colorado State University.
‡ University of Colorado Cancer Center.

(1) (a) Boger, D. L.; Wolkenberg, S. E. *Chem. Rev.* **2002**, *102*, 2477. (b) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723.

(2) (a) Nelson, S. M.; Ferguson, L. R.; Denny, W. A. *Cell & Chromosome* **2004**, *3*:2. (b) Beckerbauer, L.; Tepe, J.; Eastman, R. A.; Mixter, P. F.; Williams, R. M.; Reeves, R. *Chem. Biol.* **2002**, *9*, 427. (c) Beckerbauer, L.; Tepe, J.; Cullison, J.; Reeves, R.; Williams, R. M. *Chem. Biol.* **2000**, *7*, 805.

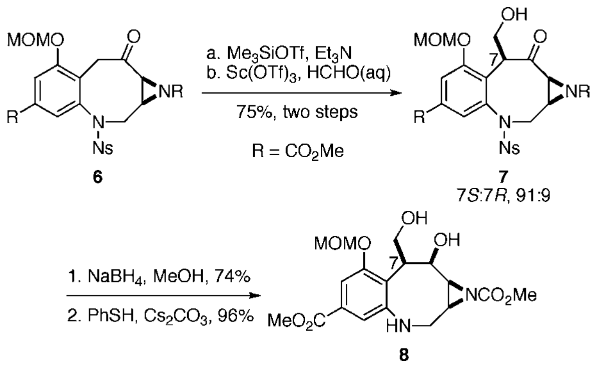
(3) Bradner, W. T. *Cancer Treat. Rev.* **2001**, *27*, 35.

10.1021/ol701960v CCC: $37.00

and mitomycin C.[4] Although our 33-step asymmetric route is among the most concise syntheses of FR900482 (**2**) extant, our interest in exploring the biogenesis of **1** and **2** has mandated that we improve the unselective hydroxymethylation aldol condensation reaction (dr $\approx$ 1:1).[5]

Throughout the course of our studies toward the synthesis of putative biosynthetic intermediates of both FR900482 and the mitomycins, it became necessary to investigate the hydroxymethylation of substrates such as **6** (Scheme 1).[6]

Scheme 1. Hydroxymethylation of Benzazocane **6**

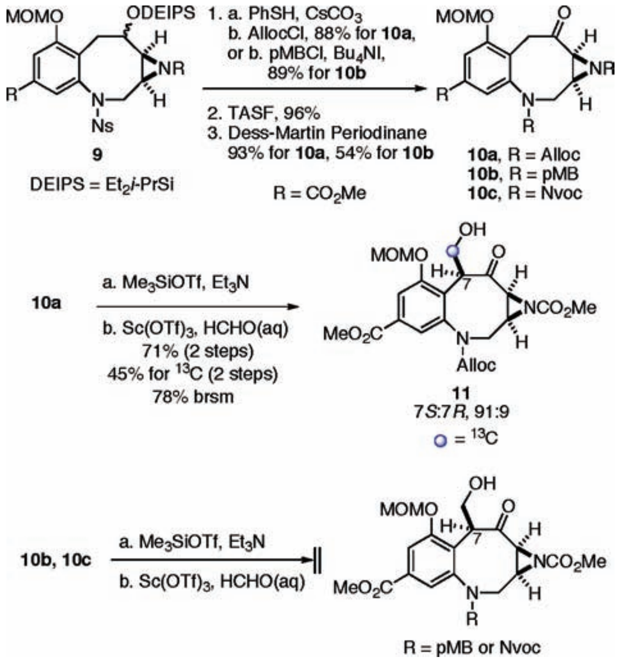


Hydroxymethylation of benzazocane intermediates en route to FR900482 under basic conditions often resulted in undesired elimination of the initially formed hydroxymethylation product. In conjunction with their synthetic studies, Rapoport[7] and Danishefsky[8] demonstrated that epoxidation and reductive ring opening of the *exo*-methylene in their respective eight- or six-membered ring substrates afforded the requisite hydroxymethyl compound indirectly. In a recent full paper describing his total synthesis of FR900482 (**2**), Fukuyama reported a one-step, stereoselective, base-catalyzed hydroxymethylation requiring 115 equiv of aqueous formaldehyde.[9] Such a large molar excess is impractical in the context of the preparation of putative biosynthetic intermediates where an expensive isotopically labeled source of formaldehyde would be employed.[10]

