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Rearrangement of Zaragozic Acid A Derivatives

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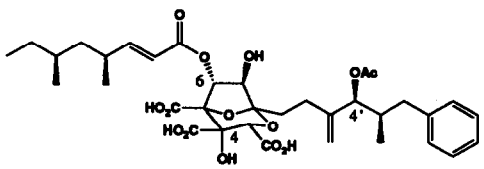
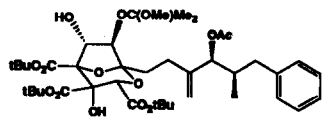
Abstract: The C_6 mesylate of desacyl zaragozic acid A tris tBu ester has been observed to undergo rearrangement in the presence of CsF in DMF.

Zaragozic Acid A (1) is a member of a family of natural products recently reported by two independent groups.[1,2] These novel compounds are very potent squalene synthase inhibitors.[1,3] Recently, we described a chemoselective removal and replacement of the C4' and C6 acyl groups of the natural product.[4] In this paper we report the rearrangement of zaragozic acid A derivatives **3** and **4**.



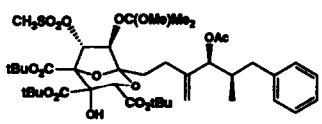
Zaragozic Acid A (1)

As part of a program aimed at the preparation of zaragozic acid A analogs, we were interested in replacing the C_6 ester group with nitrogen bearing substituents. The mesylate **3** was prepared from the diol **2**[4] in 92% yield, and then treated with 15 eq NaN_3 in DMF to give new products (one spot by TLC) in *ca* 70% yield. The IR indicates the absence of the azido group. The NMR, beside showing the absence of the mesylate group, reveals the products to be composed of 2 isomeric rearranged compounds (**7a** and **7b** in a ratio *ca* of 2:1). The mass spectrum [$C_{37}H_{52}O_{12}$; *m/z* 711, $(M+Na)^+$] is consistent with the proposed structure. Further details of the structure determination will be described shortly.



