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Chemoenzymatic Studies: From Cycloheptatriene to the Core of Zaragozic Acids

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Abstract: (1*R*,4*S*,6*S*)-4-Acetoxy-6-triisopropylsilyloxy-2-cyclohepten-1-ol, prepared from cycloheptatriene utilizing an asymmetrization of the precursor diol with *Candida antarctica* lipase B/isopropenyl acetate, was converted to (1*S*,3*R*,4*S*,5*S*,6*R*,7*R*)-4,6,7-triacetoxy-5-benzyloxymethyl-4-acetoxymethyl-2,8-dioxabicyclo[3.2.1]octane representing the core of zaragozic acid by a strategy involving Rubottom oxidations and ozonolysis.

In efforts directed towards finding inhibitors of squalene synthase, the enzyme controlling the first step on the route to cholesterol after the farnesyl pyrophosphate branch point, screening by researchers at Merck[1] and Glaxo[2] independently resulted in the discovery a new family of natural products. The Merck group gave the new compounds the name zaragozic acids after the Spanish city of Zaragoza where those compounds were found for the first time in fungal cultures. The Glaxo researchers named the new compounds squalestatins after their squalene synthase inhibiting effect. The five zaragozic acids and the various squalestatins isolated so far have been shown to be potent and selective inhibitors of mammalian and fungal squalene synthase.[3] All of these acids share a common core 2,8-dioxabicyclo[3.2.1]octane skeleton (Figure 1), which is extremely polar as a result of carboxyl groups in positions 3, 4 and 5 as well as hydroxyl groups at C4 and C7. An alkyl side chains is found at C1 and a long chain acyloxy side chain at C6.

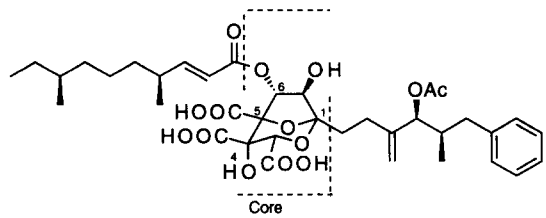
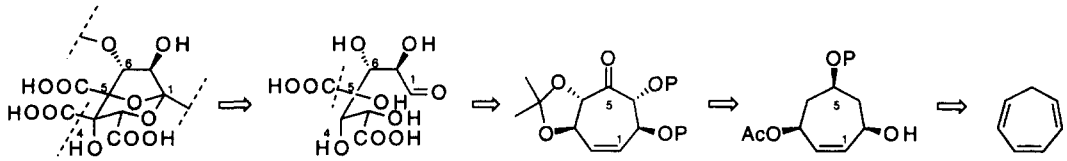


Figure 1. Zaragozic Acid A, a typical member of the zaragozic acid/squalestatin family.

Three total syntheses have been published: one by Carreira *et al.* (zaragozic acid C),[4] one by Nicolaou *et al.* (zaragozic acid A),[5] one by Evans *et al.* (zaragozic acid C).[6] Heathcock *et al.*[7] has presented a relay synthesis. All of these synthetic approaches are amenable to the synthesis of others in the class and each involves a late stage acylation of a C6 hydroxyl. However, beyond that, the strategies implemented in these syntheses are quite different. Various methods for the synthesis of the core at various levels of oxidation have been developed.[3,8]

Herein is described a novel synthetic approach to the key portion, the core of zaragozic acids. The acyclic carbon framework revealed by opening the ketal functionality of the core and its relative stereochemistry suggested the possibility of using seven-membered ring chemistry (Scheme 1) as explored in our labs in recent years.[9] The synthetic plan was reduced to an available enantiopure cycloheptenetriol derivative, which can be made in multigram scale by enzymatic asymmetrization of the corresponding meso diol.

Scheme 1. Retrosynthetic analysis of zaragozic acids/squalestatin



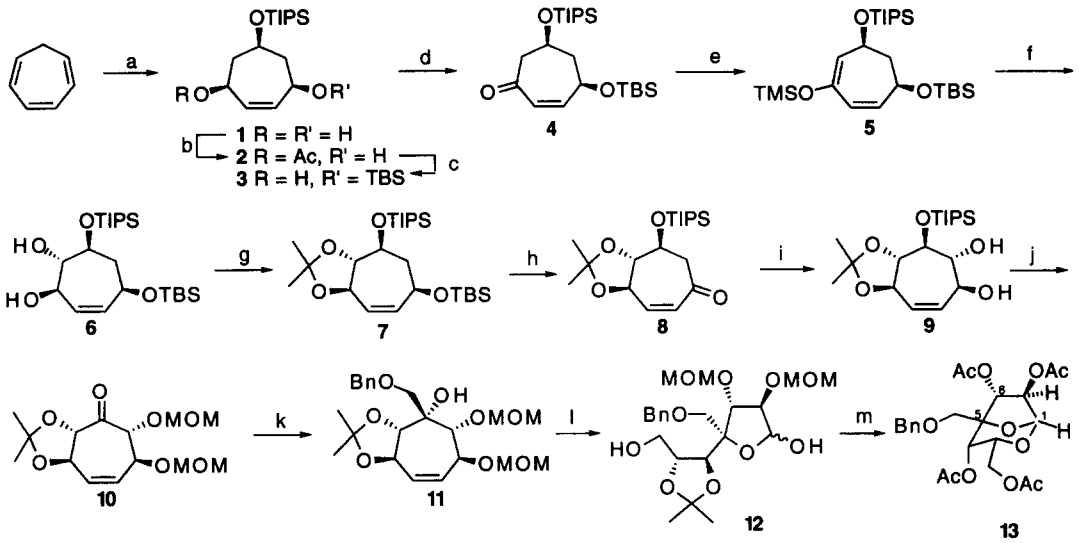
Enantiopure **2**,[10] chemoenzymatically prepared from *meso*-**1** using *Candida antarctica* lipase B biocatalyst (SP-435) and isopropenyl acetate, was converted to the corresponding TBS ether **3**. Removal of the acetyl group of **3** followed by oxidation of the resulting alcohol gave enone **4**. Rubotton oxidation[11] of the TMS enol ether **5** followed by reduction of the resulting enone under Luche conditions gave allylic alcohol **6** as a single diastereoisomer (Scheme 2).

