Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1169-1170, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02488-X

A NOVEL APPROACH TO FR-900482 VIA RING FORMING METATHESIS

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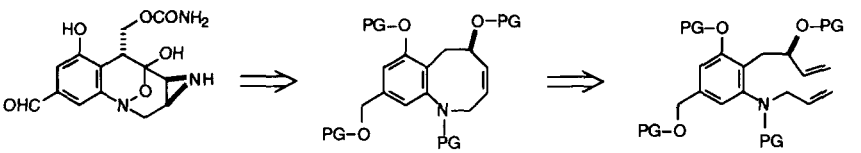
Abstract. The viability of the key step in our approach to the novel alkaloid FR-900482 (**1**) has been verified by the ring forming metathesis of **6** to give **7.**

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]

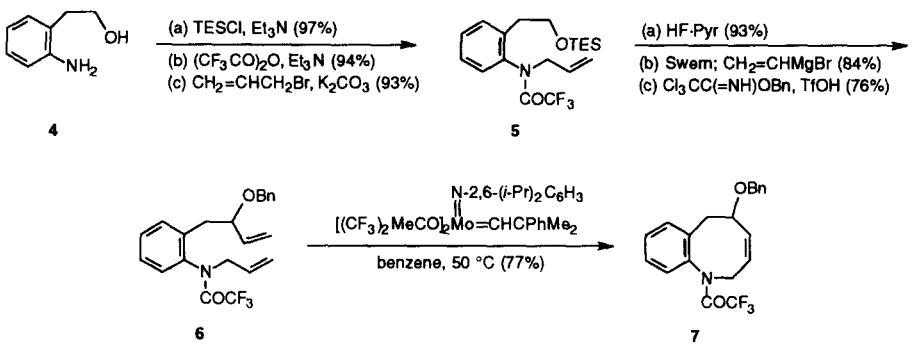
Scheme 1



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.

Acknowledgment. We wish to thank the National Institutes of Health and the Robert A. Welch Foundation for support of this research. We are indebted to Dr. M. Pätzel for conducting exploratory investigations to establish a viable route to dienes related to **6**. We are also grateful to D. R. Hamm (Catalytica Fine Chemicals) for providing generous quantities of the molybdenum catalyst.

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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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(*Received in USA* 19 *October* 1994; *accepted* 16 *December* 1994)