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Structurally Simplified Zaragozic Acid (Squalestatin): Stereoselective Preparation of a 3,4-Unsubstituted Derivative

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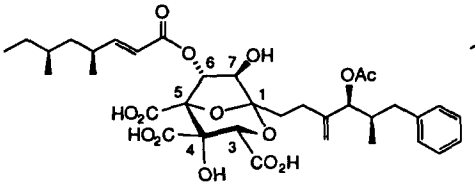
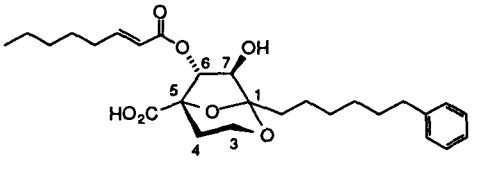
Abstract: *Stereoselective preparation of a structurally simplified 3,4-unsubstituted zaragozic acid derivative was achieved starting from D-glucose. The present approach involved the stereoselective addition of a vinyl Grignard reagent, selective cleavage of 1,2-diol, and regioselective acylation of the hydroxyl group at C-6.* © 1997 Elsevier Science Ltd.

Zaragozic acids (squalestatins), which have strong activities to inhibit squalene synthase and farnesyl-protein transferase, were isolated by the Merck and Glaxo groups.[2] Zaragozic acids have a densely oxygenated hydrophilic bicyclic core connected with two hydrophobic side chains which were thought to work as a mimic of presqualene pyrophosphate. Zaragozic acids have attracted a great deal of attention[3] due to both their structural complexity and potential inhibitory activities. Total synthesis of zaragozic acids has already been accomplished by several groups,[4] and investigation on structure-activity relationships of zaragozic acid has also extensively been carried out.[5] We were particularly interested in the fact that the carboxyl group at C5 is essential for their inhibitory activities and other carboxyl groups at C3 and C4 can be esterified or deleted.[5] These results led us to design the structurally simplified derivative **2** which has only one carboxyl group at C5 in the core moiety. We describe here the stereoselective preparation of **2** starting from diacetone-D-glucose in which the C_5 segment (C1,7,6,5-CO_2H) is derived from D-glucose.



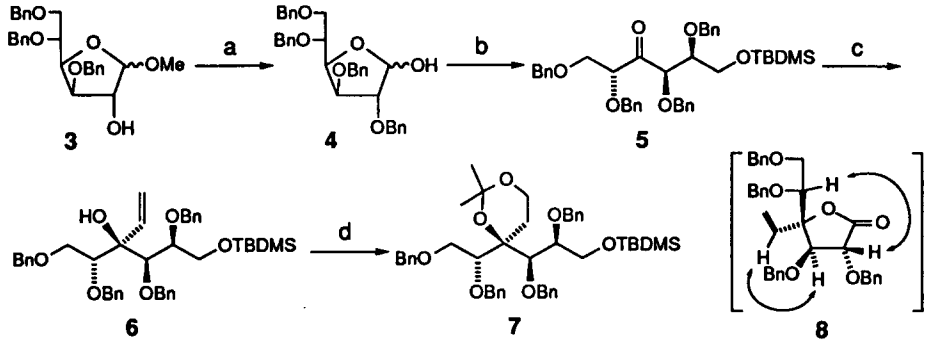
Zaragozic acid A (**1**)



2

Our strategy was to construct the C5 quaternary chiral center by the nucleophilic addition of a vinyl metal reagent[4c] to the ketone **5**. Since the ketone **5** has a *pseudo* C_2-symmetry, it seemed rather difficult to achieve a stereoselective reaction. Nevertheless, we examined this approach considering that the vinyl group could serve as either a carboxyl group at C5 or a part of the bicyclic core (O2-C3-C4) in the target molecules if some selectivity could be realized. Systematic investigation on the stereochemistry of Grignard addition to *O*-protected polyhydroxy ketones was very recently reported.[6]