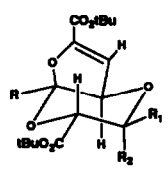
2

CH_3SO_2Cl, Et_3N, DMAP
CH_2Cl_2, 0 °C, 4 h



3

NaN_3, DMF
70 °C, 48 h

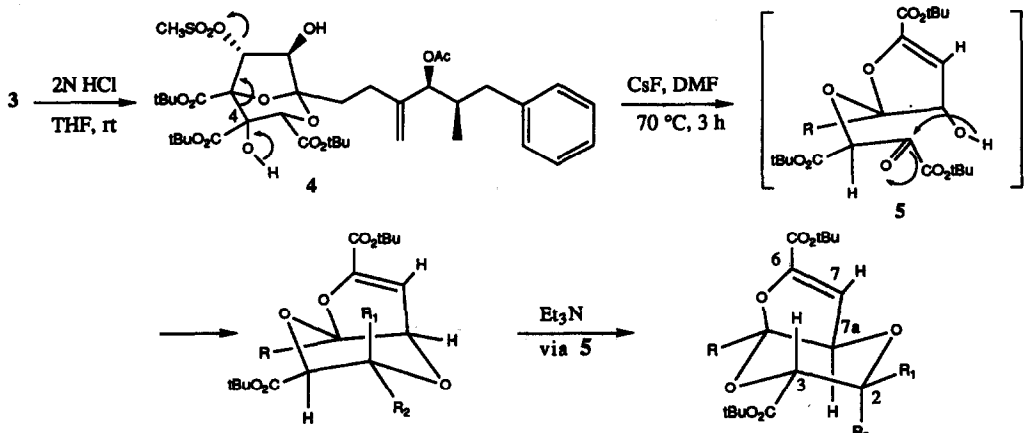


R = $C_6H_5CH_2CH(CH_3)CH(OAc)CH(=CH_2)CH_2CH_2$-

7a; $R_1 = CO_2tBu$, $R_2 = OH$

7b; $R_1 = OH$, $R_2 = CO_2tBu$

In an attempt to prepare the C_6-C_7 epoxide, compound **4** prepared from **3** quantitatively, was treated with CsF (10 eq) in DMF at 70 °C for 3 h to give four rearrangend products, which are assumed to arise *via* a Grob-type fragmentation path[5] initiated by the C_4-OH group followed by recyclization in a different mode to give a fused ring system. A detailed examination of this reaction reveals that it affords a mixture of two major kinetic products (polar spot; **6a** : **6b** *ca* 1 : 1) and two minor thermodynamic products (mobile spot, **7a** : **7b** *ca* 2 : 1) in >90% yield. The thermodynamic products were identical with rearrangement products obtained from **3** by treatment with NaN_3 in DMF mentioned previously. The ratio of the kinetic and thermodynamic products is *ca* 3 : 1 as estimated by TLC. The kinetic isomers were observed to transform partially to the thermodynamic isomers during preparative TLC, and quantitatively upon treatment with Et_3N in ethyl ether or methylene chloride at ambient temperature. However, the kinetic isomers were separated, essentially free from the thermodynamic isomers, by fast flash column chromatography (silica gel; hexanes:ethyl acetate; v/v, 1:4). The isomerization of **6** to **7** is assumed to occur *via* ring opening to give the acyclic intermediate **5** which isomerizes at C_3 followed by recyclization. The ratio of the four isomers changed upon standing in NMR solvents favoring **7**.



Detailed ^1H-^1H and ^1H-^{13}C NMR[10] experiments were used to identify the basic skeletal rearrangement, and NOE difference studies along with ^1H and ^{13}C spin-spin coupling constants were employed to establish the stereochemistry and ring conformations. The following discussion is for the major thermodynamic isomer **7a**, but also applies to the other three isomers. One-bond ^1H-^{13}C correlation data indicates one of the two oxygen bearing carbon (C_6 and C_7) in the starting material

now appears to be part of an olefinic system. The proton at 5.90 ppm (H_7, doublet, J =2.6 Hz) was correlated to C_7 at 108.5 ppm. The one-bond coupling constant for this carbon was 183.9 Hz, consistent with the dihydrofuran system shown.[6] Further support for this unsaturation was obtained from the upfield shift (*ca* 4 ppm) of the ester carbonyl at C_6. The adjacent carbon (C_{7a}, correlated to H_{7a} at 4.86 ppm) was still at a chemical shift (75.4 ppm) consistent with an oxygen bearing carbon. Long-range heteronuclear correlation data, obtained in an HMBC experiment,[7] showed all expected two and three bond correlations including the correlation from H_{7a} to C_2, consistent with the new ring system.

With the basic skeleton in hand, NOE difference results and coupling constants were used to assign the stereochemistry at C_2 and C_3. One key piece of data was a four-bond spin-spin coupling between H_3 and the hydroxyl at C_2 (^4J =1.4 Hz) best explained by a "W" pathway between these protons.[8] This coupling can only be present if H_3 and the hydroxyl are diaxial. NOE difference studies show a 1.4% enhancement from H_7 to H_3 while the small enhancement from H_{7a} to H_3 was ~0.5% thus also supporting the structure as shown. A Dreiding model suggests a small NOE between H_{7a} and H_3 or none at all. In **7b** the same enhancements from H_7 and H_{7a} were observed to H_3 supporting the same stereochemistry at C_3. Strong support comes from the long-range ^1H-^{13}C coupling where in **7a** the $^3J_{H3\text{-}2CO}$ is 1.0 Hz while in **7b** the same three-bond path yields a 5.6 Hz coupling, the latter consistent with a diaxial orientation between H_3 and the C_2-ester carbonyl.[9] The lack of the four-bond coupling between H_3 and the C_2 hydroxyl was also consistent with an equatorial orientation of this hydroxyl. Similar arguments can be used to establish the stereochemistry in one of the kinetic isomers (**6a**) where a four-bond coupling (^4J =1.6 Hz) between H_3 and the C_2-OH supports their diaxial orientation. An NOE enhancement of 2.2% from H_{7a} to H_3 and no observable enhancement from H_7 to H_3 supports the stereochemistry in **6a** as shown. Unlike the thermodynamic isomers, where the six-membered ring in both isomers exists in a chair form, the six-membered ring in **6b** appears to exist in a boat form. In this isomer the NOE enhancement from H_{7a} to H_3 is also 2.2%, but a large three-bond ^1H-^{13}C coupling from H_3 to the C_2-carbonyl (as seen in **7b**) is not present. The small coupling of 1.6 Hz from H_3 to the C_2-carbonyl and steric hindrance between C_7-C_{7a} and C_2-CO_2tBu would support a boat conformation in **6b**.

