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# Rapid Synthesis of the 7-Deoxy Zaragozic Acid Core

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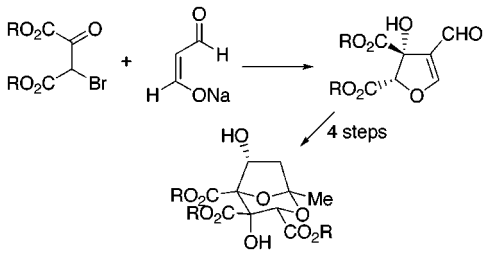
## ABSTRACT




**We have developed an efficient synthesis of the 7-deoxy zaragozic acid core. The synthesis begins with a Feist–Bénary reaction that assembles all three carbons of the polycarboxylic acid portion of the core. This reaction is followed by highly diastereoselective aldol and dihydroxylation reactions that set the remaining stereocenters of the core. The synthesis finishes with lactol oxidation and lactone alcoholysis/ketal formation reactions to construct the bicyclic ring system of the core.**

The zaragozic acids have been the subject of intense synthetic effort, for both their potent biological activity and their structural complexity (Figure 1).[1] Although mechanism-based toxicity prevents their use as cholesterol-lowering agents, similar toxicity does not necessarily limit the use of the zaragozic acids in other therapeutic areas, such as in the treatment of fungal infections.[2]

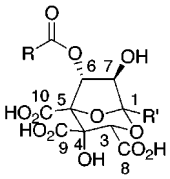



**Figure 1.** The zaragozic acid core.

We recently initiated a synthesis of the zaragozic acid core, with the goal of a practical synthesis that could produce a number of analogues. We report here the first result of this synthetic effort, a racemic synthesis of the 7-deoxy core that proceeds in six steps from commercially available starting materials in 6.6% overall yield. The 7-dexoy core is present in two of the natural products of the zaragozic acid family (Figure 1).[3]

We based our route to the zaragozic acid core on the easy availability of highly oxygenated intermediates by way of the "interrupted" Feist−Bénary reaction.[4] This reaction produces highly oxygenated dihydrofurans by the condensation of simple $\beta$-dicarbonyl compounds with $\alpha$-haloketones. Our first attempt at the core began with triester **1** (Scheme 1). We postulated that hydroxyl-directed oxidation of **1** would yield a lactol with *cis*-oriented tertiary hydroxyls. Ring-

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(2) Procopiou, P. A.; Watson, N. S. *Prog. Med. Chem.* **1996**, 331−378.

(3) Blows, W. M.; Foster, G.; Lane, S. J.; Noble, D.; Piercey, J. E.; Sidebottom, P. J.; Webb, J. *J. Antibiot.* **1994**, *47*, 740−754.

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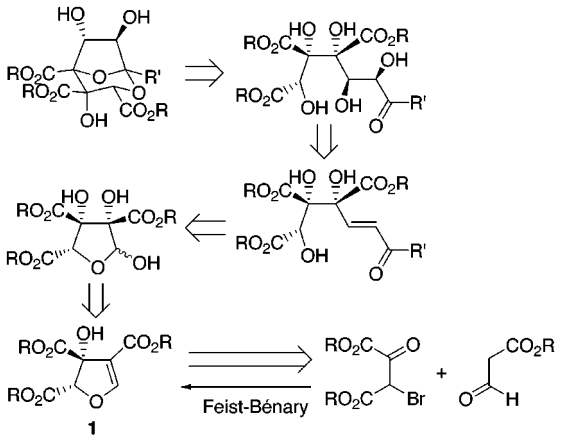
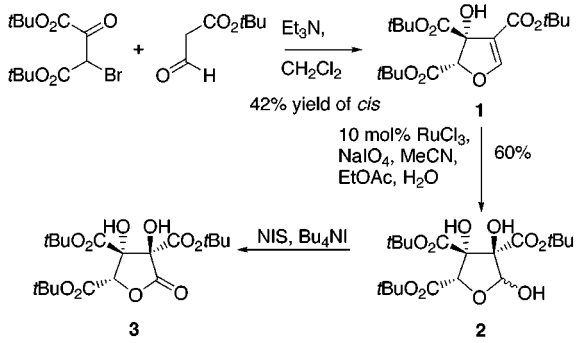
**Scheme 1**




opening Wittig reaction and dihydroxylation would yield the open form of the core.

