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Zaragozic Acid : Unusual Stereochemical Dependence in Anhydride Formation of Carbohydrate Templates

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Abstract : As a part of study on zaragozic acid bicyclic core, unusual observations in anhydro-ring formation depending on the stereochemistry at C-6 of the carbohydrate templates have been described.

With the isolation¹ of zaragozic acids/squalestatins (la-c) from the fungal culture of <u>Sporormiella intermedia</u>, <u>Phoma sp. C2932</u> and <u>Leptodonitium elatius</u>, chemists have been enriched with yet another prospect for establishing their synthetic ingenuity². The structural parameters in zaragozic acids demand new concepts and methodologies particularly for the bicyclic core that contains six contiguous chiral carbon atoms, three being quarternary centers. In order to gain experience in the preparation of the novel 2,8-dioxobicyclo[3.2.1]octan-4,6,7trihydroxy-3,4,5-tricarboxylic acid core, we recently³ implicated factors that influence the formation of the bicyclic ring core. However, the critical issue of incorporating the quarternary carbons at C-1 and C-5 positions of 1 remained unaddressed. In this and the following communication we describe studies directed towards the synthesis of the bicyclic core of zaragozic acid starting from a carbohydrate precursor.⁶



The synthesis was initiated with the commercially available 2,3:4,6-di-<u>O</u>-isopropylidene-2-keto-L-gulonic acid (2) which was converted into the methyl ester (3) (Me₂SO₄, K₂CO₃, MeCOMe, Δ , 4h) and then reduced (LAH, THF, RT, 1h) and methylated (NaH, MeI, THF, RT, 3h) to give 4. Selective hydrolysis of 4,6-isopropylidene group with 0.8% H₂SO₄ in methanol at ambient temperature was followed by the protection (TBS-Cl, Imid, CH₂Cl₂, RT, 3h), of the primary OH group as TBS-ether (5) { [α]_D +30° (c 1.3, CHCl₃)}. The secondary OH group was benzylated (NaH, BnBr, THF, RT, 6h) and TBS-ether cleaved (Bu₄NF, THF, RT, 3h) to



a) (i) Me_2SO_4 , K_2CO_3 , MeCOMe, Δ , 4h; (ii) LiAlH₄, THF, RT, 1h; (iii) NaH, MeI, THF, RT, 3h; b) (i) 0.8% H_2SO_4 , MeOH, RT, 5h; (ii) TBS-Cl, Imid, CH_2Cl_2 , RT, 3h; c) (i) NaH, BnBr, THF, RT, 6h; (ii) Bu_4NF , THF, RT, 3h; d) DMSO, $(COCl)_2$, CH_2Cl_2 , -78°, Et_3N , 1h; e) 37% HCHO, IN NaOH, RT, 4h; f) Li, NH₃ (liq.), -33°, 1.5 h; g) $Me_2C(OMe)_2$, PTSA, RT, 2h; h) (i) DMSO, $(COCl)_2$, CH_2Cl_2 , -78°, Et_3N , 1h; (ii) $Ph_3P=CH_2$, THF, 0°-RT, 5h; i) (i) 0.8% H_2SO_4 , MeOH, RT, 5h; (ii) NaH, BnBr, DMF, 0°-RT, 12h; j) OsO₄ (cat), 8:1 t-BuOH-H₂O, NMO, RT, 12h.

afford 6 whose oxidation under Swern conditions (DMSO, $(COCI)_2$, -78°, Et₃N, 1h) gave the aldehyde 7. The cross-aldol condensation followed by concomitant Cannizzarro reduction of 7 was effected⁴ by treatment with 37% formaldehyde solution and 1N NaOH to give 8 (90%). Hydrogenolysis by using Li/NH₃ at -33° removed the benzyl group from 8 to produce the triol 9 which was acetonated (Me₂C(OMe)₂, PTSA, RT, 2h) to furnish 10 { [α]_D +2° (c 0.7, CHCl₃)}. Swern oxidation of 10 and subsequent Wittig reaction (Ph₃P=CH₂, THF, 0°-RT, 5h) furnished the olefin 11 which was transformed into the product 12 { [α]_D +35° (c 1.1, CHCl₃)} by using routine reactions (0.8% H₂SO₄, MeOH, RT; NaH, BnBr, DMF).

