Two Novel Strategies for the Construction of the Core Acetal of the Zaragozic Acids

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Abstract: Novel strategies for the construction of the core 2,8-dioxabicyclo[3.2.1]octane ring system of zaragozic acids/squalestatins non-based on usual ketalisation are described.

Key words: Zaragozic acids, carbohydrate lactone, Wittig reaction, 1,4-addition

Zaragozic acids/squalestatins are newly discovered fungal metabolites exhibiting high inhibition of squalene synthase, an enzyme involved in the cholesterol biosynthesis.[2] Their biological properties made these compounds interesting leads for the discovery of new cholesterol-lowering drugs. Some members of this family are inhibitors of the *ras* farnesyl transferase and may have some interest in relation with cancer therapy. Accordingly, it explain the considerable body of synthetic work aimed at the total synthesis of these compounds.[3] Last but not least, these compounds show intricate structures merely composed of a core bicyclic system of nine carbons with six contiguous chiral centres, three of which being quaternary. This was sufficient to trigger synthetic efforts toward the synthesis of this core 2,8-dioxabicyclo[3.2.1]octane structure. [2, 4]

Most of the strategies for the construction of the bicyclic structure rely on the formation of an acetal between an appropriate carbonyl group (C-1) and two alcohol functions.[2] However, given the high number of hydroxyl groups in the core structure, this approach is not straightforward because of the formation of unexpected acetals and ring size modification by equilibration in acidic medium.[5] In this context we tried to devise new routes for the formation of this acetal ring which would not be based on acetal formation in acidic medium but would be formed in basic medium or by nucleophilic attack on suitable derivative. We report in this paper two different and efficient routes to model 2,8-dioxabicyclo[3.2.1]octane ring systems starting from sugars.[6]

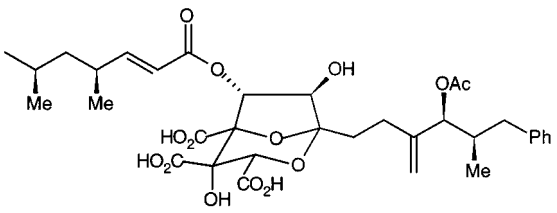
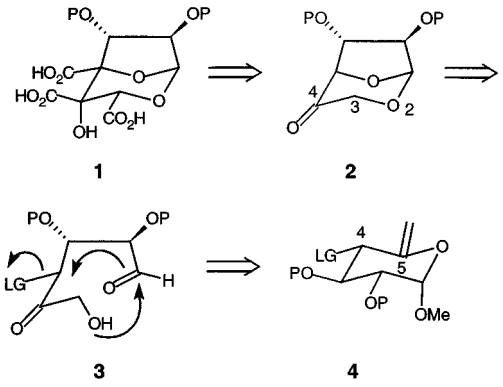


Figure 1 Zaragozic acid A / Squalestatin S1

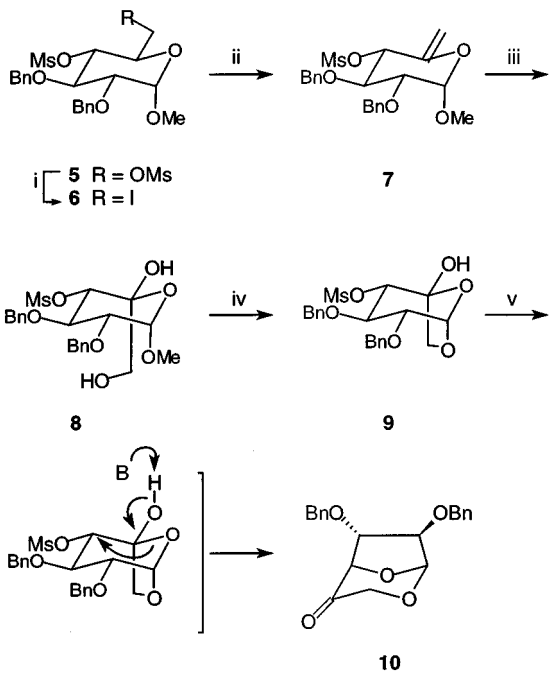
D-glucose is a suitable material since the hydroxyls at C-2 and C-3 have the absolute configuration required in zaragozic acids (C-6 and C-7). The aldehyde group at C-1 is also suitable both for acetal formation and chain extension. Our retrosynthetic analysis of the core structure **1** of zaragozic acid takes into account these different features. In our first model study the ketonic key intermediate **2** was chosen as a reasonable target. Chain extension at C-4 and C-3 of **2** should open the way to zaragozic acids. We planned to form the dioxabicyclic system of **2** by nucleophilic displacement of a suitably oriented leaving group (LG) as depicted on structure **3**. The keto group at C-5 in **3** should came from the C-5 of the glucose ring. A straightforward formation of this carbonyl group without sugar ring opening by way of laborious protection sequences would be the dihydroxylation of the 5,6-double bond of the unsaturated sugar **4**.



