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A Short Synthesis of the Bicyclic Core of the Zaragozic Acids

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Abstract

A synthesis of the highly functionalized bicyclic core of the zaragozic acids is described, in which the key step involves the construction of the C4 quaternary carbon center by a CeCl$_3$-promoted aldol reaction between the α-D-xylofuranuronic acid derivative **2** and D-(R)-glyceraldehyde acetonide. © 1998 Published by Elsevier Science Ltd. All rights reserved.

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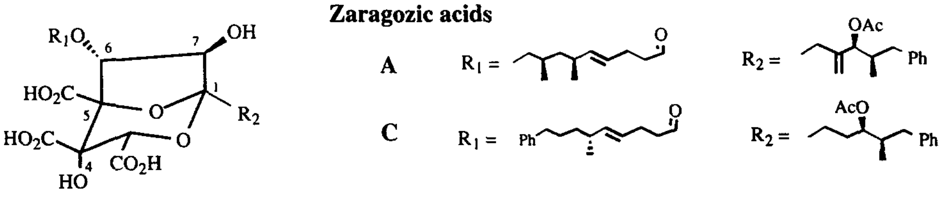
The zaragozic acids (squalestatins), a family of naturally occuring fungal metabolites isolated in 1992, have been found to be potent inhibitors of the enzyme squalene synthase and thus of potential therapeutic use for the treatment of hypercholesterolaemia. Structurally, these compounds share a common densely functionalized 2,8-dioxabicyclo[3.2.1]octane skeleton **1**. The complexity of this structure combined with the biological activity of these natural products has served to stimulate a large amount of synthetic activity in a number of laboratories,[1] and culminated in the total syntheses of zaragozic acids A[2] and C.[3]



In a new synthetic approach, we envisaged the construction of the bicyclic core of the zaragozic acids starting from the readily available α-D-xylofuranuronic acid derivative **2**[4] in which the configuration at C2 and C3 correlates with the configuration at C6 and C7 of the target. As shown in the retrosynthetic analysis (Scheme 1), our plan involves the introduction of the three-carbon unit at C4 by aldol condensation of the enolate generated from **2** and D-(R)-glyceraldehyde acetonide **3**[6]. Assessment of the feasibility of quaternization at C4[7] as well as internal ketalization would lead to a short alternative synthesis of **1**. The success of such an approach depends on

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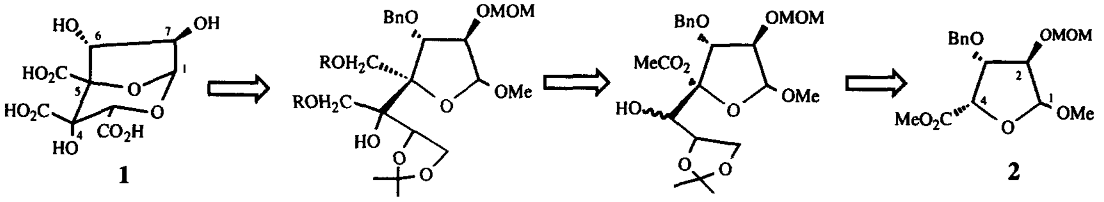
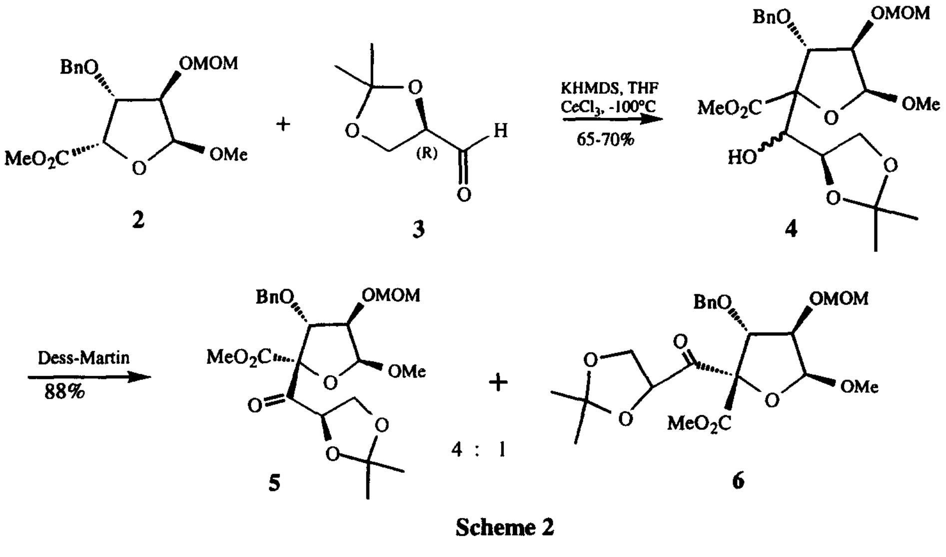
two crucial requirements: (a) The generation of an enolate from **2** and its reaction with a (D)-glyceraldehyde derivative bearing in mind that such a nucleophilic center which carries an adjacent oxygen is prone to epimerisation and β-elimination,[8] and (b) the stereoselective introduction at C4 of the new C-C bond from the β-face of the enolate. We believed that the facial selectivity in the attack upon the aldehyde could be induced by the benzyloxy group at C3α.



