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# New Technology for the Construction of Bicyclo [6.2.1] Ring Systems

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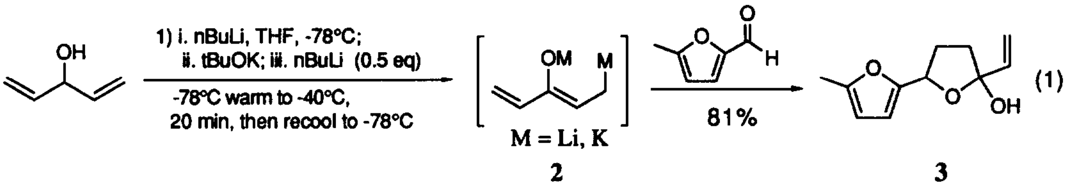
**Abstract**: Three new methods are presented in this synthesis of an 11-oxabicyclo[6.2.1]-undec-1,5,9-triene. They include: (1) the preparation of the dianion of 3-hydroxy-1,4-pentadiene; (2) an intramolecular Diels-Alder reaction accelerated by silica gel saturated with water; and (3) a tandem Grob fragmentation and homoallylic elimination of a cyclic sulfate. Overall, the synthesis of (1*E*, 5*E*, 9*Z*)-2-(t-Butyldimethylsiloxy)-8-methyl-11-oxabicyclo[6.2.1]-undec-1,5,9-triene (1) was completed in 9 steps starting from 5-methylfurfural.

Herein we present a series of new synthetic methods aimed at the selective construction of bicyclo [6:2:1] ring systems.[1] The new methods developed for this carbocyclic synthesis include: (1) preparation of a pentadienyl dianion, (2) the first example of a Diels-Alder reaction accelerated by $SiO_2/H_2O$, and (3) a Grob fragmentation/homoallylic elimination sequence.

Our approach to the stereocontrolled construction of macrocycle **1** was predicated upon the cleavage of an internal bond in a rigid tricyclic precursor, compound **4**.[2] This tricyclic compound, in turn, could be prepared via an intramolecular Diels-Alder reaction of hemiacetal **2**.[3] Finally, the substrate for the Diels-Alder reaction would be assembled via addition of the homoenolate of 1-penten-3-one to 5-methylfurfural.

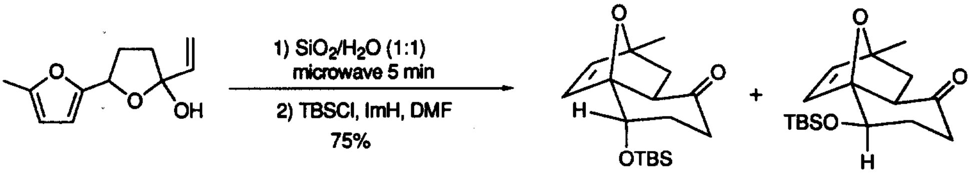
Thus, in the first step of our synthesis, the dianion of 3-hydroxy-1,4-pentadiene (**2**) was generated using Schlosser's base[4] and then added to 5-methylfurfural (eq 1). Dianion **2** behaved like the homoenolate of 1-penten-3-one,[5] and reacted exclusively at the terminal carbon to give hemiacetal **3** as a single diastereomer.



Initial attempts to prepare this dianion via the potassium alkoxide of 3-hydroxy-1,4-pentadiene were unsuccessful, as the alkoxide decomposed prior to addition of n-BuLi.[6] An alternative procedure involving generation of the lithium alkoxide of 3-hydroxy-1,4-pentadiene, followed by sequential addition of t-BuOK and nBuLi, was far superior.

Both the temperature and concentration of this reaction also proved critical to dianion formation. Our optimal conditions involved addition of one equivalent of n-BuLi to 3-hydroxy-1,4-pentadiene at -78°C, followed by sequential addition of one equivalent of t-BuOK in THF and 0.5 equivalent of nBuLi. The resulting red solution was stirred at -40°C for 20 min in order to complete dianion formation, then recooled to -78°C and treated with 0.5 equivalent of 5-methylfurfural. The concentration of the reaction solution under these conditions was 0.04M. We noted that when the reaction solution was more concentrated, a bright orange solid precipitated from solution as it was warmed to -40°C. Although this solid could be dissolved with additional THF, subsequent reaction with 5-methylfurfural gave a poor yield of the desired product.

