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The Synthesis of the Zaragozic Acids: Equilibrium Control of Stereochemistry in the Dioxabicyclo[3.2.1]octane Core.

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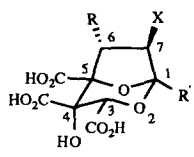
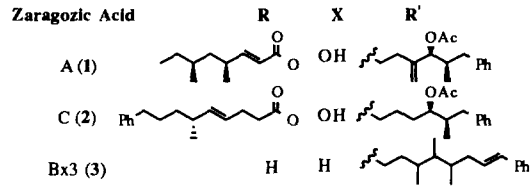
Abstract: The synthesis of the core of zaragozic acid Bx3 and a general strategy for the synthesis of the dioxabicyclo[3.2.1]octane core of the zaragozic acids is described. © 1997 Elsevier Science Ltd.

In this letter, we describe a new strategy for the synthesis of bicyclic ketal containing natural products and the use of these cyclizations in the synthesis of the 2,8-dioxabicyclo[3.2.1]octane core of zaragozic acid Bx3.[1] For the acid-catalyzed bicyclization of a dihydroxyketone, generally occurring *late in the synthetic strategy*, there is only one possible ketal isomer that may form. In contrast, polyhydroxyketones can afford multiple bicyclic ketals. If it were possible, *early in a synthetic strategy*, to control the bicyclization to favor the formation of only one isomer, then the bicyclization of polyhydroxyketones could be used to prepare ketal-containing targets.[2] The bicyclic ketal could also serve as a template for the stereoselective introduction of functionality required to complete the synthesis.

Figure 1





The zaragozic acids (squalestatins, Figure 1) are potent inhibitors of the enzyme squalene synthase (IC_{50} =12 nM), and antifungal agents.[3,4] The unique structure and biological activity of the zaragozic acids have stimulated interest among synthetic chemists, resulting in total syntheses of zaragozic acids A[5] and C[6] and several partial syntheses.[7] Our retrosynthesis (Figure 2) called for the introduction of the carboxylic acid at C-3, and oxidation of alcohols at carbons 4 and 5 late in the synthesis, affording simplified ketals **5** and **6**. These ketals could be formed from tetrahydroxyketone **7** through controlled cyclization.

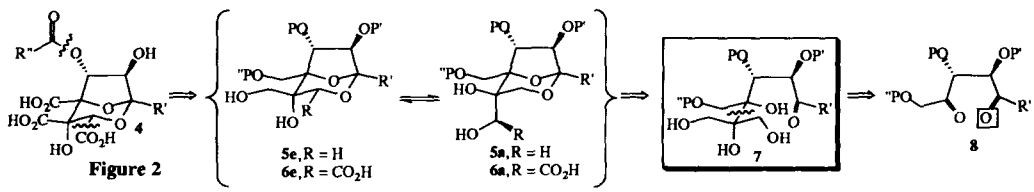


Figure 2

The zaragozic acid Bx3 framework was easily assembled from allyl acetone (**9**) (Figure 3). We blocked **9** as its ketal (ethylene glycol, TsOH, PhH, reflux) and oxidized the terminal alkene. Opening of the epoxide with benzyloxide (BnOK, THF) afforded the expected hydroxy ether. Oxidation of the resulting secondary alcohol ($(COCl)_2$, DMSO, TEA)[8] gave **10**. We then extended the carbon chain via a two step procedure using the *O*,2-dianion of allyl alcohol followed by dihydroxylation. We prepared the dianion from 2-bromopropen-1-ol and 1 equiv of MeMgBr, followed by 2.2 equivalents of *t*-BuLi.[9] Treatment of ketone **10** with this dianion gave the desired tertiary allylic alcohol. This material then underwent a facile transketalization reaction (TFA, 0.1 equiv, CH_2Cl_2) to yield bicyclic ketal **11**. We then dihydroxylated the exocyclic alkene (OsO_4, *t*-BuOH, H_2O, $K_3Fe(CN)_6$) to obtain a 1:2 mixture of **12a** and **12e**. These ketals could be separated by silica gel chromatography. Each of the purified isomers could be treated with TFA, resulting in the smooth formation of an equilibrium mixture of **12a** and **12e** in a 1:2 ratio. Through recycling, we could convert the majority of the material to either **12a** or **12e**.

