Communications to the Editor

Synthesis of the Tetracyclic Mitomycin Skeleton via a Dialkylvinylsulfonium Salt

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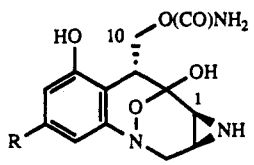
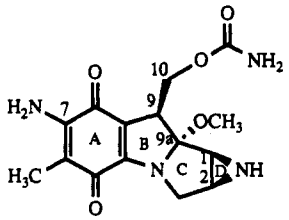
The natural product mitomycin C has proven to be a clinically useful antitumor agent.[1] Mitomycin C is not active in the quinone form and requires activation by either enzymatic or chemical reduction.[2,3] Mild acidic treatment also results in alkylated mitosene derivatives.[4] The activated mitomycin C undergoes loss of methanol and is capable of monofunctional and/or bifunctional covalent interaction with DNA.[2] The discovery of mitomycin C has resulted in two total syntheses of this important natural product.[5,6] Two new natural products, FR900482 and



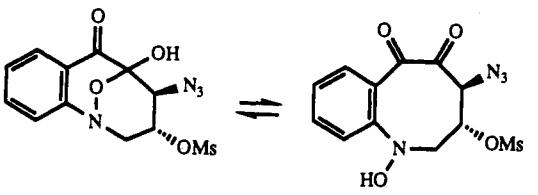
R = CHO **FR900482**
R = CH_2OH **FR66979**



Mitomycin C

FR66979, have recently been isolated from a *Streptomyces sandaensis* culture.[7] These compounds,[8] like mitomycin C,[2-4,9] appear to be activated by either enzymatic or chemical reduction and to alkylate DNA. The novel structure and potential usefulness of FR900482 make it an attractive synthetic target.[10] New, efficient syntheses of these two classes of antitumor antibiotics may lead to mitomycin and FR900482 analogs with improved anticancer activity and less toxicity.

Our strategy was inspired by a bicycloannulation reaction reported in 1983, in which a tetracyclic aziridino mitosene analog was formed from 2-(*N*-phenylformimidoyl)indole and methyl 2-bromopropenoate in a single step.[11] In a similar manner, we have found that 2-formylindole reacts with dimethylvinylsulfonium iodide[12] or ethylmethylvinylsulfonium iodide in the presence of sodium hydride to give the tetracyclic oxirane **1** (Scheme 1). In this reaction, the vinylsulfonium salt presumably undergoes conjugate addition by the anionic indole to form the sulfur ylide *in situ*. The sulfur ylide then reacts at the carbonyl center to form an alkoxide, which displaces dimethyl sulfide. The oxirane is very prone to ring opening, thus our usual procedure is to add a solution of sodium azide in aqueous acetone to the oxirane and isolate the azido alcohol **2**. We have formed the mesylate **3**, which undergoes oxidation upon treatment with 2-phenylsulfonyl-3-phenyloxaziridine (Davis' reagent)[10g,13,14] to give **4**. Initially we were unable to obtain the molecular ion from the mass spectrum of the azido mesylate **4**; therefore, we believed we had formed compound **9**, which possesses the FR900482 skeleton. This



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seemed to be in agreement with earlier results, in which a 2,3,9,-9a-tetrahydro-9a-hydroxy-9-methoxy-9-methyl-1*H*-pyrrolo[1,2-*a*]indole was oxidized to the hydroxylamine hemiketal ring system of FR900482 with Davis' reagent.[10g] Treatment of **4** with triphenylphosphine in the presence of triethylamine[10f,15] results in the formation of **5**. It was unclear whether triphenylphosphine reduces the hydroxylamine of the open keto form of **9** or whether **4** was the true intermediate. The two diastereomers of **4** can be separated by column chromatography, although they both reach an equilibrium of approximately 7:2 after 72 h in $CDCl_3$ as measured by ^1H NMR. Therefore, we introduced the *tert*-butyldimethylsilyl group to the less stable of the two diastereomers to give a 66% yield of **7** as a 1:2 mixture of diastereomers. Apparently some equilibration of the diastereomer of **4** takes place under the reaction conditions. We then obtained an 81% yield of **8** from **7** as the same 1:2 mixture of diastereomers (**7** cannot equilibrate), which indicates that **4** rather than **9** is the