As reported in the preceding paper, the appropriate Feist−Bénary reaction afforded the desired *cis*-dihydrofuran, **1**, in moderate yield (Scheme 2).[4] Oxidation under conditions

**Scheme 2**

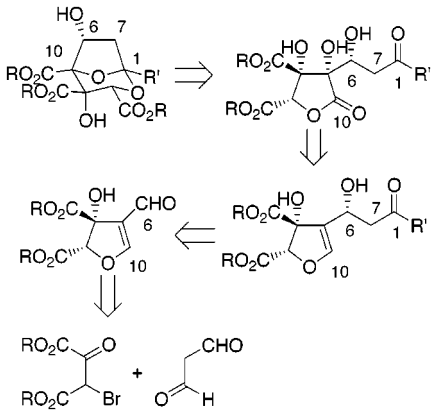



likely to give directed epoxidation (MCPBA or $VO(acac)_2$) did not afford any usable product. However, dihydroxylation of **1** yielded lactol **2** as mixture of interconverting anomers.[5] Oxidation of **2** with *N*-iodosuccinimide (NIS) and tetrabutylammonium iodide (TBAI) yielded lactone **3**.[6] An X-ray crystal structure of **3** revealed that the dihydroxylation had occurred, but to form the *trans*-oriented tertiary alcohols.

The preference for dihydrofurans to hydroxylate on the face opposite to the tertiary hydroxyl and the ability to oxidize the lactol to the lactone led us to consider an alternative strategy (Scheme 3). Reversal of the roles of $C_6$ and $C_{10}$ of the dihydrofuran would give the correct stereochemistry for the zaragozic acid core. In this route, an aldol reaction could append the side chain and $C_1$- and $C_7$-carbons

(4) Calter, M. A.; Zhu, C. *Org. Lett.* **2001**, *4*. 205−208.
(5) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312−2313.
(6) Hanessian, S.; Wong, D. H.-c.; Therien, M. *Synthesis* **1981**, 394−395.

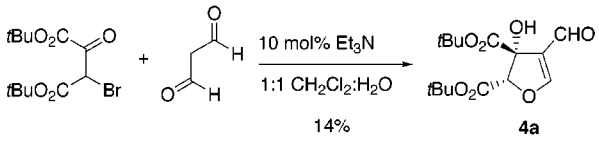
**Scheme 3**



of the core. The diastereoselectivity of the aldol reaction and the timing of the alkene oxidation remained open issues.

The route outlined above required Feist−Bénary products such as **4a**, with the carbon that would eventually be $C_6$ of the core at the aldehyde oxidation state. This product in turn required malondialdehyde as a starting material. As reported earlier, we were able to carry out Feist−Bénary reactions with an aqueous solution of this aldehyde (Scheme 4).[4] These

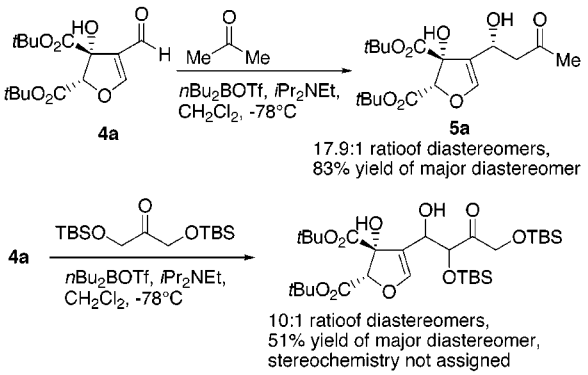
**Scheme 4**




unoptimized conditions favored formation of the *trans* product, but we were able to isolate a small amount of the desired *cis* aldehyde, **4a**.

We next explored the aldol reaction of **4a** with a number of enolates (Scheme 5). The lithium enolate of acetone yielded a stereorandom mixture. The dibutylboron enolate,

