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Zaragozic Acid A : Interesting Observations in Anhydro-ring Formation of Densely Functionalised Carbohydrate Templates

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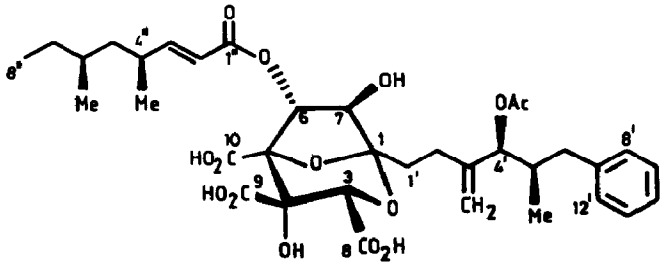
Abstract : A methodology which produced highly substituted 1,6-anhydrofuranose derivative, symbolising 2,8-dioxobicyclo[3.2.1]octan core of zaragozic acid, has been described.

Zaragozic acid A (1) was isolated[1] from the fungal culture of Sporormiella intermedia and belong to the family of potent picomolar competitive inhibitor of squalene synthase. Being an inhibitor of ras farnesyltransferases, zaragozic acid (1), holds tremendous promise in the study of protein prenylation and as a potential anticancer agent[2]. Zaragozic acid A (1) contains multiple functional groups and array of stereochemical centers assembled in an unprecedented 2,8-dioxobicyclo[3.2.1]octan-4,6,7-trihydroxy-3,4,5-tricarboxylic acid core. In fact, 2,8-dioxobicyclo[3.2.1]octane core of 1 could be visualised as a densely functionalised 1,6-anhydrofuranose derivative. This correlation, therefore, prompted us to place emphasis on 1,6-anhydro-ring formation of suitably and heavily substituted sugar precursors[3]. We wish to record our interesting findings which would undoubtedly find wider use and comprehensive understanding of the factors influencing the outcome of anhydro-ring formations.



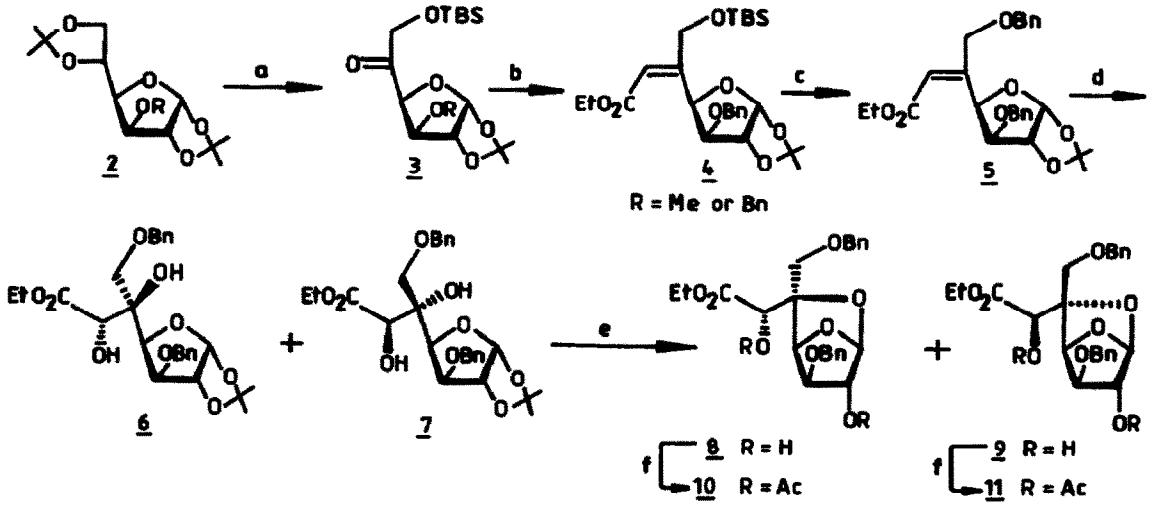
Zaragozic acid 1

1,2;5,6-Di-O-isopropylidene-α-D-glucofuranose derivative (2, R=Bn or Me) was treated with 0.8% H_2SO_4 (MeOH, RT) to hydrolyse the 5,6-O-isopropylidene group, and then silylated (TBS-Cl, Imid. CH_2Cl_2, RT) and oxidised (DMSO $(COCl)_2$, Et_3N, CH_2Cl_2 -78°) to give the 5-ulose derivative (3, R=Bn or Me)[4]. Subsequent Wittig reaction (Ph_3P=CHCOOEt, CH_2Cl_2, RT) gave the Z-olefin (4, R=Bn or Me). Successive desilylation of 4 (R=Bn) followed by benzylation (NaH, BnBr, THF, RT) gave 5. We observed no formation of γ-lactone during either desilylation or benzylation reaction.