With benzazocane **6** in hand, we explored alternate hydroxymethylation conditions. We were especially intrigued by the lanthanide triflate-catalyzed Mukaiyama aldol reaction of enoxysilanes developed by Kobayashi.[11] Accordingly, treatment of benzazocane **6** with trimethylsilyl triflate provided the silyl enol ether which was used without purification in the hydroxymethylation step. Exposing the enoxysilane to a catalytic amount of ytterbium(III) triflate and 5 equiv of formaldehyde over 48 h provided alcohol **7** in 70% yield as a 84:16 ratio of diastereomers. Scandium(III) triflate was a superior catalyst and furnished the alcohol **7** in 82% yield (75% over two steps) as a 91:9 ratio of diastereomers in only 3 h (Scheme 1). The major diastereomer in the aldol reaction was determined to be the 7*S*-stereoisomer by X-ray crystallographic analysis of a derivative, diol **8**. This derivative was prepared by stereoselective carbonyl reduction and removal of the *N*-nosyl residue of the initial hydroxymethylation product, alcohol **7**.[12]

Having developed an efficient method for the hydroxymethylation of benzazocane **6**, we were interested in exploring the scope and generality of this protocol with more substrates. Specifically, we were interested to see the effect, if any, different protecting groups on the benzazocane nitrogen might have on the selectivity and general outcome of the aldol reaction. Consequently, *N*-alloc benzazocane **10a** was prepared from compound **9**[4] (Scheme 2). Treatment of the *N*-alloc benzazocane **10a** to identical hydroxymethylation conditions described earlier to prepare compound **7** provided the 7*S*-stereoisomer of alcohol **11** in 71% yield over two steps with 94:6 dr. We also attempted the same aldol reaction of **10a** with 5 equiv of aqueous ^{13}C-labeled formaldehyde to furnish labeled alcohol ^{13}C-**11** in slightly lower yield (45% for two steps, 78% brsm, unoptimized). Somewhat surprisingly, treatment of *N*-pMB benzazocane **10b**[5] to the same

Scheme 2. Hydroxymethylation of Benzazocanes **10a**−**c**



---

[4] Ducept, P.; Gubler, D. A.; Williams, R. M. *Heterocycles* **2006**, *67*, 597 and references cited therein.

[5] (a) Judd, T. C.; Williams, R. M. *J. Org. Chem.* **2004**, *69*, 2825. (b) Judd, T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683.

[6] Prepared in two steps (TASF-mediated desilylation, Dess−Martin oxidation) from the corresponding silyl ether **12a** reported in ref 4.

[7] Paleo, M. R.; Aurrecoechea, N.; Jung, K.-Y.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130.

[8] The benzylic, exocyclic olefin in Danishefsky's synthesis of FR900482 was the product of a Heck cyclization: Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722.

[9] Suzuki, M.; Kambe, M.; Tokuyama, H.; Fukuyama, T. *J. Org. Chem.* **2004**, *69*, 2831.

[10] For example, $^{13}CH_2O$ solution, 20 wt % in H_2O, 99% ^{13}C, CAS No. 3228-27-1, Aldrich Catalog No. 489417, costs US$266.00/gram.

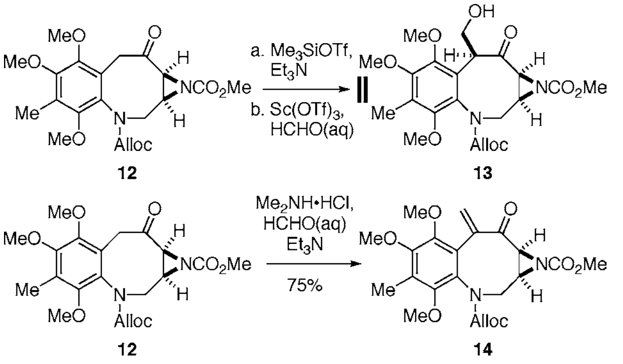
[11] (a) Kobayashi, S.; Hachiya, I. *J. Org Chem.* **1994**, *59*, 3590. (b) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236.

[12] X-ray data for compound **8** are included as Supporting Information.

conditions did not provide any of the desired alcohol. Even more startling was that *N*-Nvoc (Nvoc = 6-nitroveratryloxycarbonyl or 3,4-dimethoxy-6-nitrobenzyloxycarbonyl) benzazocane **10c**[13] did not undergo hydroxymethylation under these conditions. Attempted hydroxymethylation of **10b** and **10c** was apparently unsuccessful since, in each case, the requisite enoxysilane intermediate could not be formed under a variety of conditions.