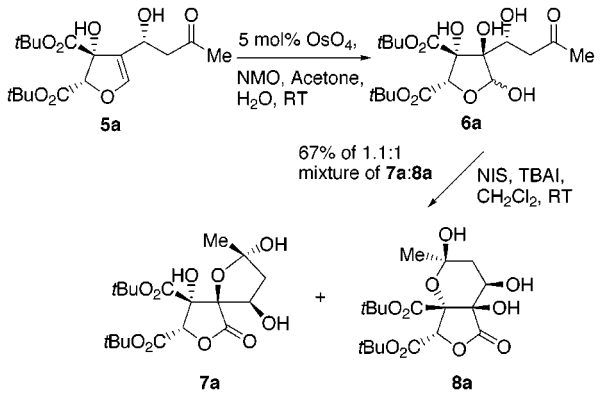
**Scheme 5**



however, yielded the desired diastereomer **5a** with excellent selectivity.[7] The stereochemistry of the major product of the addition was proven by an X-ray crystal structure of a later intermediate. Preliminary experiments also indicated that α-siloxyenolates gave very selective additions, although the stereochemistry of this product has not yet been proven. Adducts of this type should give entry into the fully oxidized core present in the majority of the zaragozic acids.

Oxidation of **5a** with $OsO_4$ and *N*-methylmorpholine-*N*-oxide (NMO) afforded triol lactol **6a** (Scheme 6).[8] This

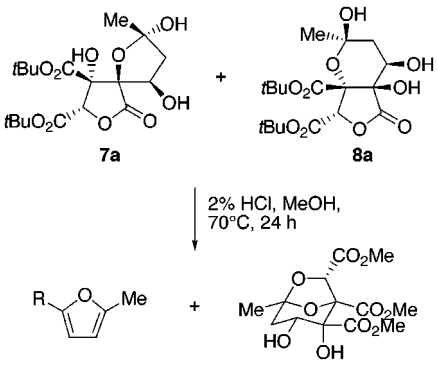
**Scheme 6**




compound existed as a mixture of two anomers. We were unable to confirm the relative configuration of the newly formed quaternary center at this stage, so we proceeded to the lactol oxidation. Oxidation of **6a** under conditions mentioned earlier provided **7a** and **8a** as a mixture of isomeric lactols. These lactols interconverted, indicating that they derived from the same dihydroxylation isomer and only differed in the position and stereochemistry of hemiacetal formation. An X-ray crystal structure of **7a** showed that both the aldol reaction and the dihydroxylation had proceeded with the desired diastereoselectivity.

We next attempted rearrangement of the mixture of **7a** and **8a** with 2% HCl in methanol at 70 °C (Scheme 7). These conditions were reported by Nicolaou for the rearrangement

**Scheme 7**




of similar substrate.[9] $^1$H NMR analysis of aliquots from the reaction revealed that **7a** and **8a** were first converted into a mixture of mixed methylketals. Further exposure to the reaction conditions resulted in formation of furan-containing byproducts, along with less than 10% of a bicyclic ketal. Later comparison to a similar compound (**10**) revealed that the bicyclic ketal possessed the undesired ring structure, with the $C_3$- and $C_4$-hydroxyls cyclized on the $C_1$-carbonyl.

Looking for an explanation for the difficulty in alcoholizing the lactone as a prelude to ketal formation, we examined of the X-ray structure of **7a** (Figure 2). This structure

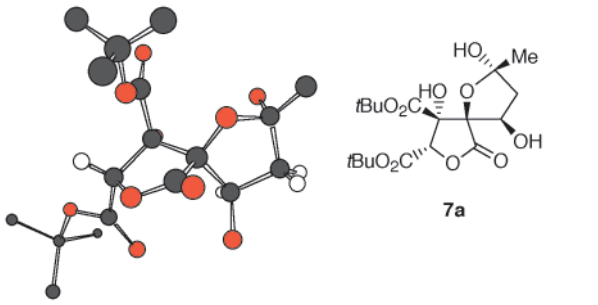
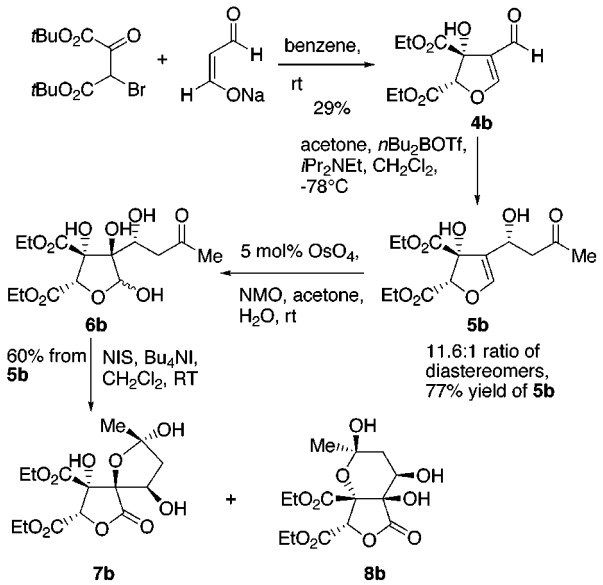



