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A NOVEL APPROACH TO FR-900482 VIA RING FORMING METATHESIS

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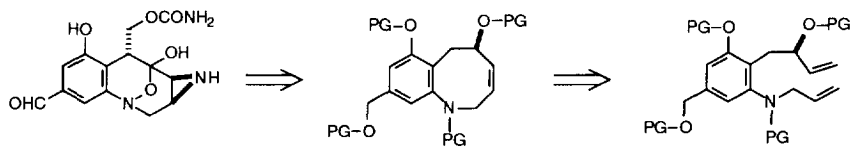
Abstract. The viability of the key step in our approach to the novel alkaloid FR-900482 (**1**) has been verified by the ring forming metathesis of **6** to give **7.**

The unusual antitumor antibiotic FR-900482 (**1**), which was isolated from *Streptomyces sandaensis* No. 6897, appears to act by forming interstrand DNA-DNA and DNA-protein cross links.[1] Structurally, it resembles the mitomycins[2] in that it has an aziridine ring and a carbamoyloxymethyl group, but it lacks a quinoid ring and possesses the unique feature of a hydroxylamine function whose hydroxyl group participates in a hemiketal array. There have been several reports of studies directed toward the synthesis of **1**, and an elegant total synthesis has recently been reported by Fukuyama.[3] In the context of developing new approaches to alkaloid natural products using ring forming olefin metathesis reactions,[4,5] it occurred to us that such a process might be applied to the construction of a highly substituted benzoazocine such as **2**, which is related to a simpler intermediate in Fukuyama's synthesis. We now report the successful realization of this cyclization in a model system.[6]

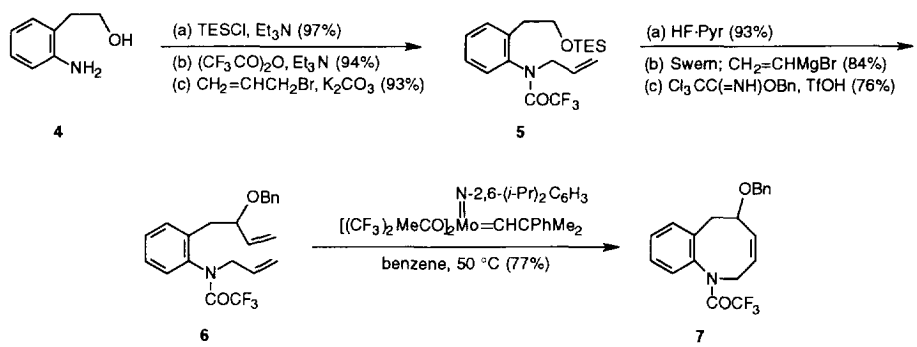
Scheme 1



1 **2** **3**

To test the key step in our approach to FR-900482, the α,ω-diene **6** was prepared in good overall yield from the commercially available amino alcohol **4** by a straightforward sequence of reactions. Following protection of the primary alcohol in **4**, the requisite allyl group was introduced by *N*-allylation of the

Scheme 2



4 **5** **6** **7**

trifluoroacetamide in 85% overall yield.[7] Deprotection of the alcohol function in **5** followed by a one-pot oxidation and Grignard addition, and final *O*-protection gave **6** in 59% yield for the three steps. Upon treatment with the molybdenum carbene complex {$PhMe_2CCH$=Mo=N-[2,6-(i-Pr)$_2C_6H_3$][$OCMe(CF_3)_2$]$_2$, 15 mol%}[8] in degassed benzene, **6** underwent facile ring forming metathesis in 77% yield. The application of a related cyclization to the total synthesis of FR-900482 is in progress, and the results of these investigations will be reported in due course.

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7. The structure assigned to each compound was in full accord with its spectral (^{1}H and ^{13}C NMR, IR and mass) characteristics. Yields cited are for compounds judged to be >95% pure by ^{1}H NMR. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC or flash chromatography and gave satisfactory identification by high resolution mass spectrometry.
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