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Novel Transformations of Zaragozic Acid A Derivatives with Cesium Fluoride

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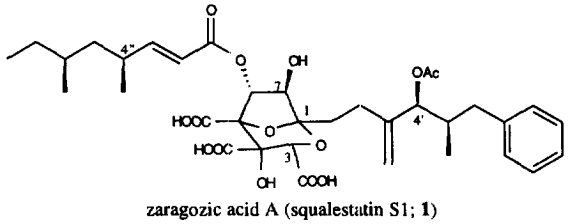
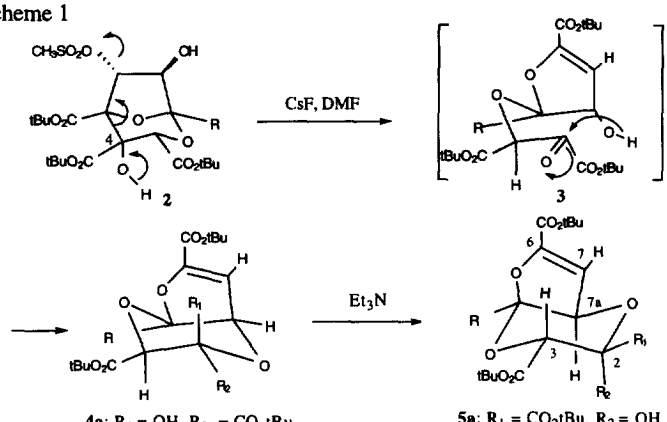
Abstract: C4-Hydroxy protected zaragozic acid A derivatives, upon treatment with CsF in DMF, underwent novel transformations to give tricyclic compounds. The process was initiated by intramolecular C3 proton abstraction by the C7 alkoxide anion to form the enolate ion, which can cyclize by two different pathways. © 1999 Elsevier Science Ltd. All rights reserved.

In recent years there has been intensive effort directed toward the development of inhibitors of squalene synthase, the key enzyme that catalyzes the head-to-head reductive dimerization of farnesyl diphosphate to squalene via the cyclopropane intermediate, presqualene diphosphate.[1] Zaragozic Acid A (squalestatin S1; **1**) is a natural fungal metabolite, which exhibits potent competitive inhibition of rat liver squalene synthase with an apparent K_i value of 7.8 x 10^{-11} M.[2,3] Previously we described a chemoselective removal and replacement of the C4' and C6 acyl groups of this natural product,[4] and disclosed the structure-activity relationships of its C1 and C6 side chains.[5] Attempts to prepare the C6-C7 epoxide from **2** led to the formation of four rearranged products: two kinetic (**4a** and **4b**) and two thermodynamic isomers (**5a** and **5b**) as shown in Scheme 1.[6] The rearrangement arises via a Grob-type fragmentation path[7] initiated by the C4-OH group to give **3**, followed by recyclization to give the fused ring compounds.[6] In this paper we report other novel transformations of C4-OH protected zaragozic acid A derivatives.



zaragozic acid A (squalestatin S1; **1**)

