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Total Synthesis of (+)-Zaragozic Acid C

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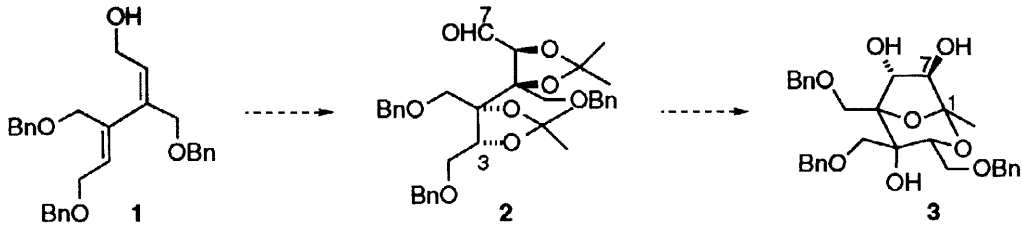
Abstract: A total synthesis of (+)-zaragozic acid C is described. Key steps are an acid-mediated acetonide deprotection-dithiane removal-ketalisation procedure, providing selectively the 2,8-dioxabicyclo[3.2.1]octane core of the natural product, and the simultaneous introduction of the C3, C4 and C5 carboxylic acids *via* triple oxidation.

The zaragozic acids (squalestatins) have attracted intense interest in the synthetic community due to their biological activity (they are potent inhibitors of squalene synthase) and intriguing structure.[1] Several syntheses of models of the bicyclic core have been reported,[1, 2-9] along with total syntheses of zaragozic acid C by Carreira,[10] Evans[11] and Hashimoto[12] and of zaragozic acid A by Nicolaou[13] and by Heathcock.[14] Previously, we have described a concise synthesis of the model core **3** employing double asymmetric dihydroxylation of the 1,3-diene **1** to introduce the stereochemistry at C3-C6.[15] Here we describe the adaptation and advancement of our strategy to complete a total synthesis of (+)-zaragozic acid C.



Scheme 1

As in our model synthesis,[15] we planned to introduce the C1-sidechain of the natural product by using a 1,3-dithiane as an acyl anion equivalent. The required 1,3-dithiane **5** was readily prepared from the known alcohol **4**[10] using standard transformations (Scheme 2).[16] However, despite examining a range of bases, solvents and additives, we were unable to effect clean metallation of **5**. Eventually, this problem was solved by oxidation (*m*CPBA) to the monosulfoxide **6**, which was obtained as a mixture of diastereomers. Deprotonation with BuLi and addition of the resulting anion to the core aldehyde **2**[15] occurred smoothly. Deoxygenation to regenerate the 1,3-dithiane was effected using P_2I_4 in the presence of Et_3N.[17] At this stage, the mixture of C7-epimers **7** and **8** from the addition to the aldehyde was not separable, but removal of the C4'-TBDPS ether (necessary in any case since this was found, in accord with Nicolaou,[13] not to withstand the later ketalisation reaction) gave the alcohols **9** (more polar isomer) and **10** which were readily separable by flash chromatography. Selective acetylation of the C4'-hydroxyl of the desired epimer **9** provided **11**.

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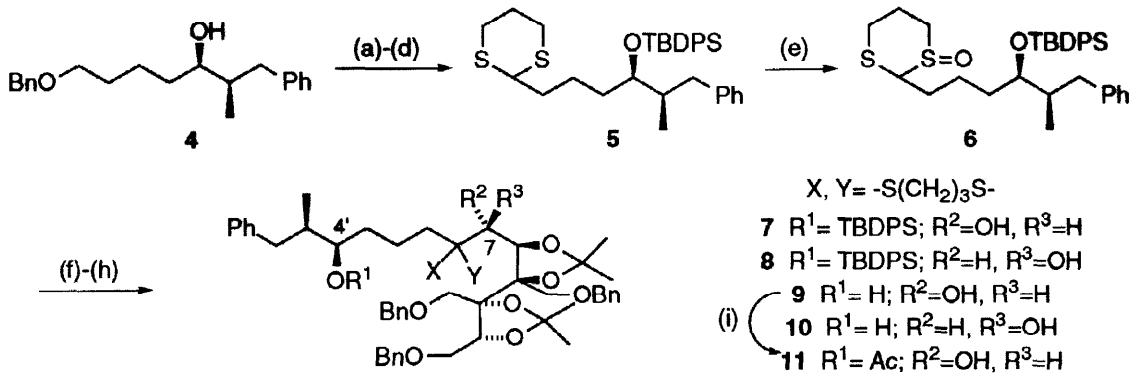
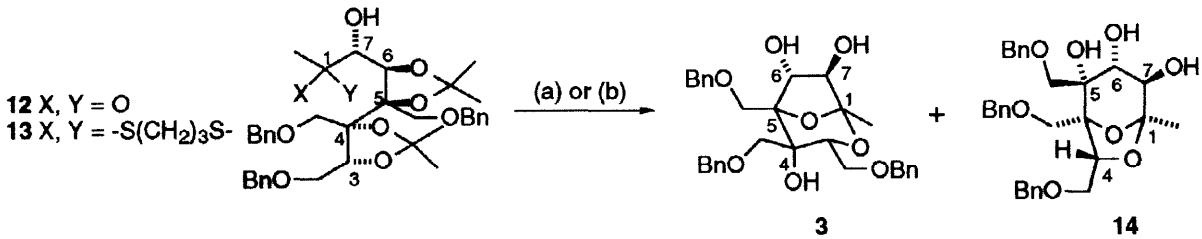


