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Synthesis of the Mitomycin and FR900482 Ring Systems via Dimethyldioxirane Oxidation

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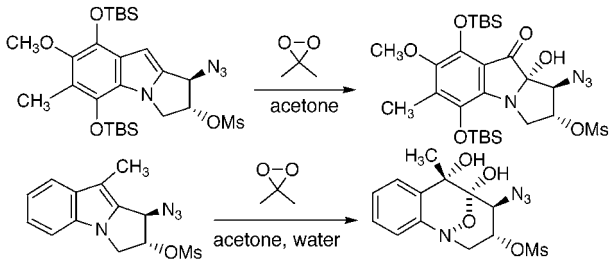
ABSTRACT

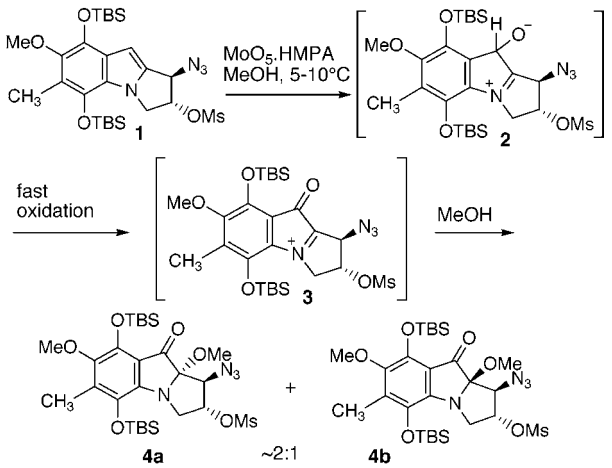


Dimethyldioxirane oxidizes a 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole unsubstituted at the C-9 position stereoselectively to form a hydroxy ketone with all the basic elements of the mitomycin ring system. On the other hand, a 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole derivative substituted with an alkyl group at C-9 undergoes an oxidative ring expansion in the presence of dimethyldioxirane to give an FR900482 analogue.

Dimethyldioxirane (DMDO) has proven to be a versatile oxidizing agent for a wide variety of functional groups.[1] An exceedingly useful and common transformation is the epoxidation of alkenes. Chiral versions of this reagent have been shown to convert alkenes into oxiranes with high enantioselectivities.[2] Computational studies indicate that the oxygen atom transfer proceeds through a concerted mechanism.[3] It has also been shown to oxidize the C2−C3 indole double bond.[4]

Our interest in developing efficient routes to the tetracyclic ring systems of mitomycin C and FR900482 had previously resulted in the discovery that the C9−9a double bond of 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole **1** can be oxidized with MoO_5·HMPA to form a ∼2:1 mixture of the diastereomers **4a** and **4b** (Scheme 1).[5] Unfortunately, the preparation of this reagent for the specialized oxidation required by the 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole system varied considerably from batch to batch. Therefore, an investigation of the

Scheme 1



(1) (a) Adam, W.; Curci, R.; Edward, J. O. *Acc. Chem. Res.* **1989**, *22*, 205−211. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201. (c) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1993**, *164*, 45−62.

(2) (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847−859. (b) Frohn, M.; Shi Y. *Synthesis* **2000**, 1979−2000.

(3) Gisdakis, P.; Roesch, N. *J. Phys. Org. Chem.* **2001**, *14*, 328−332 and references therein.

(4) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867−8868.

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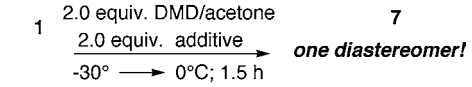
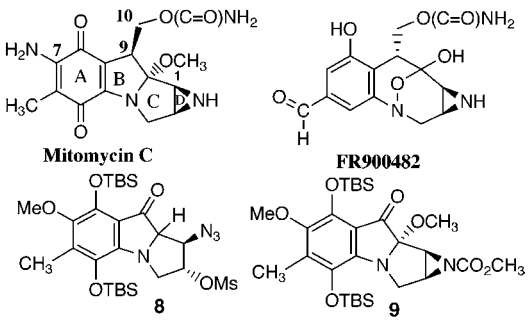
Table 1. Effect of Additives on the Formation of **7**



