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A Symmetry-Based Approach to Zaragozic Acid: Synthesis and End-Differentiation of an Advanced Intermediate

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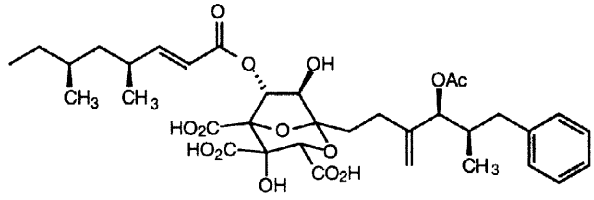
Abstract: Reported is a novel, symmetry-based strategy for the synthesis of the zaragozic acids. Two enantioselective dihyroxylations are used to set the absolute stereochemistry of a C-2 symmetric intermediate. A sequence of a furan photo-oxidation followed by a diastereoselective dihydroxylation breaks the symmetry and sets two quaternary stereocenters. Finally, a group selective lactonization is used to protect one of two secondary hydroxyls. This accomplishes the critical end-differentiation of this intermediate. An approach to protecting group removal and oxidation is also presented.

The zaragozic acids, or squalestatins, are a class of compounds with potent inhibitory activity toward squalene synthase, the enzyme that catalyzes the first committed step in cholesterol biosynthesis (Scheme 1).[2] Additionally, they have been found to inhibit ras farnesyl transferase.[3] Therefore, these compounds show promise as leads for the development of cholesterol-lowering or anticancer substances. The unique structures of the zaragozic acids, along with their fascinating biological activities, have prompted efforts from this laboratory[4] and others[5-7] to develop efficient synthetic routes to these natural products.



Zaragozic Acid A (Squalestatin 1)

Scheme 1

The strategy devised for the construction of zaragozic acid, shown in Scheme 2, relies on the cyclization of an acetal-centered radical **2** onto a radical acceptor to construct the 2,8-dioxabicyclo[3.2.1]octane ring system **1** at a late stage in the sequence. It was anticipated that this strategy would allow the exploitation of symmetry elements within the molecule to the fullest extent. A radical precursor such as **3**, in which C(Z)Y represents some radical acceptor, would be constructed from an appropriately protected diol **4**. The diol **4** would be synthesized from compound **5** by a sequence of reactions that would accomplish, among other things, the differentiation of the two primary alcohols as well as the two secondary alcohols. The task of differentiating these hydroxyl groups might be aided by the fact that compound **5** is not truly symmetric due to the different configurations of the stereocenters bearing the tertiary alcohols. Compound **5** would arise from a dihydroxylation of a truly symmetrical intermediate such as compound **6**. The synthesis of **6** would primarily involve the assembly of an appropriately functionalized and configured tetrasubstituted olefin and the enantioselective formation of the secondary alcohol stereocenters. Initial efforts in this laboratory on a model system resulted in the development of a novel method to accomplish the radical-based annulation represented by **3**→**2**→**1**.[4] Reported in this communication is a rapid and stereoselective

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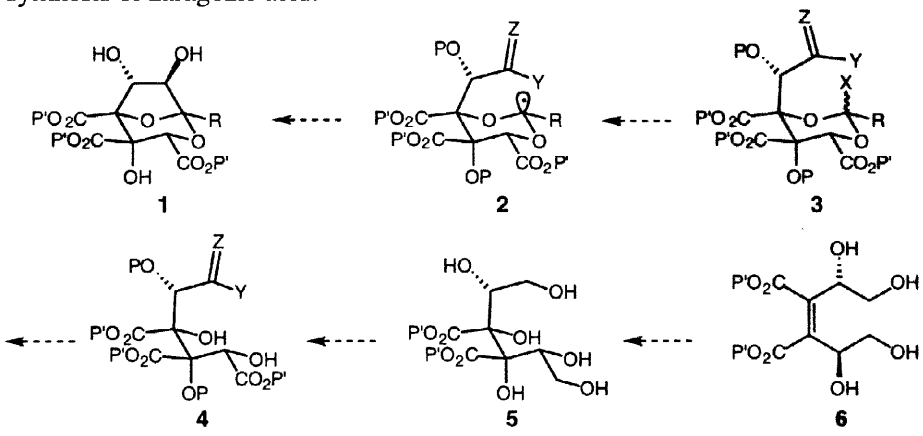
synthesis of a pseudo-symmetrical intermediate corresponding to **5**, and the differentiation of its functionality to produce a pivotal intermediate corresponding to **4**.[8] The establishment of this route should facilitate an efficient completion of the synthesis of zaragozic acid.