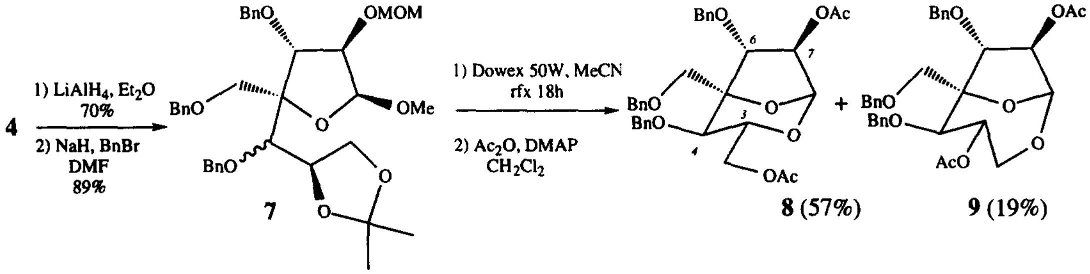
Scheme 1

Initial attempts to effect the aldol condensation of ester **2** with aldehyde **3** *via* the lithium, sodium or potassium enolates (using LDA, LiHMDS, NaHMDS or KHMDS) in THF at -100°C were disappointing. Under these conditions, the desired product **4** was isolated in only 0-10% yield. At higher temperature, β-elimination occured followed by the degradation of the resulting product. With the zinc enolate, formed from the potassium enolate by metal exchange at -100°C, a higher yield of **4** was obtained (20-30%). After considerable experimentation,[9] we found that addition of a precooled 1:1 mixture of cerium chloride and aldehyde **3** in THF to the solution of the potassium enolate in THF at -100°C gave **4** reproducibly in 65 to 70% yield. ^{1}H NMR analysis showed that **4** is a mixture of *three* out of the four possible diastereomers in 2.5:1.5:1 ratio. Dess-Martin oxidation[10] of the mixture afforded *two* readily separable β-ketoesters **5**, $[\alpha]_D$ +10.8 (c 1.45, CH_2Cl_2), and **6**[11] in a 4:1 ratio and in a combined yield of 88%. This established that the major diastereomers obtained fom the aldol reaction possessed the same configuration at C4.