The catalytic osmylation of 5 (OsO_4, NMO, MeCOMe-H_2O, RT) gave a diastereomeric mixture of diols in the ratio of 7:3 as judged by HPLC analysis[5]. The major product was assigned anti-configuration (between C_6-C_7) (6) while minor product the syn-configuration (between C_6-C_7) (7) based on ample literature precedents[6]. The mixture (6/7) did not separate by chroma-

tography and therefore subjected to the treatment of PTSA in refluxing chloroform to afford chromatographically separable anhydro-derivatives (100%) (Scheme 1).

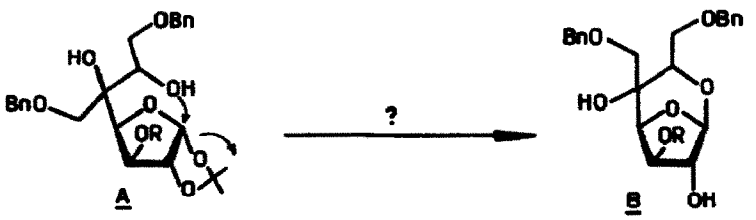
Scheme-1



a) (i) 0.8% H_2SO_4, MeOH, RT, 12 h; (ii) TBS-Cl, Imid, CH_2Cl_2, RT, 3 h; (iii) DMSO, $(COCl)_2$, -78°, Et_3N, 1 h; (b) Ph_3P=CH-COOEt, CH_2Cl_2, RT, 18 h; (c) (i) Bu_4NF, THF, RT, 3 h; (ii) NaH, BnBr, THF, RT, 4 h; (d) OsO_4 (Cat.), NMO, CH_3COCH_3-H_2O, RT, 8 h; (e) PTSA, $CHCl_3$, Δ, 6 h; (f) Ac_2O, Py, DMAP, $CHCl_3$, 18 h.

The major product from the above reaction was first transformed (Ac_2O, Py, DMAP, RT) into the corresponding acetate derivative (95%) and then both the products were comparatively analysed by the ^1H NMR spectroscopy. The ^1H NMR spectral data suggested the structure **8** { $[\alpha]_D$ +70° (c 0.4, $CHCl_3$) } to the parent 1,5-anhydrofuranose and **10** { $[\alpha]_D$ +28° (c 1.4, $CHCl_3$) } for its diacetate derivative. The chemical shifts of ring protons of **8** as well as **10** were conveniently established by proton decoupling experiments. Compound **10** showed a distinct downfield shift for signals due to H-2 (δ 4.92, double-doublet) and H-7 (δ 5.97, singlet) indicating the presence of acetyl groups at these positions. The characteristic coupling constants noted for H-1 to H-4 confirmed the furanose form of the molecules (**8** and **10**)[7]. On the basis of similar observations in the ^1H NMR spectrum, we proposed structures **9** { $[\alpha]_D$ -15° (c 0.6, $CHCl_3$)}and **11** { $[\alpha]_D$ -62° (c 0.4, $CHCl_3$) } to the minor component and its diacetate derivative respectively. The chemical ionization - mass spectra of **8** and **9** showed highest mass peak at m/z 445 (M^++1). Interestingly, we did not observe the formation of 1,6-anhydro structures in these transformations.