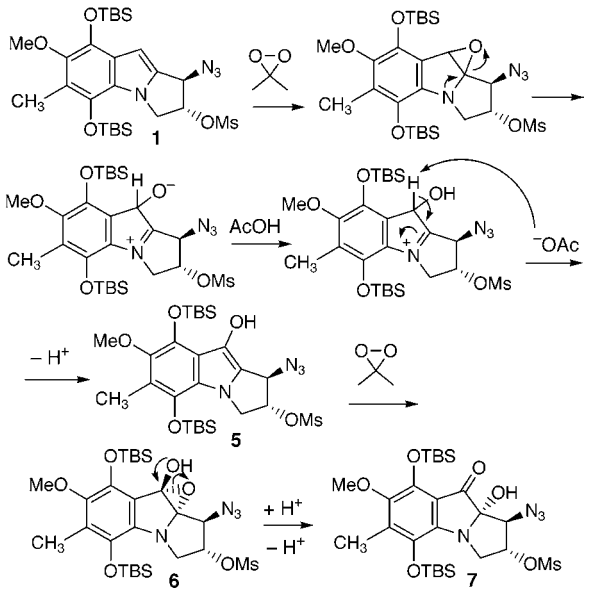
additive	yield	additive	yield
none	44%	CH_3CO_2H	71%
H_2O	53%	$ClCH_2CO_2H$	66%
CH_3OH	56%	F_3CCO_2H	66%

oxidation of **1** with DMDO was undertaken. To our surprise, the oxidation of **1** with 2 equiv of DMDO was completely stereoselective, resulting in the formation of a single diastereomer. Even in the presence of methanol, no methoxy group could be incorporated into the C-9a position (Table 1).



The stereoselectivity and the inability to introduce a methoxy group directly into the C-9a position suggests that a different mechanism is operating from that observed previously when **1** is oxidized with MoO_5·HMPA.[5] In the latter case, oxidation of the C9−9a double bond presumably leads to formation of intermediate **2**, which must be rapidly oxidized to the iminium ion **3**. Reaction with methanol results in the ∼2:1 mixture of the diastereomers **4a** and **4b** (Scheme 1). Under the DMDO oxidation conditions, the proton at C-9 must be removed to give the enol **5**, which undergoes a second oxidation to form **6**. Rearrangement results in the hydroxy ketone **7** (Scheme 2). It seemed reasonable that acid conditions might favor formation of the enol intermediate. Accordingly, a series of acid additives were attempted (Table 1). The addition of 2 equiv of acetic acid added to the reaction mixture gave the best obtained yield of 71%. The proposed mechanism was further supported by the isolation of ketone **8** upon treatment of **1** with 2 equiv of DMDO at −78 °C with a temperature increase to −30 °C over a period of 25 min before removal of the solvent and purification by flash chromatography. An 8% yield of ketone **8** was obtained as one diastereomer, although the stereochemistry of the C-9a hydrogen is uncertain. Although a subsequent methylation step of **7** was necessary (93% yield), the overall yield of 66% for the DMDO oxidation and methylation steps and the fact that a single diastereomer was formed made this a superior method over the MoO_5·HMPA oxidation in methanol (46% for the formation of **4a**). Ketone **7** was converted into **9** by sequential treatment with triphenylphosphine, methyl chloroformate in the presence of pyridine, and dimethyl sulfate in the presence of sodium hydride. Ketone **9** was identical to that prepared via the MoO_5·HMPA synthetic route.[5]

Scheme 2



From these results, it seemed reasonable that DMDO might also prove to be useful in preparing the FR900482 ring skeleton. DMDO had been used earlier to oxidize N-4 of a 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole derivative after oxidation of the C9−9a double bond with osmium tetroxide.[6] In prior work, we had found that the FR900482 ring system could be formed by oxidizing the C9−9a double bond of a 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole analogue with a stoichiometric amount of osmium tetroxide, followed by oxidation of N-4 with magnesium monoperoxyphthalic acid,[7] but were interested in finding a way to accomplish both oxidations in a one-pot reaction.