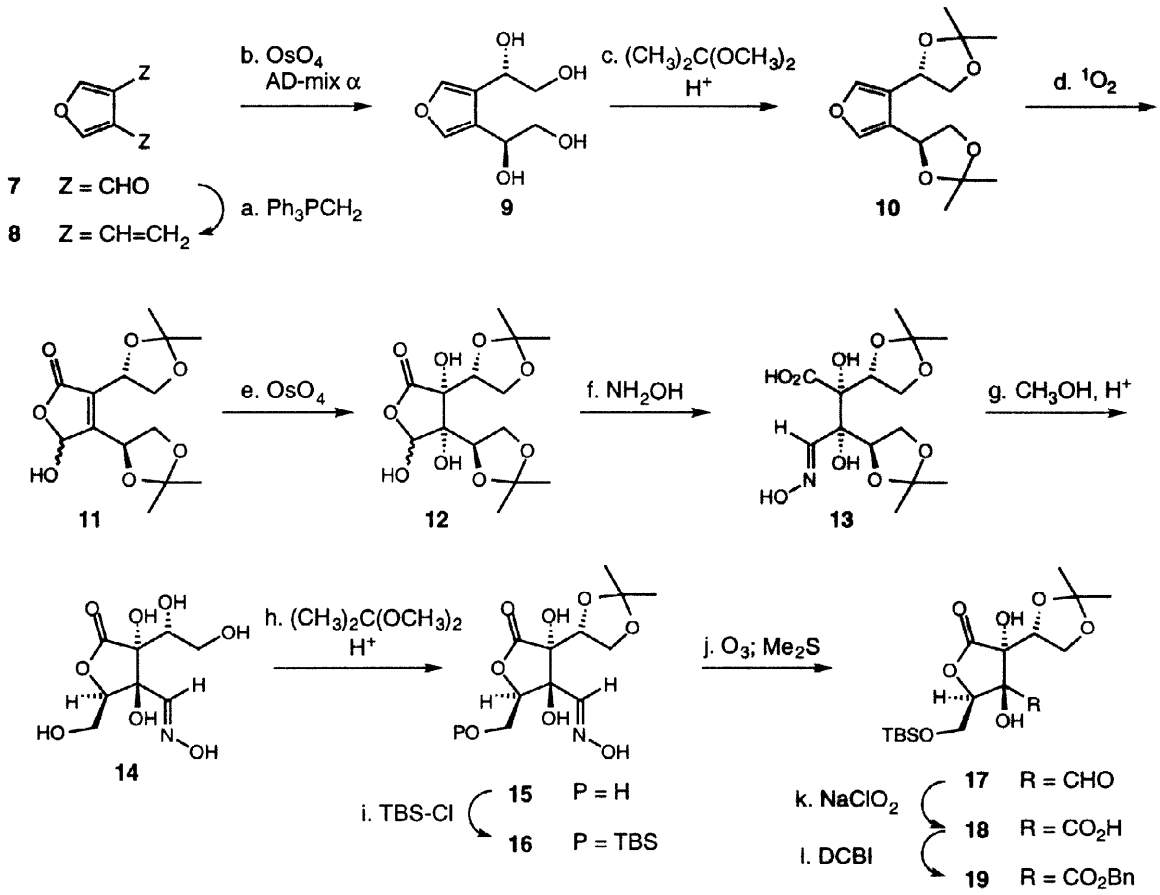
Scheme 2

The furan dialdehyde **7** (Scheme 3), which is easily prepared in two steps from commercially available dimethyl 3,4-furandicarboxylate,[9] was chosen as a starting material. This furan serves as both a symmetrical scaffold and as a protecting group for the carboxylates and the tetrasubstituted olefin of **6**. Wittig olefination produced compound **8**, which was treated directly with AD-mix-α to install four hydroxyl groups and establish each of the secondary alcohol stereocenters in the appropriate (*S*)-configuration.[10] The symmetry of compound **8** provided a substantial benefit to this reaction. Since each dihydroxylation was quite enantioselective, and two sequential dihydroxylations were performed in the same synthetic operation, the tetraol **9** was produced in high enantiomeric excess (>98%).[11] The tetraol **9** was then protected in a straightforward manner as the bis-acetonide **10**. At this stage, the furan was oxidized using singlet oxygen at -20 °C.[12] This oxidation not only provided one of the three carboxylates of zaragozic acid, but also unveiled another carboxylate precursor as an aldehyde engaged in a hemiacetal and produced the desired tetrasubstituted olefin **11**. A final dihydroxylation of **11** installed the two tertiary alcohol stereocenters, and provided the key intermediate **12**. Although compound **12** existed as a mixture of diastereomers at the hemiacetal carbon, the dihydroxylation of compound **11** appeared to be completely face-selective, and none of the product having the opposite configuration at the tertiary alcohol carbons was observed. The structure of triol **12** was determined by single crystal X-ray analysis.[13]

It was hypothesized that the carboxylate contained within **12** could be harnessed for the discrimination of the two secondary alcohols in a group-selective lactonization. The aldehyde was first protected by treatment of **12** with hydroxylamine hydrochloride and pyridine, thus smoothly producing the oxime **13** and liberating the carboxylic acid functionality. Removal of the acetonides from compound **13** produced an extremely polar intermediate, presumably a hexaol, which was not isolated, but was allowed to lactonize upon prolonged exposure to the reaction conditions to provide compound **14** as the sole product.