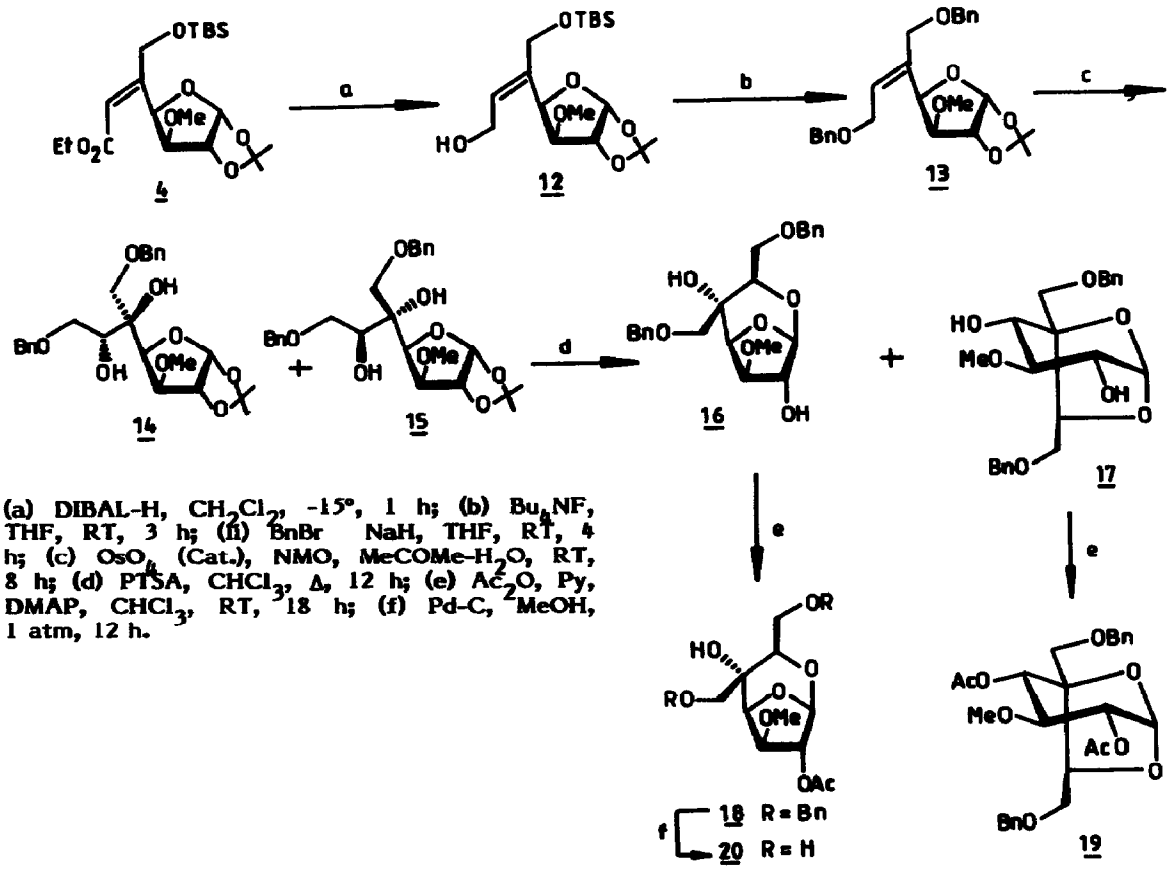
Scheme-2



The generation of the undesired 1,5-anhydrofuranoses instead of the requisite 1,6-anhydrofuranoses could perhaps be due to the presence of carbethoxy group (C_7) which might have diminished the nucleophilicity of the adjacent 6-OH group. We reasoned, therefore, conversion of COOEt → CH_2OBn, prior to cyclisation step, will enhance the nucleophilicity of 6-OH group to direct its participation in 1,6-anhydro-ring formation (scheme 2).

With this anticipation, we modified some experiments in which **4** (R=Me) { $[\alpha]_D$ -85° (c 2.6, $CHCl_3$) } was first reduced with DIBAL-H (CH_2Cl_2, -78° → 0°) to produce the allylic alcohol (**12**) { $[\alpha]_D$ -60° (c 1.1, $CHCl_3$) } (87%). Subsequent desilylation (Bu_4NF, THF, RT) and benzylation (NaH, BnBr, THF, RT) of **12** afforded the dibenzylate derivative (**13**) (91%). The catalytic osmylation (OsO_4, NMO, MeCOMe-H_2O, RT) provided the diastereomeric mixture of diols (**14** and **15**) (100%) which was treated with PTSA in refluxing chloroform to give, after chromatography, two products (**16** and **17**), each of which was acetylated (Ac_2O, Py, DMAP, RT) independently to provide the corresponding acetylated derivatives (**18** and **19**) (Scheme 3).

Scheme-3



(a) DIBAL-H, CH_2Cl_2, -15°, 1 h; (b) Bu_4NF, THF, RT, 3 h; (ii) BnBr NaH, THF, RT, 4 h; (c) OsO_4 (Cat.), NMO, MeCOMe-H_2O, RT, 8 h; (d) PTSA, $CHCl_3$, Δ, 12 h; (e) Ac_2O, Py, DMAP, $CHCl_3$, RT, 18 h; (f) Pd-C, MeOH, 1 atm, 12 h.