Scheme 2 (a) TBDPSCl, imidazole, DMF, 100 °C, 24 hr (93%); (b) $BCl_3.Me_2S$ (7 eq), CH_2Cl_2 RT, 1 hr[18] (93%); (c) $(COCl)_2$ / DMSO, CH_2Cl_2, then Et_3N (97%); (d) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, RT,1 hr (92%); (e) *m*CPBA, CH_2Cl_2, 0 °C (78%); (f) (i) **6** (3 eq), BuLi (3.1 eq), THF, -78 °C, 15 min; (ii) Add aldehyde **2** (1 eq), -78 °C, 15 min; (g) P_2I_4 (0.55 eq), Et_3N (1 eq), CH_2Cl_2, RT, dark, 15 min (59% from aldehyde **2**); (h) TBAF, THF, 80 °C (36% **10**, 32% **9**); (i) Ac_2O (4 eq), DMAP, pyridine, 80 °C, 30 hr (85%).

At this stage, it was necessary to examine the key ketalisation reaction. In our model studies with a C1-methyl compound,[15] we reported that treatment of ketone **12** with 2% HCl / MeOH afforded a mixture of isomeric ketals **3** and **14** (Scheme 3). Subsequently, we found that a similar ratio was obtained using the TFA / H_2O cyclisation conditions employed by Evans.[11] Our reaction appeared to be proceeding under kinetic control, since we found that resubmitting the separate isomers **3** and **14** to the reaction conditions did not result in their interconversion, at least in a 24 hr time period (interconversion did occur over longer periods). We speculated that the relative rate of hydrolysis of the two acetonide groups in **12** might have an effect on the ketal ratio: conceivably, hydrolysis of the C6-C5 acetonide might be followed by rapid cyclisation of the C5-OH onto the C1-carbonyl, and the resulting five-membered ring might stay closed until hydrolysis of the second acetonide and subsequent closure of the second ring occurred. Conversely, if the C4-C3 acetonide were hydrolysed first, then rapid closure of the C4-OH onto the C1 carbonyl might result in the isomeric system **14** as the final product. In order to test this hypothesis, we decided to remove both acetonides *before* unmasking of the C1 carbonyl. To our delight, treatment of the protected dithiane **13**[15] with TFA / H_2O effected not only acetonide removal, but also remarkably facile dithiane deprotection and ketalisation, leading to the ketal **3** as the only observed isomer in 78% yield. Notwithstanding the validity of our initial mechanistic hypothesis,[19] this modification represents a substantial improvement on the original synthesis.