Reprotection of this vicinal diol as an acetonide yielded compound **15**. Subsequent protection of the remaining primary hydroxyl as its TBS ether produced compound **16**, in which all four non-tertiary alcohols are distinguished from each other. X-ray analysis of compound **16** confirmed the structural assignments.[18]

Finally, the oxime was converted to an ester by the following series of transformations. Stirring compound **16** in a buffered, saturated solution of ozone for 16 hours, followed by reductive work-up[14] yielded the unstable aldehyde **17**. This aldehyde was subjected to Pinnick oxidation conditions[15] to produce carboxylic acid **18**. The crude acid was esterified with dicyclohexylbenzylisourea (DCBI)[16] to produce **19**.[17,18]



Reagents and conditions: (a) Ph_3PCH_2 (2.1 eq), THF, 0 °C to rt, 1 hr (77%); (b) AD-mix-α (0.5 eq), $K_3Fe(CN)_6$ (3 eq), K_2CO_3 (3 eq), *tert*-BuOH-H_2O (1:1), 0 °C to rt, 17 hr (51%); (c) *p*-toluenesulfonic acid (0.2 eq), 2,2-dimethoxypropane-DMF (1:1), rt, 36 hr (69%); (d) O_2 (g), Rose Bengal (0.01 eq), $EtN(i\text{-}Pr)_2$ (2 eq), hv (500 W Quartz Halogen Lamp), CH_2Cl_2, -20 °C, 11 hr (74%, 5:1 ratio of diastereomers at the hemiacetal carbon); (e) OsO_4 (1 eq), pyridine, 0 °C, 12 hr (66%, 2:1 ratio of diastereomers at the hemiacetal carbon); (f) NH_2OH•HCl (2 eq), pyridine (5 eq), THF-CH_3OH (1:1), 65 °C, 6 hr (94%); (g) PPTS (1 eq), CH_3OH, 65°C, 20 hr; (h) PPTS (1 eq), 2,2-dimethoxypropane (1.1 eq), DMF, rt, 5.5 hr (68% for two steps, 84% based on recovered **14**); (i) TBS-Cl (1.05 eq), imidazole (2.5 eq), DMF, rt, 12 hr (56%, 68% based on recovered **15**); (j) i. O_3, NH_4OAc (15 equiv), CH_2Cl_2-CH_3OH (4:1), -70 °C, 16h; ii. $(CH_3)_2S$, -78 °C for 2 h then rt for 2h (55%); (k) $NaClO_2$ (3 equiv), NaH_2PO_4 (1.05 equiv), 2-methyl-2-butene (4.2 equiv), *tert*-BuOH-H_2O (4:1), rt, 3 h; (l) DCBI (1.5 eq), toluene, 100°C, 1.5 hr (60% for two steps).