Dmitrienko et al. had previously reported that the 2,3-dihydro-1*H*-pyrrolo[1,2-a]indole **10** formed dimer **12** upon treatment with DMDO (Scheme 3).[8] They postulated that this occurred via the zwitterionic intermediate **11**. We concluded that if water intercepted this type of intermediate, then a second oxidation at N-4 should take place leading to the desired hydroxylamine hemiketal ring system. Therefore, a methyl group at C-9 was introduced by Vilsmeier−Haack

(5) Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049−6052. In our hands, the preparation of an active oxidant capable of forming **4a** and **4b** proved to be capricious. The MoO_5·HMPA oxidant was prepared by the method of Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127−137.

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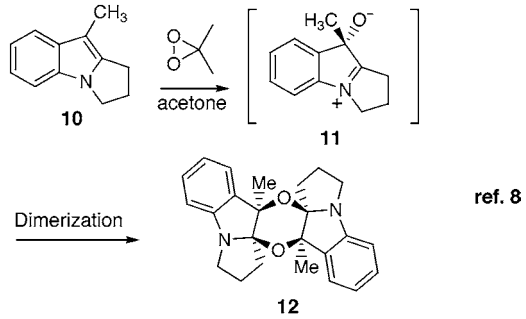
(8) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159−1160.

Scheme 3[a]



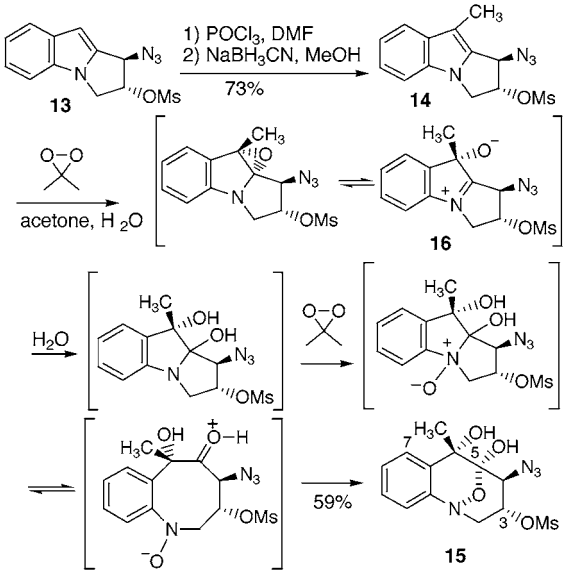
[a] Dmitrienko et al. *J. Am. Chem. Soc.* **1997**, *119*, 1159−1160.

formylation of 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole **13**,[9] followed by reduction with sodium cyanoborohydride to give **14** in a 73% overall yield.[10] Oxidation with DMDO in the presence of water gave a 59% yield of **15**, a model compound for a possible FR900482 synthetic intermediate.[11] It appears as a single diastereomer in its ^{1}H and ^{13}C NMR spectra in $CDCl_3$.

We have tentatively assigned **15** the structure shown in Scheme 4 by analogy to a similar compound synthesized previously by the Dmitrienko group.[12] Scheme 4 illustrates a plausible mechanism to account for the formation of **15**. The main features are the interception of the zwitterionic intermediate **16** by water, followed by oxidation of N-4.

In conclusion, DMDO has proven to be a mild and effective reagent to stereoselectively introduce an oxygen substituent at the C-9a position of a mitomycin derivative by oxidizing 2,3-dihydo-1*H*-pyrrolo[1,2-a]indoles unsubstituted at the C-9 position. DMDO has also been shown to oxidatively ring expand 2,3-dihydo-1*H*-pyrrolo[1,2-a]indoles substituted with a C-9 alkyl group to the corresponding FR900482 ring system. To the best of our knowledge, this is the first example of a 2,3-dihydo-1*H*-pyrrolo[1,2-a]indole analogue being oxidatively transformed into the FR900482 skeleton in a single step.

Scheme 4



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Supporting Information Available: Complete experimental details are provided for compounds **7**, **8**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026738Y

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(10) Djuric, S. W.; Herbert, R. B.; Holliman, F. G. *J. Heterocycl. Chem.* **1985**, *22*, 1425−1428.

(11) HMQC and HMBC experiments have confirmed the atom connectivity of **15**. The HMBC experiment shows strong cross-peaks between the C-6 methyl hydrogens and carbons 5, 6, and 6a. We thank Dr. George Doss for his assistance with these experiments.

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