Catalytic osmylation⁵ $(OsO_4^{-}, NMO, 8:1, t-BuOH-H_2O, RT, 12h)$ of 12 gave a 1:1.5 mixture of the diols (13a/13b) which was conveniently separated by silica gel chromatography. The correct stereostructures of $13a \{ [\alpha]_D + 17^\circ (c \ 1.7, CHCl_3); MS:\underline{m/z} \ 474 \ (M^+) \}$ and $13b \{ [\alpha]_D + 10^\circ (c \ 1.5, CHCl_3); MS:\underline{m/z} \ 474 \ (M^+) \}$ could not be ascertained by the ¹H-NMR spectroscopy. However, the acid catalysed anhydro-ring formation of 13a and 13b were independently studied which not only provided the absolute stereochemistries but revealed unprecedented observations of stereochemical dependence in anhydro-ring formation, perhaps noted for the first time. For example 13b on refluxing with PTSA in CHCl₃ gave the 2,7-anhydro-product 14 which was conventionally acetylated (Ac₂O, Py, DMAP, RT, 12h) to produce the diacetate



a) PTSA (Cat.), $CHCl_3$, Δ , 2h; b) Ac_2O , Py, DMAP, RT, 12h.

15 {[α]_D -60° (c 0.9, CHCl₃)}. Compounds 14 and 15 were structurally investigated by the ¹H NMR studies. The proton decoupling experiments unambiguously provided the chemical shift values for H-3, H-4, H-6, H-7a and H-7b. The characteristic doublets in the ¹H NMR spectrum of 15 for H-3 and H-6 were located in the downfield region at δ 5.46 (J=3.2 Hz) and δ 4.88 (J=3.8 Hz), indicating the presence of acetyl groups at these positions. The two protons at C-7 appeared as a doublet [3.96 ppm, J=14.0 Hz, H-7 (equatorial)] and double-doublet [4.20 ppm, J=3.8, 14.0 Hz, H-7 (axial)] revealing pyranose structure (15) and eq-eq and eq-ax relationship between H-6 and H-7 protons (Fig.A).



On the other hand compound 13a (PTSA, $CHCl_3$, Δ) provided the 2,6-anhydro-derivative 16 which was acetylated as described above to afford the diacetate derivative 17 { $[\alpha]_D$ +65° (c 0.7, $CHCl_3$)}. In the ¹H NMR spectrum of 17 the doublet (J=3.2 Hz) due to H-3 was located at 5.56 ppm revealing the presence of acetyl group. The second acetyl group was placed at C-7 because two double-doublets due to H-7a and H-7b were observed at δ 5.38 (J=10.0, 14.0 Hz) and δ 4.24 (J=10.0, 14.0 Hz). The ring proton (H-6) was observed at 3.56 ppm as a triplet (J=10.0 Hz). These parameters of the ¹H NMR spectrum of 17 suggested the 2,6-anhydro structure. Further confirmation of structures of 15 and 17 were revealed from the CI-MS spectrum which revealed the highest mass peak at m/z 501 (M⁺+1).

The above studies conclusively provided the structures of parent compounds 13a and 13b which on acid treatment selectively formed the five membered (2,6)- and the six membered (2,7)-anhydro-ring systems respectively. Further studies on the bicyclic core of zaragozic

acid is described in a subsequent communication.

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- All new compounds showed satisfactory spectral and elemental/mass analysis. ¹H NMR (200 MHz, CDCl₃) and optical rotation data of some selected compounds :
 6 δ 1.38, 1.49 (2s, 6H), 3.40 (s, 3H), 3.57 (s, 3H), 3.80 (ddd, 1H), 4.00 (d, 1H, J=3.6 Hz), 4.34 (m, 1H), 4.44, 4.70 (2d, 2H), 4.57 (s, 1H), 7.3 (m, 5H), [α]_D 45° (c 1.3, CHCl₃);
 12 δ 1.34, 1.46 (2s, 6H), 3.36 (s, 3H), 3.40, 3.68 (2d, 2H), 3.54 (s, 2H), 4.06 (s, 1H), 4.44 (ABq, 2H), 4.54, 4.72 (2d, 2H), 4.60 (s, 1H), 5.15-5.5 (m, 2H), 6.06 (dd, 1H), 7.3 (m, 10H); 15 δ 2.00, 2.08 (2s, 6H), 3.36 (s, 3H), 3.44 (ABq, 2H), 3.56, 3.80 (2d, 2H), 3.88 (d, 1H, J=3.2 Hz), 3.96 (d, 1H, J=14.0 Hz), 4.20 (dd, 1H, J=3.8, 14.0 Hz), 4.34, 4.56 (2d, 2H), 4.64 (ABq, 2H), 4.88 (d, 1H, J=3.8 Hz), 5.46 (d, 1H, J=3.2 Hz), 7.30 (s, 10H); 17 δ1.80, 2.10 (2s, 6H), 3.40 (s, 3H), 3.50 (ABq, 2H), 3.56 (t, 1H, J=10.0 Hz), 3.68 (ABq, 2H), 4.10 (d, 1H, J=3.2 Hz), 4.24 (dd, 1H, J=10.0, 14.0 Hz), 4.36 (d, 1H), 4.42, 4.70 (2d, 3H), 5.38 (dd, 1H, J=10.0, 14.0 Hz), 5.56 (d, 1H, J=3.2 Hz), 7.3 (m, 10H).

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