Scheme 1 Retrosynthetic analysis

The synthesis began with the known crystalline dimesylate **5** which is easily prepared in 4 steps from glucose.[7] Selective displacement of the primary mesylate gave the crystalline iodo derivative **6** in excellent yield. Formation of the double bond was achieved by treatment with sodium hydride in DMF in 73% yield.[8] Brief treatment of **7** under Shing conditions ($RuCl_3$, $NaIO_4$)[9] gave the expected diol **8**. In our first experiment purification of this compound on a silical gel column resulted in the removal of the aglycon and formation of the 1,6-anhydro derivative **9**. Later on, this reaction was best performed by treatment of **8** with silica gel in dichloromethane in 73% overall yield. To our delight, treatment of **9** with DBU in THF gave the bicyclic structure **10** in 74% yield.[10, 15] It is likely that the

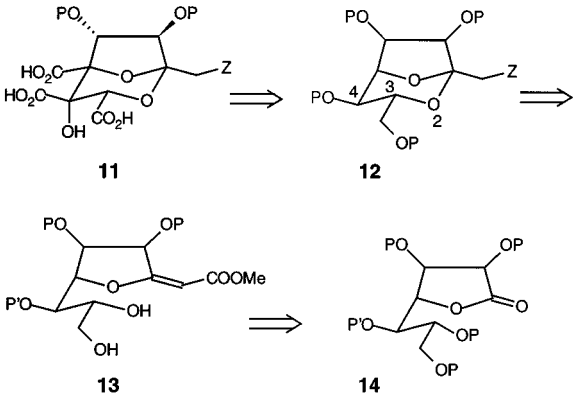
base promotes proton abstraction of the hemiacetal and subsequent opening of the pyranose ring. The newly formed hemiacetal was then well positioned to displace the mesylate group forming a five-membered ring. An approach to the core structure of zaragozic acids based on a related nucleophilic ring opening of an epoxide appeared while this work was in progress.[4j]



Scheme 2 Reagents: i: NaI, butanone, reflux, 90%; ii: NaH, DMF, 73%; iii: $RuCl_3$, $NaIO_4$, $AcOEt/CH_3CN/H_2O$, 30s; iv: SiO_2, CH_2Cl_2 71% over 2 steps; v: DBU, THF, 74%.

In the second approach, (Scheme 3) we planned to introduce a carbon chain at C-1 of the zaragozic acid core structure early in the synthesis. Accordingly, the target structure should be **11** and the key compound of our model studies was then **12**. An ester (Z) should be suitable for further chain elongation and this ester could suitably activate the double bond of olefin **13**. to promote the 1,4-addition of hydroxyl groups. Examples of such a reaction with this type of olefin to form furanic structures have been recently described by our group.[11] Heptose **14** which could be in turn transformed into **13** should be now a good starting compound.