With these interesting results in hand for benzazocanes constituted with the FR900482 framework, we were intrigued whether this methodology could be useful in our studies toward the asymmetric total synthesis of the mitomycins and their corresponding biosynthetic precursors. As shown in Scheme 3, employing identical hydroxymethylation conditions as before failed to provide the desired alcohol from benzazocane **12**.[14] In tandem with unsuccessful results observed for FR900482-based benzazocanes **10b** and **10c**, our lack of success in forming the enoxysilane intermediate likely hindered hydroxymethylation of these substrates. Alternatively, attempts to engender enoxysilane formation under basic conditions (LHMDS, Me_3SiCl) also failed. Carbamates other than *N*-alloc (*N*-Boc and methyl) were prepared but also failed to undergo hydroxymethylation. Curiously, attempted hydroxymethylation of **12** using conditions developed by Fukuyama,[9] as well as other conditions, only afforded enone **14** (Scheme 3).

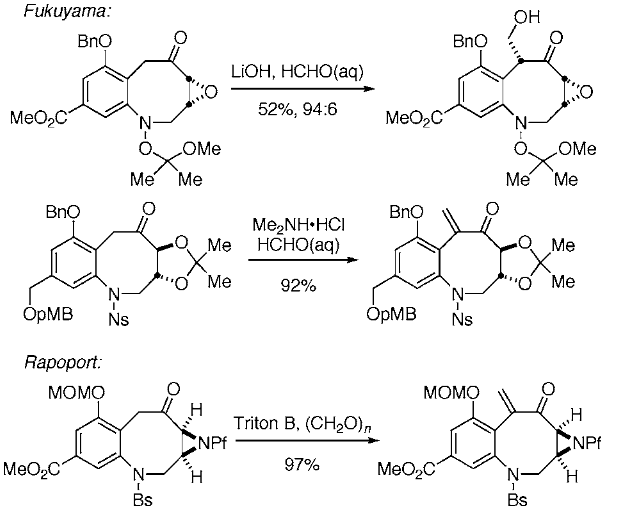
Scheme 3. Failed Hydroxymethylations of Benzazocane **12**



From the hydroxymethylation results for both FR900482- and mitomycin-based benzazocanes, we surmise that the electronics of the substrate play a crucial role in the success of this reaction. This observation is not without precedent for this family of molecules.

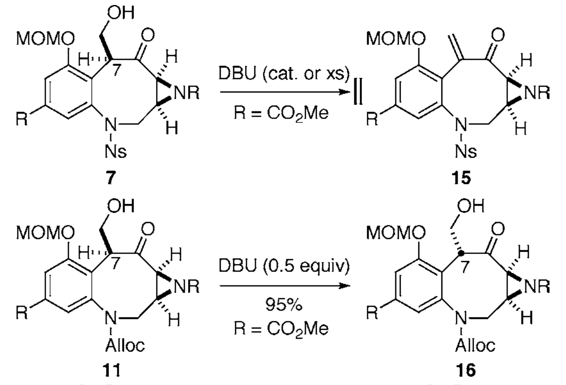
Illustrated in Scheme 4 are hydroxymethylation conditions used by Fukuyama[9] and Rapoport[7] in their total syntheses of FR900482, respectively. The major differences among these substrates that may affect the hydroxymethylation reaction are the substituents on the arene ring and the protecting group on the benzazocane nitrogen. From the examples shown in Scheme 4, as well as our own, we may conclude that the more electron-rich the substrate, the more prone it is toward elimination. Curiously, formation of an enoxysilane intermediate from an electron-rich arene appears to be considerably more difficult for application in the scandium(III) triflate-mediated hydroxymethylation reaction which we describe.

Scheme 4. Electronic Effects on Hydroxymethylation



One powerful and unanticipated consequence of the Lewis acid catalyzed Mukaiyama aldol approach is that it may be used for the construction of either the FR900482 or the MMC scaffold. Because the hydroxymethylation reaction is stereoselective and kinetically controlled, the initially formed 7*S*-stereoisomer of compound **11** matches the C-9 stereochemistry of MMC (**1**). On the other hand, equilibration of compound **11** to the thermodynamically favored 7*R*-isomer **16** under carefully controlled, base-catalyzed conditions should allow access to FR900482, potential late-stage biosynthetic intermediates and their congeners (Scheme 5).

Scheme 5. Attempts to Epimerize Hydroxymethylation Products



7*S*:7*R*, 91:9

7*S*:7*R*, 12:88

Unfortunately, all attempts to epimerize *N*-nosylsulfonamide **7*S*-7** gave the undesired enone **15** resulting from elimination.

---

[13] Williams, R. M.; Rollins, S. B.; Judd, T. C. *Tetrahedron* **2000**, *56*, 521.

[14] Prepared in two steps (TASF-mediated desilylation, Dess−Martin oxidation) from the corresponding silyl ether **13b** reported in ref 4.