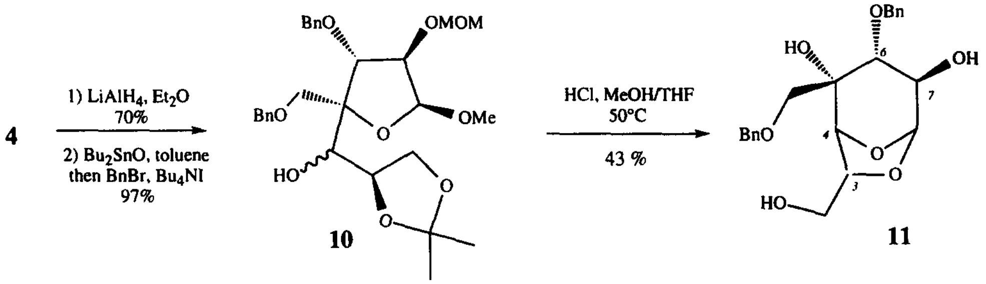


Scheme 2

Having introduced the C4 side chain onto the furanose ring, we next examined the ketalisation step. To this end, lithium aluminum hydride reduction of **4** afforded the expected diol which was protected as the dibenzyl ether **7** as a separable mixture of diastereomers. The major isomer was subjected to Dowex resin in refluxing acetonitrile for 20 h, and the crude product was treated with acetic anhydride in the presence of dimethylaminopyridine in dichloromethane to give a mixture of the desired ketals **8**[11] (57%) and its isomer **9** (19%). The structure and configuration of **8** were proven by extensive NMR experiments. In particular, the observed coupling constant between H6 and H7 (J=2.6 Hz) along with important cross-peaks in the NOESY spectrum between H3 and H6 provide strong arguments for the configuration depicted. Moreover, the observed *J* H3-H4 value of 10 Hz is in support with the *trans*-diaxial configuration in the chair conformation of the six membered ring.



As it has been already reported for such a system,[12] the ketalization step can lead to the undesired bicyclic ketal if the hydroxyl group at C4 (Squalestatins numbering) is unprotected. In fact, when compound **10**, readily prepared by reduction of **4** and subsequent stereoselective protection of the primary hydroxyl group using the stannylene procedure,[13] was heated with HCl in MeOH-THF at 50°C for 24 h, the ketal **11**, mp 129-130°C; $[\alpha]_D$ +62 (c 1.10, $CHCl_3$), was formed in 43% yield and 23% of the starting material was recoverd. Like for compound **8**, the structure of ketal **11** was deduced on the basis of ^1H and ^{13}C NMR experiments.



In summary, we have achieved a short synthesis of the bicylic core of zaragozic acids which features as the key step an aldol condensation of the readily available ester **2** with (R)-glyceraldehyde acetonide.

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11. All new compounds are fully characterized by their spectroscopic and analytical data. **9**: $[\alpha]_D$ +32 (c 0.9, $CHCl_3$), IR ν_{max} 2930, 2869, 1740, 1454, 1371, 1227, 1099, 1025 cm^{-1}. ^1H ($CDCl_3$) δ 7.40-7.15 (15 H, m, Harom), 5.57 (1 H, d, J = 4.5, H_1), 5.10 (1 H, dd, J = 2.6, J = 4.5, H_7), 4.78 (1 H, d, J = 11.8), 4.65 (1 H, d, J = 6.8), 4.62 (1 H, d, J = 7.6), 4.56 (1 H, d, J = 11.8), 4.50 (1 H, d, J = 7.6), 4.47 (1 H, d, J = 6.8), 4.27 (1 H, d, J = 2.6, H_6), 4.22 (1 H, dd, J = 2.2, J = 12.0, $H_{3'a}$), 4.02 (1 H, dd, J = 5.3, J = 12.0, $H_{3'b}$), 3.97 (1 H, d, J = 10.0, H_4), 3.92 (1 H, d, J = 11.9, $H_{5'a}$), 3.87 (1 H, d, J = 11.9, $H_{5'b}$), 3.78 (1 H, ddd, J = 2.2, J = 5.3, J = 10.0, H_3), 2.07 (3 H, s), 2.03 (3 H, s) ppm. ^{13}C ($CDCl_3$) δ 170.9, 169.8 (C, C=O acetates), 138.3, 137.6, 137.9 (C, Bn), 128.4, 128.1, 128.0, 127.9, 127, 8, 127.6 (CH, Bn), 96.2 (CH, C_1), 85.7 (C, C_5), 81.0 et 80.7 (CH, C_6 et C_7), 74.0 et 73.8 (CH_2, $C_{5'}$ et $C_{3'}$), 72.1 (CH), 71.8 (CH_2 Bn), 69.9 (CH), 68.1 and 63.7 (CH_2 Bn), 20.8 and 20.5 (CH_3, acetates) ppm.
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