Scheme 3

In summary, a novel approach to the synthesis of the zaragozic acid family of compounds is presented. The extensive utilization of symmetry facilitates a short and efficient sequence to highly functionalized zaragozic acid intermediates. A high yielding method of end-differentiation was also developed. Most of the necessary functionality of the core structure, including four of the six contiguous stereocenters as well as two of the three carboxylates, has been installed in the course of this work. Future efforts of this laboratory will be focused on the introduction of the acetal radical precursor and the radical acceptor (cf. **3**), and finally the assembly of the complete core system. The outcome of these studies will be reported in due course.

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18. Spectroscopic data for **16** and **19**. **16**: $[\alpha]^{20}_D$ = +78.8° (*c* 1.0, $CHCl_3$); IR (film) 3362 (br), 2930, 1782, 1462, 1373, 1257, 1110, 1070, 984, 840, 783 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 5.17 (s, 1H), 4.71 (t, 1H, *J* = 3.75 Hz), 4.52 (dd, 1H, *J* = 6.16, 8.57 Hz), 4.12 (m, 3H), 3.81 (t, 1H, *J* = 8.57), 3.69 (s, 1H), 1.47 (s, 6H), 0.89 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.28, 147.87, 109.99, 80.49, 79.57, 78.24, 74.22, 64.44, 60.43, 25.94, 25.77, 25.61, 18.08, -5.64, -5.68; MS *m/z*: EI+ 390 $(M-CH_3)^+$; HRMS (EI+) calcd. for $C_{16}H_{28}O_8NSi$ $(M-CH_3)^+$: 390.1584, found: 390.1574. **19**: $[\alpha]^{20}_D$ = +14.17° (*c* 0.48, $CHCl_3$); IR (film) 3454, 2928, 2855, 1782, 1742, 1456, 1373, 1258, 1112, 1070, 838, 781, 736, 697, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.30 (m, 2H), 4.85 (dd, 1H, *J* = 4.9, 5.8 Hz), 4.59 (t, 1H, *J* = 7.15 Hz), 4.13 (s, 1H), 4.12 (dd, 1H, *J* = 6.6, 9.1 Hz), 4.02 (dd, 1H, *J* = 6.0, 11.2 Hz), 3.98 (dd, 1H, *J* = 4.47, 11.12 Hz), 3.90 (dd, 1H, *J* = 7.4, 9.0 Hz), 3.66 (s, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.34,170.57, 134.12, 128.87, 128.74, 128.43, 109.83, 80.74, 80.45, 78.48, 75.33, 68.91, 64.95, 60.30, 25.85, 25.75, 25.04, 18.30, -5.58, -5.61; MS *m/z*: EI+ 481 $(M-CH_3)^+$, CI+ 481 $(M-CH_3)^+$; HRMS (EI+) calcd. for $C_{23}H_{33}O_9Si$ $(M-CH_3)^+$: 481.1894, found: 481.1865. X-ray crystal structure of **16**: