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

George A. Kraus
Iowa State University, gakraus@iastate.edu

Hiroshi Maeda
Iowa State University

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Abstract
Zaragozic acid A (1) is a natural product isolated from Sporormiella intermedia and Leptodonitium elatius. It is an important synthetic objective because it is a competitive inhibitor of squalene synthase. 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. As part of our continuing interest in bridged compounds, we sought an efficient route to a suitably functionalized bicyclic intermediate and report herein the direct synthesis of diol 2.

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Communications

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

George A. Kraus* and Hiroshi Maeda

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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Zaragozic acid A (1) is a natural product isolated from Sporormiella intermedia and Leptodonitum elatus.1 It is an important synthetic objective because it is a competitive inhibitor of aqualene 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 synthetic routes to introduce the α-hydroxy acid subunit via keto acid formation 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 synthetic routes to introduce the α-hydroxy acid subunit via keto acid formation.

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.

We next converted hemiacetal 5 (generated from D-arabinose in five steps5) into thioacetal 6 in 58% overall yield 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 reagents6 (HgCl2, CdCO3; PhI(OCOCF3)2; Ti(N03)3; Et30BF4; 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 aceta 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-butane 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-butane in the presence of trimethylsilil triflate 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.


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

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