Scheme 1

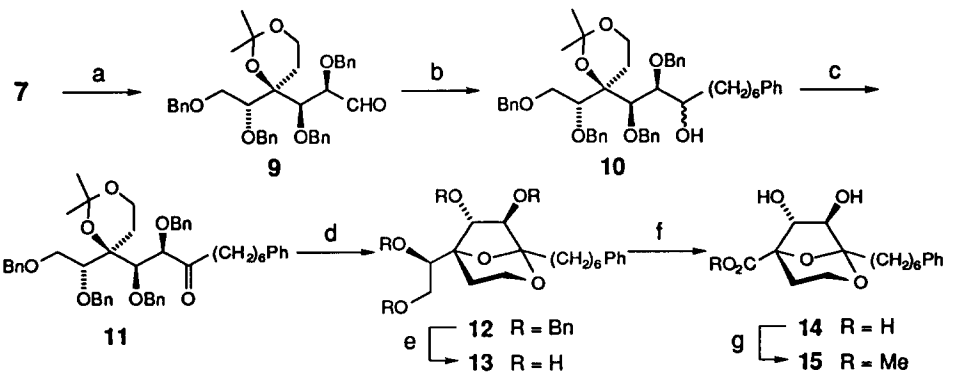


Reagents and conditions: **a** (i) BnBr, NaH/DMF, r.t., 5h, 99%; (ii) 2*N* H_2SO_4/AcOH, 60°C, 12h, 96%. **b** (i) $LiAlH_4$/THF, r.t., 30min, 90%; (ii) TBDMSCl, imidazole/DMF, r.t., 12h, 98%; (iii) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, -60°C, 20min, 96%. **c** CH_2=CHMgBr/ THF, -78°C, 2h, 98%. **d** (i) 9-BBN/THF, reflux, 12h; then 3*N* NaOH, 30% H_2O_2, r.t., 1h, 88%; (ii) $(MeO)_2CMe_2$, PPTS/benzene, reflux, 3h, 93%.

Known methyl furanoside **3**, prepared from diacetone D-glucose,[7] was converted to ketone **5**[8] in 80% overall yield (5 steps). (Scheme 1) Then the reaction of ketone **5** with various nucleophiles was examined, and we found that vinylmagnesium bromide added to **5** with excellent diastereoselectivity (98%, >95 : 5).[9] Stereochemistry of the newly formed quaternary center was determined as shown by NOESY spectrum after converting **6** into lactone **8** [(i) TBAF, 99%; (ii) PCC, 73%]. Two pairs of diagnostic NOEs were observed as indicated in Scheme 1. The unexpectedly high diastereoselectivity is quite interesting, but how the remote TBDMS-oxymethyl group participates in the transition state is still unclear.

With the stereochemistry established as shown, the strategy was fixed to transform the vinyl group to a hydroxy ethyl group (C-C-OH) requisite for the part of the bicyclic core moiety. Thus, **6** was subjected to hydroboration with 9-BBN to give 1,3-diol (not shown) in 88% yield after oxidative workup.[10] 1,3-Diol was then protected as acetonide to obtain fully protected polyhydroxy compound **7** in 93% yield.

Scheme 2

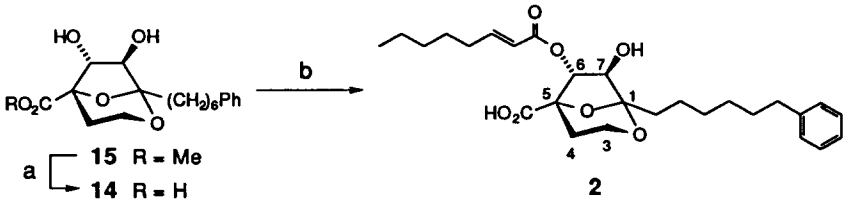


Reagents and conditions: **a** (i) TBAF/THF, r.t., 3h; (ii) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, -60°C, 20min. **b** $Ph(CH_2)_6MgBr$, Li_2CuCl_4/THF, 0°C, 2h, 81% (3 steps from 7). **c** $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, -60°C. **d** PPTS/THF-MeOH, reflux, 3h, 86% (2 steps from 10). **e** Pd/C, H_2/THF, r.t., 8h. **f** (i) $NaIO_4$/THF-H_2O, r.t., 1h; (ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4/*t*-BuOH-H_2O, r.t., 1h. **g** CH_2N_2/Et_2O, r.t., 1h, 63% (4 steps from 12).

A side chain at C1 was introduced by the reaction of 6-phenylhexylmagnesium bromide[11] with aldehyde **9** to provide alcohol **10** as an epimeric mixture in 81% overall yield (3 steps) from **7**. (Scheme 2) Construction of a bicyclic system was achieved by Swern oxidation of **10** followed by treatment of the resulting ketone **11** with PPTS in refluxing THF-MeOH for 3 hr to afford **12** in 86% yield from **10**. The benzyl protecting groups in **12** was removed by catalytic hydrogenation, and the resulting tetraol **13** was subjected to an oxidative cleavage with $NaIO_4$. As expected, only the vicinal diol at the side chain at C5 was cleaved and the other one in the bicyclic ring was untouched due to the fixed *anti* orientation of the two hydroxyl groups. The resulting aldehyde was oxidized to the dihydroxy carboxylic acid **14**, which was treated with CH_2N_2 for purification to isolate methyl ester **15** in 63% overall yield from **12**.