The structure of **17** { $[\alpha]_D$ +29° (c 0.3, $CHCl_3$)} and its diacetate derivative (**19**) { $[\alpha]_D$ +58° (c 0.4, $CHCl_3$)} were scrutinised on the basis of the ^1H NMR and mass spectral data. For example CI-MS of **17** showed highest mass peak at m/z 417 (M^++1). The proton decoupling

experiments of **19** assured the chemical shifts of ring protons. For instance the ^{1}H NMR spectrum of **19** showed signals due to H-2 (double-doublet, $J_{1,2}$ = 1.0, $J_{2,3}$ 8.5 Hz) and H-4 (doublet, $J_{3,4}$ = 8.9 Hz) at 4.82 and 5.31 ppm respectively accounting the acetyl groups at O-2 and O-4. The coupling constants observed for H-2 to H-4 were characteristic of pyranose forms (trans-diaxial relationship) of **17** and **19.**

The required 1,6-anhydrofuranose structure present in **16** {$[\alpha]_D$ +13° (c 0.7, $CHCl_3$)} was given on the basis of following studies. Acetylation of **16** gave the monoacetate (**18**) whose formation was expected as the tertiary OH group at C-5 would resist the reaction. The proton decoupling experiments accurately determined chemical shifts of ring protons of **18.** The downfield shift of resonances due to H-2 at 5.39 ppm (doublet, $J_{2,3}$ = 2.0 Hz) provided the information of acetyl group at 0-2. In addition, H-1 and H-4 of **18** appeared at 5.15 (singlet) and 4.87 (doublet, $J_{3,4}$ = 6.5 Hz) which suggested the assigned structure. In order to substantiate the structure of **18**, hydrogenolysis (Pd/C, H_2, MeOH, 1 atm) was conducted to give the triol (**20**) {$[\alpha]_D$ -25° (c 1.2, $CHCl_3$)} (92%) (in which the two hydroxymethyl groups were nicely placed as hidden carboxylic acid groups). The ^{1}H-NMR spectrum - δ 2.14 (s, 3H), 3.53 (s, 3H), 4.04 (dd, 1H, J=4.0, 4.5 Hz), 4.18 (dd, 1H, J 2.0, 6.1 Hz) 4.53 (d, 1H, J 6.1 Hz), 5.18 (s, 1H), 5.37 (d, 1H, J 2.0 Hz) and the mass spectrum (CI-MS : m/z 279 (M^++1) of **20** were compatible with the 1,6-anhydro furanose structure.

In the preceding lines, we have demonstrated factors implicated in the formation of 1,6-anhydrofuranose structure related to zaragozic acid A (**1**). Based on the analogy, we now propose the total synthesis of **1** in which suitable substitutions at positions 1 and 4 and the stereochemical features will be carefully considered.

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8. All new compounds showed satisfactory spectral and elemental/mass analysis. ^{1}H NMR data of some selected molecules: **9** - δ 1.10 (t, 3H, J=6.0 Hz), 3.57 (m, 1H), 3.68 (d, 1H, J=9.3 Hz), 3.75 (dd, 1H, J=4.0, 8.0 Hz), 3.83 (m, 1H), 3.89 (dd, 1H, J=4.6, 8.0 Hz), 3.98 (d, 1H, J=9.3 Hz), 4.54 (ABq, 2H), 4.67 (d, 1H, J=11.3 Hz), 4.71 (bs, 1H), 4.76 (d, 1H, J=4.0 Hz), 4.77-4.83 (m, 2H), 7.3 (m, 10H); **18** - δ 2.12 (s, 3H), 3.83 (m, 3H), 4.15 (m, 2H), 4.52 (ABq, 2H), 4.58 (ABq, 2H), 4.87 (d, 1H, J=6.5 Hz), 5.15 (s, 1H), 5.39 (d, 1H, J=2.0 Hz), 7.30 (m, 10H); **19** - δ 1.88, 2.14 (2d, 6H), 3.40 (s, 3H), 3.63 (ABq, 2H), 3.89 (m, 3H), 4.12 (m, 1H), 4.48 (s, 2H), 4.64 (ABq, 2H), 4.82 (dd, 1H, J=1.0, 8.5 Hz), 5.31 (d, 1H, J=8.9 Hz), 5.48 (d, 1H, J=1.0 Hz), 7.30 (m, 10H).

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