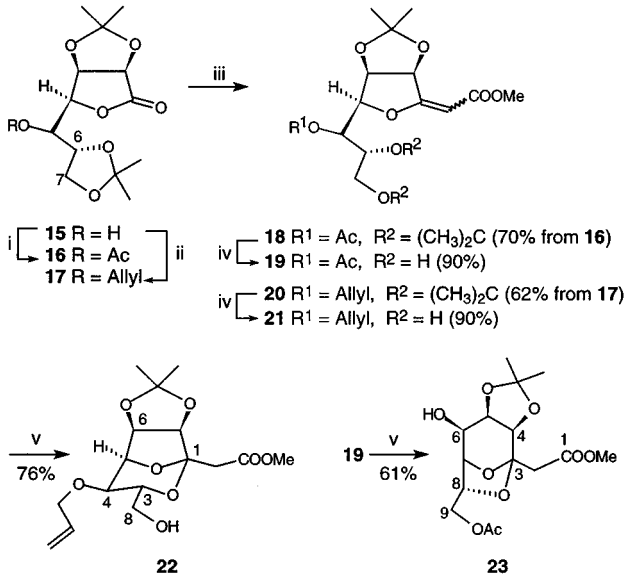
Olefin **18** readily available from the D-glucoheptono lactone derivative **16** was chosen as starting material.[12] Selective hydrolysis of the 6,7-acetal gave diol **19** which was treated with DBU in THF to promote the expected 1,4-addition. A single compound was obtained in 61% yield. However the NMR data of this compound was in favour of structure **23**. The chemical shift of the two protons of the methylene group C-9 (δ: 4.17 and 4.52) clearly indicated the presence of an acetate group at this carbon. On the other hand NOE experiments showed a close proximity between one methyl of the isopropylidene ring and the H-6 proton which was also coupled with the hydroxyl proton. Furthermore oxidation of the hydroxyl group gave the corresponding ketone (not shown here) whose NMR spectrum showed that H-4 and H-5 appeared as two doublets (J = 7.0 Hz). We therefore concluded that the thermodynamically favoured 6,8-dioxabicyclo [3.2.1]octane[13] was formed rather than the expected 2,8-dioxabicyclo[3.2.1] one. It is likely that under the basic conditions required for the 1,4-addition, the acetate group of **19** migrates to the primary position and that formation of the furanose ring occurs followed by ring size modification from the 5-fused ring to the less strained 6-membered ring.



Scheme 3 Second retrosynthetic analysis

Aempts to protect the hydroxyl group of **15** with a methoxymethyl ether or benzyl ether were unsuccessful. However introduction of an allyl protecting group can be performed in modest yield using the tin methodology.[14] Lactone **15** was treated with tributyltin oxide in toluene under azeotropic reflux to provide the intermediate stannyl derivative which was alkylated with allyl bromide in the presence of tetra-n-butylammonium bromide at 80°C. The allyl derivative **17** was formed together with a yet unidentified isomer. Column chromatography gave the pure derivative **17** which was treated under our Wittig conditions to provide the olefin **20** in 62% (*E* + *Z* mixture). Selective hydrolysis under standard conditions proceeded in 90% yield to give the diol **21**. Cyclisation of this diol gave compound **22** in 76% yield establishing the definitive route to our model core structure of zaragozic acids.[15]

We have presented two novel strategies for the construction of the 2,8-dioxabicyclo[3.2.1]octane core of the zaragozic acid. These synthetic appproaches open the way to total synthesis of these compounds. However an important problem to address is the introduction of the C-5 carboxylic chain at the early beginning of the synthesis. Accordingly, in the first approach, this would lead to the formation and substitution of a tertiary mesylate at C-4 of glucose. Probably the second approach would be more fruitful. Indeed, a number of lactones like **17** having a substituent at C-4 have been synthetized in several approaches toward zaragozic acids.[3a, 3d, 3e, 4e, 4k, 4q] Application of our Wittig-based methodology to suitable lactones would likely open a new route to zaragozic acids synthesis. This approach is currently investigated in our group.



Scheme 4 Reagents: i: Ac_2O, pyr; ii: 1) $(Bu_2Sn)_2O$, toluene, reflux; 2) AllylBr, Bu_4NBr, 80°C, 48%; iii: Ph_3PCH_2COOMe, toluene, 130°C; iv: $AcOH/H_2O$ 7:3, THF, 50°C 3-5h; v: DBU, THF, rflx.

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(10) The keto group of **10** was partially hydrated but a crystalline compound was obtained by 1) Wittig homologation of **10** to the corresponding α,β-unsaturated methyl ester 2) dihydroxylation. Single crystal X-Ray diffraction studies of this compound confirmed the structure proposed for **10**.

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(13) For other examples of 6,8-dioxabicyclo[3.2.1]octane ring systems formation see refs 4h and 4d. A theoritical explanation of this favoured formation is given in ref 4h.