Acylation of C6-OH was next examined. (Scheme 3) After hydrolysis of methyl ester **15**, dihydroxy acid **14** was treated with 2-octenoyl chloride and Et_3N in CH_2Cl_2 at room temperature for 5hr to isolate the desired **2**[12] in 48% yield. Regiochemistry of **2** was based on ^{1}H-NMR analysis. Thus, a signal attributed to C6-H in the diol **15** [δ 4.34 ($J_{6,7}$=2.2Hz)] was shifted downfield in **2** [δ 4.97 ($J_{6,7}$=2.2Hz)], while C7-H appeared at δ 4.08 for **15** and δ 3.99 for **2**, respectively. The other identified product was a diacylated product at C6-OH and C5-CO_2H (mixed anhydride of **2**). Although not direct evidence, NOE was observed between C6-H and C3-H in the 6-*O*-cinnamoyl analog (not shown). Formation of the acylation product at C7-OH could not be detected. Regioselectivity of the present method is quite useful considering the lack of regioselectivity in the case of an ester derivative.[4] We assume the reaction proceeded through the initial formation of a mixed anhydride of **14** and 2-octenoic acid, followed by the intramolecular acyl migration to the hydroxyl group at C6.

Scheme 3



Reagents and conditions: **a** K_2CO_3/H_2O-MeOH, r.t., 3h. **b** 2-octenoyl chloride, Et_3N/CH_2Cl_2, r.t., 5h, 48% (2 steps from **15**).

The biological activity of structurally simplified zaragozic acid derivative **2** was then examined. Contrary to our expectation, inhibitory activity against squalene synthase was much lower than that of zaragozic acid A (**2**; IC_{50}=1.1μM. **1**; IC_{50}=0.5nM). This result may imply that the presence of polar group such as carboxyl or hydroxyl group at C4 is also necessary for significant inhibitory activity. We are currently directing our investigation along this line.

Although biological activity of structurally simplified analog **2** proved to be not promising, the present approach involved several significant features: (1) stereoselective Grignard addition to *pseudo* C_2-symmetric ketone **5**; (2) selective cleavage of vicinal glycol; and (3) selective acylation of diol through intramolecular acyl migration.

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References and Notes

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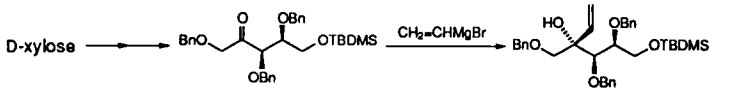
8. All new compounds were fully characterized by ^{1}H-NMR (400 or 200 MHz) and IR spectra, and satisfactory high-resolution MS was obtained for them.
9. Other nucleophiles such as TMSCN-Lewis acid or even allylmagnesium bromide showed almost no selectivity. Reaction of CH_2=CHMgBr with ketone **16** prepared from D-xylose was also examined to form **17** with high diastereoselectivity (>95 : 5). The sense of the diastereofacial selection was found to be opposite to the case of **5**. Since **17** has the wrong stereochemistry for the synthesis of the core moiety, it could not be utilized for synthetic purpose.



16 **17** (>95 : 5)

10. Dihydroxylation of **6** with OsO_4-NMO was also examined for the preparation of 4-hydroxy derivative in mind, but the dihydroxylation proceeded very slowly to afford an almost 1:1 diastereomeric mixture.
11. Grignard reaction proceeded smoothly only in the presence of a catalytic amount of Li_2CuCl_4. See also: Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841-4844.
12. The structure of zaragozic acid analog **2** was characterized as follows: $[\alpha]_D^{20}$ -36.2° (c 1.25, $CHCl_3$); IR (neat) 3300, 2940, 1730, 1650, 1460, 1270, 1170, and 1050 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, t, *J*=6.9Hz), 1.23-1.66 (14H, m), 1.71-1.86 (2H, m), 2.03 (1H, dd, *J*=3.8, 12.9Hz), 2.15-2.26 (3H, m), 2.58 (2H, t, *J*=7.5Hz), 3.99 (1H, d, *J*=2.2Hz), 4.09 (1H, dd, *J*=6.4, 12.2Hz), 4.34 (1H, ddd, *J*=3.8, 12.2, 12.5Hz), 4.97 (1H, d, *J*=2.2Hz), 5.83 (1H, dt, *J*=15.6, 1.5Hz), 7.03 (1H, dt, *J* =15.6, 7.0Hz), 7.13-7.19 (3H, m), 7.23-7.29 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 13.9, 22.4, 22.7, 27.5, 29.1, 29.6, 31.2, 31.3, 31.4, 32.4, 35.9, 36.8, 60.1, 82.8, 83.0, 84.2, 106.4, 119.8, 125.6, 128.2, 128.4, 142.8, 152.7, 167.4, 170.4. HRMS calcd for $C_{27}H_{38}O_7$ 474.2615, found 474.2613.

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