**Figure 2.** X-ray structure of **7a**.

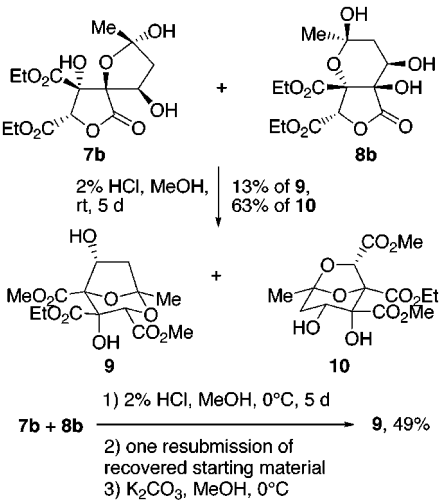
revealed that one face of the lactone carbonyl was shielded by the *tert*-butyl group of the $C_9$-ester, and the other by the $C_6$-hydroxyl. Therefore, we decided to prepare an intermediate similar to **7a** but with the carboxylates protected with less sterically demanding groups.

The synthesis of the bis-ethyl ester lactones **7b** and **8b** proceeded in a fashion similar to that of **7a** and **8a** (Scheme 8). In one minor modification, we discovered that the sodium

**Scheme 8**



**Scheme 9**




enolate of malondialdehyde furnished the desired *cis*-dihydrofuran, **4b**, with moderate selectivity and in low yield. Aldol reaction, dihydroxylation and lactone oxidation furnished a mixture of five- and six-membered lactol lactones **7b** and **8b**.

Treatment of **7b** and **8b** with 2% HCl in methanol at 70 °C again formed a mixture of furan and undesired bicylic ketal. However, we discovered that the lactols would rearrange at room temperature to form a mixture of the desired (**9**) and undesired (**10**) bicyclic ketals in a 1:5 ratio and 76% overall yield (Scheme 9). The $C_8$-carboxylate had also been converted to the methyl ester in both of these compounds. The structure of **9** was proven by NOE and X-ray crystallographic analysis, and that of **10** was inferred from the lack of an NOE enhancement between the $C_3$-H and either of the $C_7$-hydrogens (Figure 3). Encouraged by the ability of the lactone to open under mild conditions, we

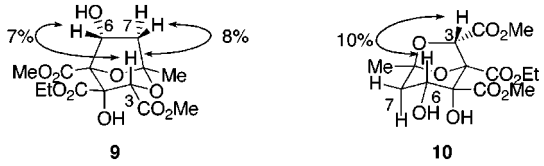



**Figure 3.** Observed NOE enhancements for **9** and **10**.

next attempted the reaction at lower temperature. Reaction at 0 °C for 5 days resulted in a 30% yield of **9**. Only very minor amounts **10** formed under these conditions. Resubmission of the recovered mixed methylketals to the same conditions resulted in a combined 52% yield of the desired ring system. However, the $C_8$-carboxylate was only partially converted to the methyl ester under these conditions. Basic methanolysis of the unpurified reaction mixture converted any diethyl ester to **9** to afford a 49% overall yield of **9** from the mixture of **7b** and **8b**. Resubmission of **9** to acidic methanol at room temperature resulted in conversion to **10**. Therefore, **9** was the kinetic product of the rearrangement, and **10** was the thermodynamic product.[10]

In conclusion, we have developed a rapid synthesis of the 7-deoxyzaragozic acid core. Two of the reactions in this synthesis proceeded with high selectivity. The route required no alcohol protecting groups, and two of the three carboxylic acids of the product were introduced at the carboxylate oxidation state. Research into an asymmetric route and one that introduces the $C_7$-hydroxyl continues.

**Acknowledgment.** We thank the Eastman Kodak Corporation and the University of Rochester Department of Chemistry for support of this projectwork.

**Supporting Information Available:** Full experimental procedures and characterization data for **5a,b**, **6a,b**, **7a,b**, **8a,b**, **9**, and **10** and a representation of the X-ray data for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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