Diol **6** was protected as an acetonide **7** in quantitative yield (Scheme 2). Selective removal (H_2SiF_6)[12] of the *tert*-butyldimethylsilyl ether in the presence of the triisopropylsilyl ether followed by PDC oxidation gave enone **8** in 78% yield. To introduce the C6 hydroxyl group, the Rubottom protocol was again used; reduction of the resulting hydroxy enone provided diol **9** (54% for the three steps). Protection of the diol as methoxymethyl ethers, removal of the triisopropylsilyl protection and oxidation of the resulting alcohol gave cycloheptenone **10**. Dess-Martin periodinane had failed to convert the alcohol to ketone **10**, but pyridinium chlorochromate was successful.

A crucial stage of our synthesis, installation of the C5 quaternary center, had been reached. It was anticipated that a nucleophile would attack from the β face, opposite to the two α substituents, of the ketone **10**. Ketone **10**, which slowly decomposes at r.t., was quickly treated with lithium benzyloxylmethide, generated *in situ* by treatment of (benzyloxymethyl)tributylstannane with 0.97 equiv of nBuLi, to afford alcohol **11** (88% yield for two steps) (Scheme 2). Ozonolysis of alcohol **11** followed by reduction of the remaining free aldehyde provided lactol **12**. Chemoselective lactolization in **12** was attributed to the acetonide protecting group. Cyclization on the other aldehyde would result in two *trans*-fused five-membered rings. Treatment of diastereomeric mixture **12** with trifluoroacetic acid followed by acetylation of the hydroxyl groups resulted in 2,8-dioxabicyclo-[3.2.1]octane derivative **13**.

The final ketalization step could be complicated by the formation of undesired ketal product **14**. The structure of our final compound **13** was confirmed by ^{1}H NMR studies and NOE experiments. Irradiation of the C(3)-H methine resulted in strong enhancement of C(6)-H methine (11.3%). Similarly, NOE enhancement of C(7)-H methine (5.5%) was observed upon irradiation of the C(1)-H methine. Irradiation of the signals

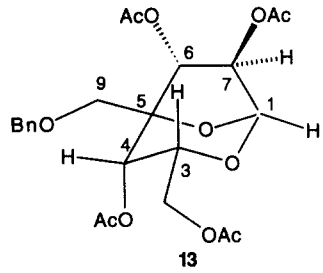
Scheme 2[a]



[a](a) See ref. 10; (b) *Candida antarctica* lipase B, isopropenyl acetate (see ref. 10); (c) TBSCl, imidazole, DMF (100%); (d) KCN, MeOH then PDC (98%); (e) TMSOTf, Et_3N, CH_2Cl_2; (f) MCPBA, pentane then $NaBH_4$, $CeCl_3$, MeOH (59%); (g) 2,.2-dimethoxypropane, camphorsulfonic acid (100%); (h) H_2SiF_6, Et_3N, CH_3CN then PDC, CH_2Cl_2 (78%); (i) reagents e then reagents f (54%); (j) MOMCl, iPr_2NEt, CH_2Cl_2 (100%); (k) TBAF, THF then PCC, CH_2Cl_2 followed immediately by Bu_3SnCH_2OBn, BuLi, THF (88%); (l) O_3, MeOH,. CH_2Cl_2 then $NaBH_4$, MeOH; (m) trifluoroacetic acid then Ac_2O, DMAP (31%).

corresponding to the C(9)-H_2 methylene protons resulted in an enhancement (3%) of the methine signal at C(4)-H. With the undesired ketal product **14**, enhancement of the C(3)-H methine should be observed upon the same irradiation (Figure 2). Furthermore, a coupling constant of 1.9 Hz between C(6)-H and C(7)-H was observed. Similar coupling constants between H6 and H7, J = 1.8 - 2.5 Hz, were found in the natural products, as well as during the courses of synthetic studies in other laboratories.[1,2,4,5,6]

	NOE
H(3) - H(6)	11.3%
H(1) - H(7)	5.5%
H(4) - H(9)	3.0%



cf.

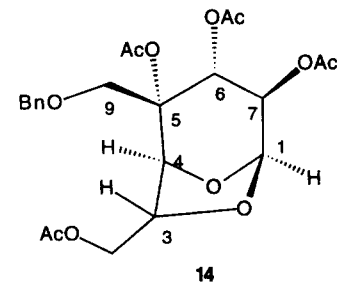


Figure 2. Nuclear Overhauser studies on product **13**.

A C(4) quaternary center with an addition carboxyl group remains to be installed. Using Carreira's strategy,[4] nucleophilic addition of lithium trimethylsilylacetylide to the ketone oxidation state of the C(4) center should produce a fully substituted core structure. Opportunity for addition of the C-1 side chain exists at the level of ketalized aldehyde **12.**

In summary, this work has resulted in development of a synthetic approach which allows for an interesting assembly of the dioxabicyclooctane skeleton common to all of the zaragozic acids and squalestatins; the advanced bicyclic core **13** was prepared in 11 steps from cycloheptene **2** with an overall 6.6% yield.

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