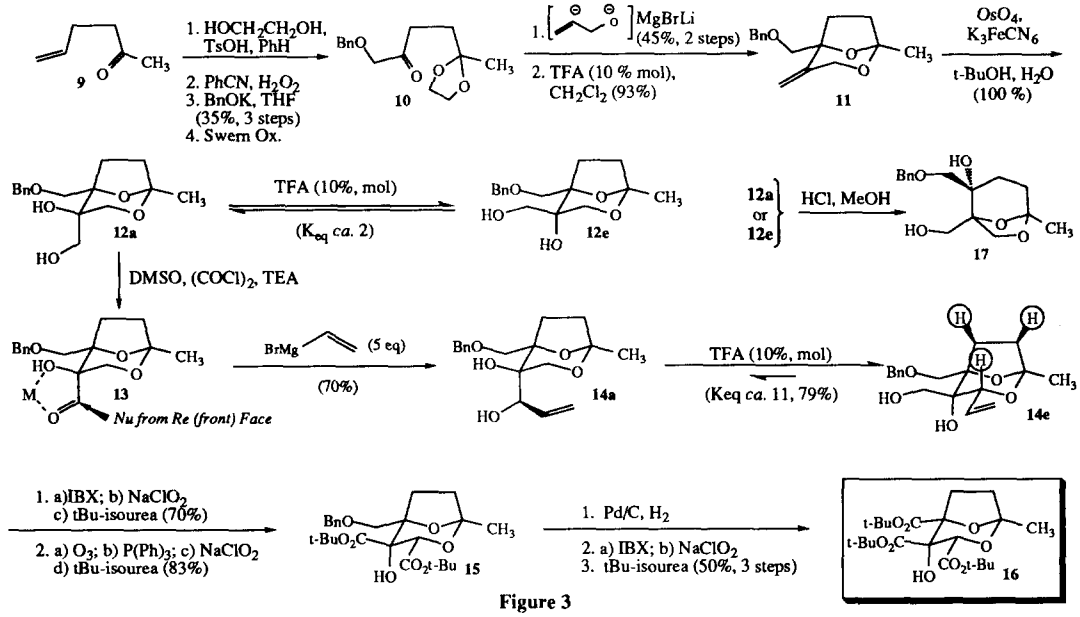


Figure 3

When ketal isomers **12** are treated with more forcing conditions, such as 2% HCl in methanol for several days, the expected equilibration takes place; however, a third ketal isomer is observed. After prolonged exposure to these reaction conditions, this new compound was the major component in the mixture. Single crystal X-ray analysis[10] showed this material to be ketal **17** wherein the tertiary alcohol at C-4 rather than the tertiary alcohol at C-5 was incorporated into the ketal moiety. The composition of the equilibrium mixture under HCl catalysis suggests that **17** is the lowest energy isomer of the three. However, there appears to be a kinetic barrier to the formation of this material.

Since **12a** and **12e** can be interconverted, both of these compounds are viable synthetic intermediates. Ketal **12a** presents an attractive option for introduction of the C-3 substituent. In **12a**, the carbon destined to be C-3 (zaragozic acid numbering) is stored as the axial hydroxymethyl group. Chelation controlled addition of nucleophiles to aldehyde **13** (prepared by oxidation of **12a**) would occur from the *Re* face of the aldehyde, away from the bicyclic system. Were this selectivity achieved, the product would be analogous to **6a** (Figure 2) and simple equilibration would provide access to analogs of **6e**.

We prepared aldehyde **13** by oxidation of diol **12a** (Figure 3).[11] We then treated this aldehyde *in situ* with excess vinylmagnesium bromide to furnish a single allylic alcohol formulated as **14a**. The final equilibration of the ketal to establish the complete carbon framework of zaragozic acid Bx3 was examined next. In analogy to the acid catalyzed interconversion of **12a** and **12e**, we treated ketal **14a** with 0.1 equiv TFA in dichloromethane and observed equilibration of **14a** and **14e** (K_{eq} = *ca.* 11). Close contacts between the circled protons (Figure 3) were observed in the nOesy spectrum of **14e** and confirmed the stereochemistry at C-3 and the integrity of the ketal.[12] We have not observed compounds analogous to **17** in this equilibration. All that remained at this point was the oxidation to the tricarboxylic acid. Since each of the carboxylic acids is stored in a different form in **14e**, each could be oxidized individually. We prepared the C-4 carboxylate by iodoxybenzoic acid (IBX)[13] oxidation of the hydroxymethyl group of **14e**, followed by oxidation of the resulting aldehyde without purification using $NaClO_2$.[14] After blocking the acid as its *tert*-butyl ester (*tert*-butylisourea[15]), ozonolysis of the alkene followed by oxidation ($NaClO_2$) and esterification (*tert*-butylisourea) gave **15**. Similarly, we fashioned the C-5 carboxylate from the benzyl ether by hydrogenolysis (5% Pd/C, H_2) followed by oxidation and esterification as before. From this sequence we obtained tri-ester **16** containing the complete stereochemical and functional array of the core of zaragozic acid Bx3.[16]

The bicyclic ketal is the core of the zaragozic acids and the reversibility of ketalization is at the center of our synthetic strategy. We have demonstrated that by taking advantage of this reversibility, the stereochemistry and functionality of the zaragozic acid ketal can be fashioned with ease. This strategy should be applicable to the more oxidized members of this class of natural products. We are currently applying this strategy to the synthesis of zaragozic acid C.

Acknowledgments: The Academic Senate of UCLA, Office of the Chancellor, and the National Institutes of Health Chemistry and Biology Training Grant (GM08496) supported this research.

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