Scheme 1



4a; R_1 = OH, R_2 = CO_2tBu
4b; R_1 = CO_2tBu, R_2 = OH

5a; R_1 = CO_2tBu, R_2 = OH
5b; R_1 = OH, R_2 = CO_2tBu

R = $C_6H_5CH_2CH(CH_3)CH(OAc)CH(=CH_2)CH_2CH_2$-

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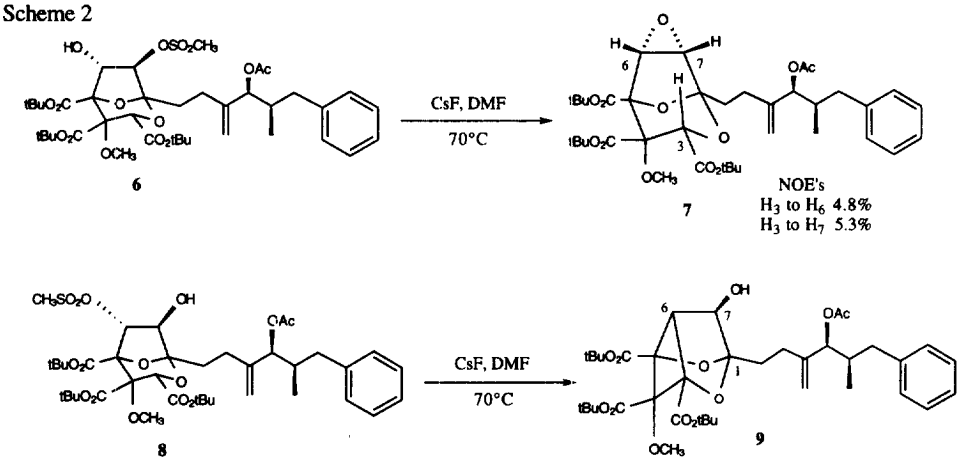
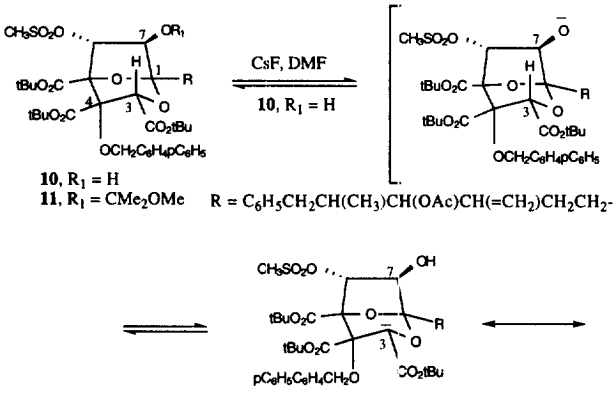
The two isomeric hydroxy mesylates **6** and **8** were prepared for these investigations (see Scheme 2).[5,8] Treatment of the isomer **6** with CsF in DMF at 70 °C for 24 h gave the epoxide **7** in 25% yield (with 10% unreacted starting material).[9] In contrast, the isomeric mesylate **8**, under similar conditions for 2 h, provided the tricyclic compound **9** in 87% yield.[10]

Scheme 2

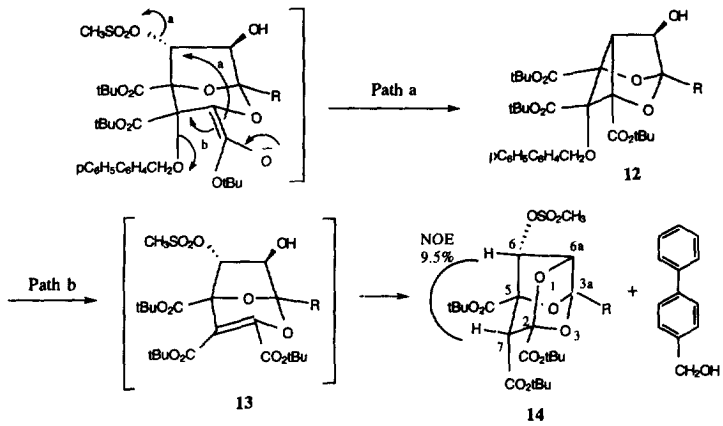


6 **7** **8** **9**

The main course of the above transformation with cesium fluoride in DMF (**8** to **9**) remained the same when the C4 hydroxy function was protected with a 4-phenylbenzyl group. The cyclobutane derivative **12** was obtained from **10** in 70% yield (see Scheme 3).[11] In addition to **12**, another tricyclic compound **14** was also isolated in ca. 2% yield along with 4-phenylbenzyl alcohol (21% yield). It is postulated that **14** was formed via Michael addition of the C7 hydroxy group to the C3-C4 double bond of the intermediate **13**, derived from **10** by elimination of 4-phenylbenzyl alcohol.



Scheme 3. Proposed mechanism of rearrangements



Scheme 3. Proposed mechanism of rearrangements (cont'd)

Furthermore, the C7-OH group was found to be essential for the formation of the cyclobutane ring (to give **12**), since the substrate **11** (R_1 = CMe_2OMe) was recovered unchanged under similar conditions (20 equiv CsF, DMF, 70°C, 4 h). Thus direct abstraction of the C3 proton by cesium fluoride is not a possibility. This finding suggests the following plausible mechanism for the transformations. The C7 alkoxide anion (presumably generated by the reaction of **10** with CsF in DMF), by virtue of its close proximity to H3 (ca. 1.8 Å), may abstract the C3 proton as shown in Scheme 3 to give the enolate ion. Similar intramolecular proton abstraction by alkoxide anion (formed from initial attack by a methoxide ion on the carbonyl of 19,10γ-lactone of gibberellin 7-methyl ester) was also observed.[13] Two pathways are then available for the intermediate carbanion: (a) intramolecular displacement of the C6 mesylate to afford the cyclobutane derivative **12**, and/or (b) elimination of 4-phenylbenzyl alcohol to give the intermediate **13**, and finally addition of the neighboring C7 hydroxy group to the C3-C4 double bond to provide another tricyclic compound **14**.[12]

In summary, these novel transformations are clearly the manifestation of the stereochemical and conformational factors present in zaragozic acid A. C4-Hydroxy protected zaragozic acid A derivatives, upon treatment with cesium fluoride in DMF, gave cyclobutane derivatives **9** and **12** in good yields.