Furans with enone side chains have been used previously as substrates in numerous intramolecular Diels-Alder reactions.[7] Initial attempts to perform a Diels-Alder reaction with hemiacetal 3, however, lead to either decomposition of the starting material or poor yields of the cycloadduct. Fortunately, we were able to take advantage of the observation that hemiacetal 3 was partially converted to cycloadduct 4 during flash chromatography on silica gel.[8] Ultimately, we determined that good yields of 4 could be achieved by adsorbing 3 onto silica gel, saturating the mixture with water,[9] and then microwaving for a total of 5 minutes.[10] This procedure yielded Diels-Alder adduct 4 in 64% overall yield from 5-methylfurfural as a 1:1 mixture of diastereomers, which were easily separated by flash chromatography.

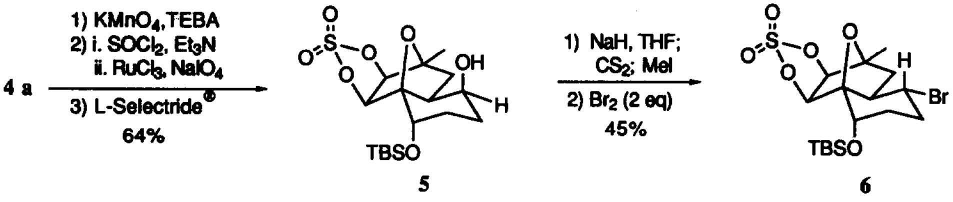


(2)

**3** **4 a** **4 b**

Addition of water to the silica was instrumental to the success of the Diels-Alder reaction. The water may perform three distinct functions during this reaction, including: (1) efficient generation of heat during the microwave process, (2) acceleration of the Diels-Alder reaction via the hydrophobic effect,[11] and (3) facilitation of the hemiacetal-hydroxy ketone equilibrium.

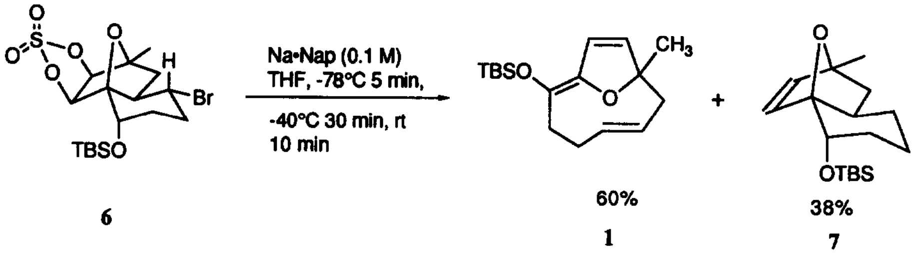
Diels Alder adduct **4a** provided a rigid framework upon which stereoselective transformations could be performed. Following silylation of the alcohol, the olefin was oxidized with $KMnO_4$[12] to give a 6.3:1 mixture of exo and endo diols in 71% yield. After separation by flash chromatography, the exo diol was readily converted to a cyclic sulfate using thionyl chloride followed by ruthenium tetroxide (95%).[13] Finally, reduction of this intermediate with L-selectride® gave only axial alcohol **5**, and in excellent yield (95%).[14] The cyclic sulfate moiety was not reduced and proved to be remarkably stable under a variety of reaction conditions.



(3)

At this point in the synthesis we had envisioned converting the axial alcohol **5** into an equatorial halide. Although there are numerous literature methods for accomplishing this type of transformation, the *only* one that proved effective was a two step procedure involving an intermediate xanthate. Thus, alcohol **5** was first converted to a xanthate in quantitative yield using NaH/$CS_2$/MeI, then treated with two equivalents of bromine.[15] Under these conditions, the equatorial bromide **6** was obtained in 45% isolated yield along with two dibromides.[16]

Treatment of bromide **6** with sodium napthalide[17] resulted in a tandem Grob fragmentation[18] homoallylic elimination reaction to give bicyclic ether **1** (60%) along with reduction product **7** (38%) as an inseparable mixture. Although the halide was readily transmetallated at -78°C, Grob fragmentation did not occur until the reaction was warmed to ca. -40°C. The intermediate allylic sulfate could not be isolated, as it underwent spontaneous elimination to give **1**.



(4)

We are currently developing extensions of the dianion/Diels Alder and Grob fragmentation/elimination technologies toward the synthesis of other macrocyclic systems.

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**References and Notes**

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