Communications

Carbohydrate-Based Strategy for the Synthesis of Zaragozic Acid via a Novel Lewis Acid-Mediated Reaction of an α-Acetoxy Sulfide

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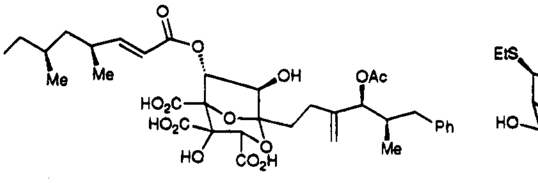
Zaragozic acid A (**1**) is a natural product isolated from *Sporormiella intermedia* and *Leptodonitium elatius*.[1] It is an important synthetic objective because it is a competitive inhibitor of squalene synthase.[2] Its inhibition at the picomolar level makes it a promising candidate in the search for drugs that regulate cholesterol levels. A few synthetic approaches to the 2,8-dioxabicyclo[3.2.1]octane skeleton have been communicated.[3] As part of our continuing interest in bridged compounds,[4] we sought an efficient route to a suitably functionalized bicyclic intermediate and report herein the direct synthesis of diol **2**.



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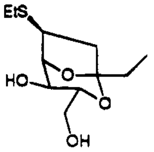

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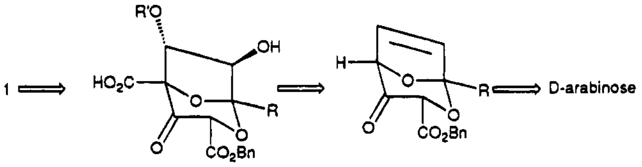
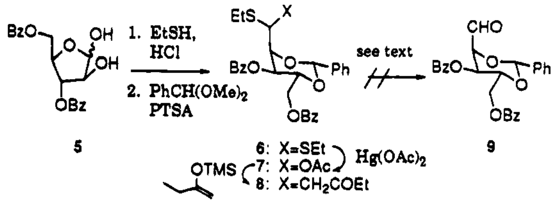
Our retrosynthetic analysis is shown below. We plan to introduce the α-hydroxy acid subunit via keto acid **3**. We plan to synthesize acid **3** from olefinic ketone **4** via the carboxylation of the bridgehead position followed by oxidation of the alkene. We envision that the functionality present in **4** could be readily accessible by oxidation of a compound similar to diol **2**.



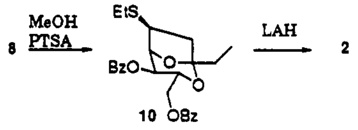
3 4

We next converted hemiacetal **5** (generated from D-arabinose in five steps[5]) into thioacetal **6** in 58% overallyield by thioacetal formation followed by protection of the 1,3-diol. Although **6** could not be prepared by treatment of the diol with benzaldehyde in the presence of *p*-toluenesulfonic acid (PTSA), it was cleanly generated using a catalytic amount of PTSA and the dimethyl acetal of benzaldehyde. Attempts to deprotect the thioacetal in **6** using a variety of reagents[6] ($HgCl_2$, $CdCO_3$; $PhI(OCOCF_3)_2$; $Tl(NO_3)_3$; Et_3OBF_4; AgOAc) failed to afford aldehyde **9**. In the course of the unsuccessful deprotection experiments, we found that treatment of **6** with mercuric acetate in acetic acid produced a stable acetate **7** as a single diastereomer in 92% yield. Unfortunately, hydrolysis of the acetate led to a mixture of products.



Since thioacetals have been employed by Mukaiyama and by Reetz in aldol-type reactions with enol silyl ethers,[7] we reacted thioacetal **6** with the enol silyl ether of 2-butanone using either trityl tetrafluoroborate or stannic chloride as the Lewis acid. Both reactions led to the decomposition of **6**. However, treatment of acetate **7** with the enol silyl ether of 2-butanone in the presence of trimethylsilyltriflate at 0 °C afforded ketone **8** in 43% yield. While boron trifluoride etherate was not effective in promoting this reaction, the use of stannic chloride at −78 °C provided ketone **8** as a single diastereomer in 65% yield. To the best of our knowledge, these reactions represent the first uses of an α-acetoxy sulfide in an aldol-type reaction.

With ketone **8** in hand, we focused on the transformation of **8** into **2**. The removal of the benzylidene acetal with 2 N sulfuric acid at 100 °C led to the cleavage of benzylidene acetal and to the closure to the bicyclic ketal **10** in 46% yield. The reaction of **8** with catalytic PTSA in methanol at 60 °C afforded ketal **10** in 69% yield. The structure of **10** was determined by COSY and NOESY



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2-D NMR experiments. Removal of the benzoate groups with LAH afforded diol **2** in 77% yield.

In summary, we have demonstrated that the 2,8-dioxabicyclo[3.2.1]octane ring system present in zaragozic acid A is efficiently accessible from D-arabinose. The key step, the reaction of acetate **7** with an enol silyl ether, appears to be a useful method for forming carbon–carbon bonds in highly functionalized systems. Efforts are now underway to generate an intermediate suitable for the total synthesis of zaragozic acid.

Note Added in Proof: Two syntheses have been reported: Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; De Riccardis, F.; Nadin, A.; Leresche, J. E.; La Greca, S.;Yang, Z. *Angew. Chem.* **1994**, *106*, 2306. Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825.

Supplementary Material Available: Experimental procedures and characterization data (3 pages).

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