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(15) Analytical data of compound **10**: R_f 0.2-035 (H:A 3/2). $[\alpha]_D$ + 46.4 (c 0.7, $CHCl_3$). IR ν (cm^{-1}): 3424, OH of hydrate; 1744, CO. ^1H NMR (400 MHz, $CDCl_3$): δ: 3.93 (d, 1H, $J_{2,3}$ 1.5 Hz, *H6*); 4.20 (ddd, 1H, $J_{1,2}$ 4.5 Hz, $J_{2,4}$ 1.5 Hz, *H7*); 4.33 (d, 1H, J = 18 Hz, *H3*); 4.43 (dd, 1H, J = 18 Hz, *H3'*); 4.47 (d, 1H, J 11.5 Hz, PhCH_2); 4.52 (broad s, 1H, *H5*); 4.53 (d, 1H, J = 11.5 Hz, PhCH_2); 4.58 (d, 1H, J = 11.5 Hz, PhCH_2); 4.67 (d, 1H, J = 11.5 Hz, PhCH_2); 5.66 (d, 1H, *H1*). ^{13}C NMR (250 MHz, C_6D_6) δ; 70.1 (*C3*); 71.9 (*C*H_2Ph); 72.9 (*C*H_2Ph) 84.1(*C6*); 85.3 (*C7*); 86.1 (*C5*); 97.4 (*C1*); 128.0-128.5 (10C *Ph*), 136.6, 136.9 (*Cquat*) 202.1 (*C5*); MS (EI 70 eV) m/z: 340.3 ($M^{+\circ}$); 249.2 (M-CH_2Ph), 204.1, 188.1, 105.1.
Analytical data of compound **22**: R_f 0.27 (H:A 2/1). $[\alpha]_D$ + 17.1 (c 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$ and D_2O) δ; 1.27 (s, 3H, CH_3 acetonide); 1.42 (s, 3H, CH_3 acetonide); 2.83 (d, 1H, J_{gem} = 15.4, CH_2CO_2Me); 2.91 (d, 1H, J_{gem} = 15.4, CH_2CO_2Me); 3.64 (s, 3H, CO_2*Me*); 3.68 (dd, 1H, J_{gem} = 12.5, $J_{6,7}$ = 8.0 Hz, *H8*); 3.78 (dd, 1H, $J_{4,5}$ = 5.3, $J_{5,6,}$ = 5.6 Hz, *H6*); 3.83 (dd, 1H, J_{gem} = 12.5, $J_{3,8'}$ = 5.8 Hz, *H8'*); 4.02 (broad dd, 1H, J_{gem} = 12.4, J = 6.2 Hz, CH_2=CH-CH_2O); 4.16 (m, 1H, *H3*); 4.26 (broad dd, 1H, J_{gem} = 12.4, J = 4.6 Hz, CH_2=CH-CH_2O); 4.32 (d, 1H, $J_{2,3}$ = 6.8, *H7*); 4.37 (dd, 1H, $J_{6,7}$ = 6.8, $J_{5,6}$ = 5.6 Hz, *H6*); 4.49 (dd, 1H, $J_{4,5}$ = 5.3, $J_{3,4}$ = 4.6 Hz, *H4*); 5.17 (dd, 1H, J_{cis} = 10.2 Hz, CH_2=CH-CH_2O); 5.23 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.5 Hz CH_2=CH-CH_2O); 5.82 (m, 1H, CH_2=C*H*-CH_2O). ^{13}C NMR (250 MHz, $CDCl_3$) δ; 25.9 and 27.7 (2C, 2 x CH_3 acetonide); 39.0 (*C*H_2CO_2Me); 51.8 (CO_2*Me*); 60.6

(*C8*); 71.4 (CH_2=CH-*C*H_2O); 75.8 (*C4*); 77.0 (*C7*); 77.5 (*C6*); 78.6 (*C3*); 79.1 (*C5*); 105.2 and 111.7 (2C, *C1* and *C*Me_2); 118.5 (*C*H_2=CH-CH_2O); 133.3 (CH_2=*C*H-CH_2O); 168.8 (*C*O_2Me); MS (EI 70 eV) m/z: 345.4 ($M+H^+$), 329.3, 229.1, 169.1, 100.1. Anal. Calc. for $C_{16}H_{24}O_8$: C, 55.8; H, 7.0; Found: C, 55.31; H, 6.85.

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