In summary, **3**, and particularly **4** were found to undergo facile fragmentation followed by ring closure to give four rearranged isomeric products.

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10. NMR data were recorded on a Bruker AM-400 and a Varian XL 400. Diagnostic ^{1}H and ^{13}C assignments are given.
Compound **3** ^{1}H NMR ($CDCl_3$): δ 5.95 (d, *J* =1.5, H_6), 5.10 (d, *J* =5.0, $H_{4'}$), 4.95 (s, H_3), 4.30 (d, *J* =1.5, H_7), 4.04 (s, 4-OH), 3.25 (s, 3H), 3.05 (s, 3H), 2.05 (s, 3H), 1.42 (s, 3H),1.34 (s, 3H), , 0.77 (d, *J* =7.0, 3H).
Compound **4** ^{1}H NMR ($CDCl_3$): δ 5.85 (d, *J* =2.0, H_6), 5.10 (d, *J* =4.5, $H_{4'}$), 4.93 (s, H_3) 4.30 (dd, *J* =4.0, 2.0 H_7), 3.95 (bs, 4-OH),.3.0 (s, 3H), 2.70 (d, *J* =4.0, 7-OH), 2.0 (s, 3H), 0.79 (d, *J* =7.0, 3H).
Compound **6a** ^{1}H NMR (CD_3CN): δ 5.90 (d, *J* =2.6, H_7), 5.12 (d, *J* =1.4, 2-OH), 4.69 (d, *J* =2.6, H_{7a}), 4.58 (d, *J* =1.4, H_3); ^{13}C NMR (CD_3CN): 168.1 (2-CO_2R), 166.0 (3-CO_2R), 159.6 (6-CO_2R), 150.1 (C_6), 112.4 (C_7) 108.4 (C_{4a}), 92.8 (C_2), 77.4 (C_{7a}), 73.0 (C_3).
Compound **6b** ^{1}NMR (CD_3CN): 5.85 (d, *J* =2.9, H_7), 4.94 (s, 2-OH), 4.56 (d, *J* =2.9, H_{7a}), 4.16 (s, H_3); ^{13}C NMR (CD_3CN): 167.1_6 (2-CO_2R), 167.1_5 (3-CO_2R), 159.5 (6-CO_2R), 152.4 (C_6), 109.6 (C_7) 109.0 (C_{4a}), 91.6 (C_2), 73.9 (C_3), 73.4 (C_{7a}); characterized as a mixture of **6a** and **6b**.
Compound **7a** ^{1}H NMR (CD_3CN): δ 5.83 (d, *J* =2.6, H_7), 5.10 (d, *J* =1.4, 2-OH), 4.86 (d, *J* =2.6, H_{7a}), 4.68 (d, *J* =1.4, H_3); ^{13}C NMR (CD_3CN): δ 168.7 (2-CO_2R), 165.7 (3-CO_2R), 159.3 (6-CO_2R), 150.8 (C_6), 108.5 (C_7), 108.3 (C_{4a}), 92.7 (C_2), 75.4 (C_{7a}), 71.0 (C_3).
Compound **7b** ^{1}H NMR (CD_3N): 5.88 (d, *J* =2.6, H_7), 5.08 (s, 2-OH), 4.92 (d, *J* =2.6, H_{7a}), 4.22 (s, H_3); ^{13}C NMR (CD_3CN): 168.3 (2-CO_2R), 166.8 (3-CO_2R), 159.2 (6-CO_2R), 150.7 (C_6), 111.3 (C_7), 108.3 (C_{4a}), 93.6 (C_2), 75.7 (C_{7a}), 72.0 (C_3); characterized as a mixture of **7a** and **7b**.

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