Acknowledgment. The authors thank Mr. R. A. Reamer for ^{13}C NMR measurements and interpretations, Ms. M. S. Hill for numbering compounds **9** and **14** according to CAS guidelines, and Mr. R. L. Bugianesi for helpful discussions.

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8. Hydroxy mesylate **6**: NMR ($CDCl_3$) δ 3.13 (s, CH_3SO_2), 3.60 (s, OCH_3), 4.72 (d, *J* = 2.5 Hz, H-7), 4.74 (s, H-3), 5.09 (d, *J* = 5.1 Hz, CHOAc), 5.54 (d,d, *J* = 2.5, 4.8 Hz, H-6). Hydroxy mesylate **8**: NMR ($CDCl_3$) δ 3.06 (s, CH_3SO_2), 3.58 (s, OCH_3), 4.29 (d,d, *J* = 2.2, 3.7 Hz, H-7), 4.99 (s, H-3), 5.11 (d, *J* = 4.8 Hz, CHOAc), 6.06 (d, *J* = 2.2 Hz, H-6).
9. Epoxide **7**: ^1H NMR ($CDCl_3$) δ 3.55 (d, *J* = 2.8 Hz, H-7), 3.66 (s, OCH_3), 4.46 (d, *J* = 2.8 Hz, H-6), 5.05 (s, H-3); ^{13}C NMR ($CDCl_3$) δ 51.4 (C-7), 53.9 (C-6), 55.7 (OCH_3), 76.7 (C-3), 78.8 (C-4), 84.3 (C-5), 104.1 (C-1), 165.7 (5-CO_2R), 165.9 (3-CO_2R), 166.0 (4-CO_2R). The epoxide can be characterized by the large one-bond coupling constants and ^{13}C chemical shifts for C6 and C7. Since the one-bond coupling in oxirane (model compound) is 175 Hz, the 205.2 and 194.1 Hz couplings for the respective C6 and C7 are expected for the strained tricyclic ring system.[14] Carbon-13 chemical shifts of 51.4 (C7) and 53.9 (C6) are reasonable for epoxide carbons.
10. Tricyclic **9**: ^1H NMR ($CDCl_3$) δ 3.06 (d, *J* = 11.9 Hz, 7-OH); 3.56 (d, *J* = 2.0, H-6), 3.60 (s, OCH_3), 4.09 (d,d, *J* = 11.9, 2.0 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 51.1 (C-6), 55.0 (OCH_3), 73.9 (C-7), 81.7 (C-5), 83.3 (C-3), 84.2 (C-4), 112.0 (C-1), 164.7, 166.0 (3-, 5-CO_2R), 167.3 (4-CO_2R). One-bond and long-range ^1H-^{13}C coupling constants were used to characterize this ring system. The one-bond coupling of 167.8 Hz for C6-H was supportive of the highly strained tricyclic system.[14] The SELJRES experiment[15] was used to determine the long-range couplings from H6 to carbons two and three bonds away. A 1.5 Hz coupling was measured from H6 to two of the carbonyls at C3 and C5. In addition, a 6.8 Hz coupling was observed to C1, consistent with a three-bond *trans* orientation of these nuclei.
11. Cyclobutane **12**: NMR ($CDCl_3$) δ 3.08 (d, *J* = 12 Hz, 7-OH), 3.63 (d, *J* = 2.1, H-6), 4.13 (d,d, *J* = 12, 2.1 Hz, H-7), 4.87 (s, CH_2Ar), 4.99, 5.0 (2 s, $=CH_2$), 5.07 (d, *J* = 5.5 Hz, CHOAc).
12. Tricyclic **13**: ^1H NMR ($CDCl_3$) δ 3.40 (d, *J* = 0.4, H-7), 4.70 (d,d, *J* = 0.8, 0.4, H-6a), 5.11 (d, *J* = 0.8, H-6). The small proton coupling constants were obtained using 0.2 Hz/point digital resolution and were verified via homo-nuclear decoupling. Tricyclic **13** had ^{13}C NMR ($CDCl_3$) δ 38.5 (SO_2CH_3), 50.4 (C-7), 80.2 (C-6), 81.9 (C-6a), 86.4 (C-5), 104.1 (C-2), 113.1 (C-3a), 161.9 (5-CO_2R), 163.3 (2-CO_2R), 164.5 (7-CO_2R). Inverse detected long-range correlation data (HMBC) were used to verify the newly formed ether bridge with a correlation from H6a to C2 (three-bond pathway). The large NOE's between H6 and H7 provide strong support for the stereochemistry depicted as shown.
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