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(14) The oxidation was achieved with 3 equiv of Davis' reagent in 10:1 THF:water. The reaction mixture was stirred at room temperature for 14 h. The solvent was then evaporated under reduced pressure, and the two diastereomeric products were purified by flash chromatography (1:3 EtOAc: petroleum ether).
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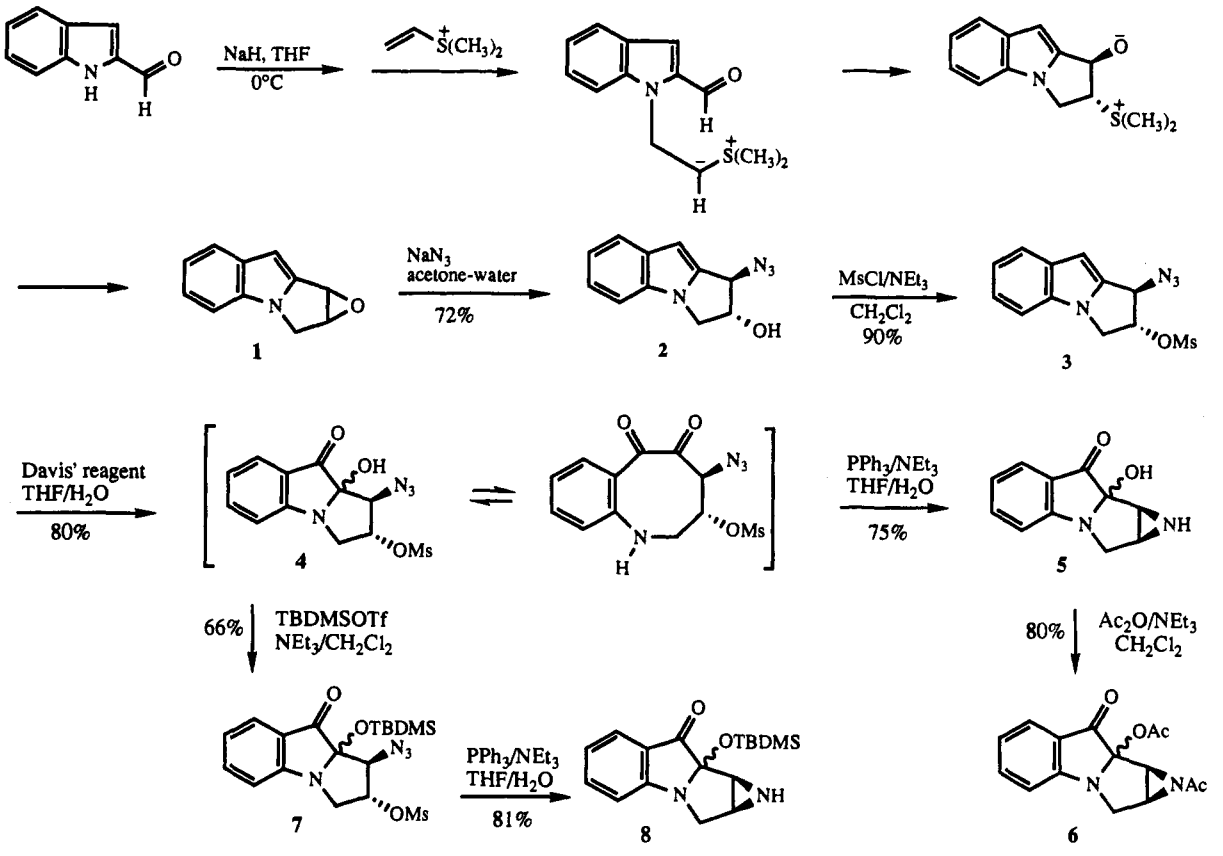
Scheme 1



immediate precursor. The electron-withdrawing effect of the keto group apparently reduces the nucleophilicity of N-4, so that **4** rather than **9** is formed. Subsequently, we have been able to obtain high-resolution mass spectral data for compounds **1–5**, which correspond to the structures shown in Scheme 1. Acetylation of **5** produces **6**, which appears to exist as a single diastereomer by ^1H and ^{13}C NMR in $CDCl_3$.

The advantage to this approach is that the third (C) ring plus the precursor functional groups to the fourth (D) ring are formed in *one* step. The oxidation with Davis' reagent gives the mitomycin ring system in another step, and the aziridine ring is formed easily in a third operation. Thus we are able to form the complete tetracyclic framework of mitomycin C in four steps (overall yield 39%) from 2-formylindole. In future work, we will explore the introduction of the carbamoyloxymethyl group via the keto functionality.

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Supplementary Material Available: Complete experimental details and NMR data for all reactions are reported; mass spectral data are available for **1–6** and **8** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.