Successful epimerization of compound **11** (7*S*:7*R*, 91:9) to 7*R*-isomer **16** (7*S*:7*R*, 12:88), but not *N*-nosylsulfonamide **7**, supports our assertion (vide infra) that electronics play a significant role in the chemistry of the benzylic position in these benzazocane architectures.

We attempted to develop a rationale to accommodate why the 7*S*-configuration predominates in successful hydroxymethylation reactions of FR900482-derived templates. Because reactions of medium-ring olefins are known to proceed from the periphery, the major, kinetic product of the hydroxymethylation reaction results from addition to the lowest energy conformation of the ring.[15,16] The possible low-energy conformations of the intermediates in these reactions were determined and analyzed using computational methods (Figure 2).[17] Conformational analysis of the likely intermediate in these reactions revealed that electrophilic addition of formaldehyde to the only available face of the electron-rich olefin in the lowest energy conformer should afford the 7*S*-isomer we observed. Furthermore, analysis of successful hydroxymethylation reactions from our group[5,13] and results reported by Fukuyama[9] suggests that electrophilic approach may proceed via a late transition state.[18] In particular, the development of $A_{1,3}$-strain[19] between the incoming hydroxymethyl group and the aryl alkoxy group as the reaction proceeds may alter the energy barrier for each conformer in the reaction. This unfavorable steric interaction in the transition state may explain differences between experimental selectivities observed and predictions we can make on the basis of computational analysis.

In summary, we report an efficient method for the hydroxymethylation of benzazocanes en route to putative synthetic and late-stage biosynthetic intermediates of FR900482 and MMC. Electronics play a major role in this reaction, as *N*-Nvoc and *N*-PMB benzazocanes of FR900482 fail to undergo hydroxymethylation. Efforts to prepare putative biosynthetic intermediates of FR900482 and the mitomycins, as well as the asymmetric total synthesis of the mitomycins, are currently under investigation in these laboratories.

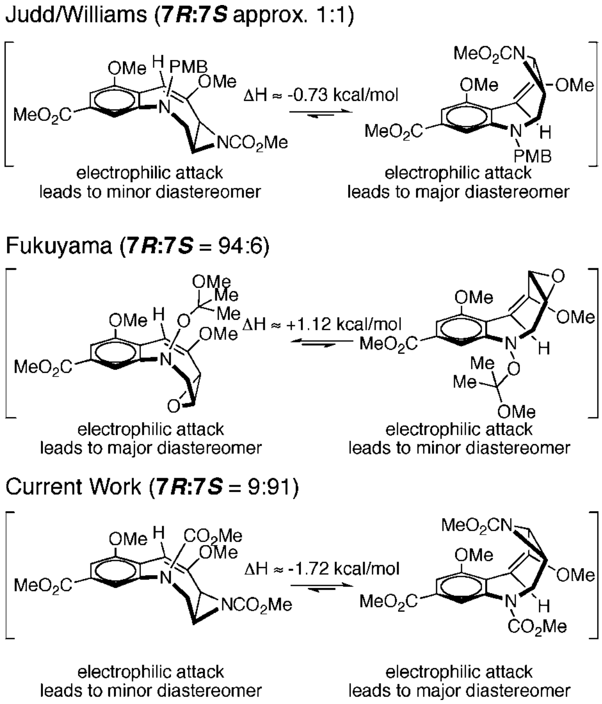


Figure 2. Comparative experimental and computational analysis of intermediates in the hydroxymethylation reaction.

Acknowledgment. Dedicated to the memory of Professor Albert I. Meyers. This work was supported by the National Institutes of Health (CA51875). We also acknowledge a Graduate Student Fellowship from Eli Lilly (to D.A.G.). Mass spectra were obtained on instruments supported by the NIH Shared Instrumentation Grant GM49631.

Supporting Information Available: Complete experimental procedures, characterization data, and spectral data for new compounds, details of theoretical experiments, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701960V

---

[15] Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

[16] This statement is valid if we assume that the energy barrier of reaction between both conformations of the olefin and the electrophile is nearly identical, according to Curtin−Hammett/Winstein−Holness kinetics: Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42.

[17] The lowest energy conformations of the eight-membered ring possessing a *cis*-olefin were determined by a Monte Carlo conformational search. These structures were refined using AM1, then HF/6-31G*. Last, the energies shown represent single-point HF/6-31G** calculations. Certain structural simplifications were made to simplify our qualitative computational experiments. These simplifications reduce computational time but do not, in our opinion, significantly alter the results. Further details and a rationale for the computational methods used are included in the Supporting Information.

[18] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

[19] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.