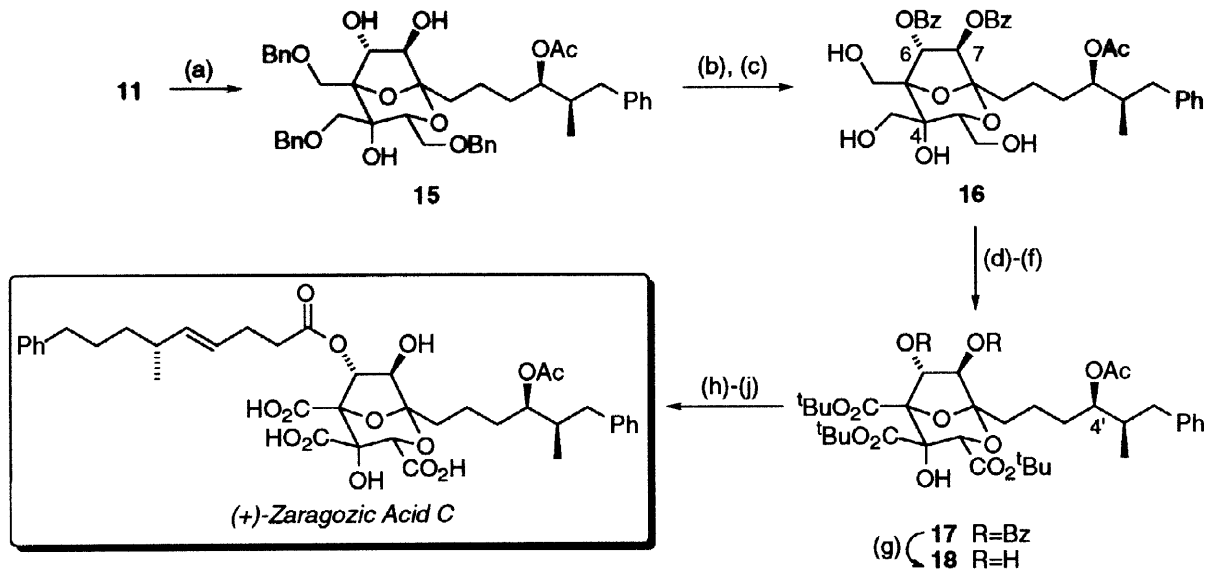


Substrate	*Conditions*	*% yield* **3**	*% yield* **14**
12	(a)	45	47
12	(b)	38	38
13	(b)	78	Not observed

Scheme 3 (a) 2% HCl / MeOH, 50 °C; (b) 20:10:1 CH_2Cl_2 / TFA / H_2O, RT, 16 hr

Pleasingly, the reaction was just as successful with the full C1-side chain: compound **11** was converted into ketal **15**[20] in excellent yield (90%) (Scheme 4). Benzoate protection at C6 and C7 followed by benzyl deprotection (H_2, Pd/C) provided **16** and set the scene for the final major challenge in the synthesis: oxidation to the tricarboxylic acid level. We hoped from the outset that this transformation could be performed simultaneously at all three sites; we were encouraged in this aim by the observation of Carreira[10] that a trialdehyde, obtained by sequential oxidations at the C3 and C5 methanols and ozonolysis of an exocyclic alkene at C4, could be converted to the corresponding triacid using sodium chlorite. However, the triple oxidation of the tetraol **16** suffered the risk that initial oxidation at one of the three primary alcohols would lead to lactol / lactone formation and hence incomplete oxidation. In the event, we were pleased to find that treatment of **16** with 3.5 equivalents of the Swern reagent,[21] followed by chlorite oxidation and *tert*-butyl esterification, provided the tris-ester **17** in a reasonable 33% overall yield for the three steps. Interestingly, use of larger excesses of the Swern reagent led to facile formation of a methylthiomethyl ether on the C4-OH. This triple oxidation is likely to be of interest to other workers in the field, as it will be required for progression of several of the reported model syntheses.

Selective removal of the C6 and C7-benzoate groups in the presence of the C4'-acetate was achieved remarkably smoothly, synthesis of diol **18** completing a formal synthesis of (+)-zaragozic acid C by intersecting with a late Carreira intermediate. Following Carreira's precedent,[10] selective esterification at C6 and final deprotection afforded (+)-zaragozic acid C, $[\alpha]_D^{24}$ +9.6 (*c* 1.0, EtOH), lit.[22] +9.6 (*c* 0.3, EtOH), HRMS (FAB) M+Na 777.3166 ($C_{40}H_{50}O_{14}Na$ requires 777.3098), identical to an authentic sample of the natural product by ^1H NMR, ^{13}C NMR, IR and TLC.



Scheme 4 (a) 20:10:1 TFA / CH_2Cl_2/H_2O, 30 min (90%); (b) PhCOCl, DMAP, pyridine (97%); (c) H_2, Pd / C (89%); (d) 3.5 eq $(COCl)_2$, 7 eq DMSO, CH_2Cl_2, -78 °C, then Et_3N (10.5 eq); (e) $NaClO_2$, pH 3.5 aq. phosphate buffer, 5:1.2 ^tBuOH : β-isoamylene; (f) *N, N'*-Diisopropyl-*O-tert*-butylisourea, CH_2Cl_2 (33% from **16**); (g) K_2CO_3, MeOH (75%); (h) $(Boc)_2O$, Et_3N, CH_2Cl_2, cat. 4-pyrrolidinopyridine (70%); (i) (4*E*, 6*R*)-6-methyl-9-phenyl-4-nonenoic acid,[23] DCC, DMAP, CH_2Cl_2 (87%); (j) 25% aq. TFA, CH_2Cl_2 (96%).

The completion of this total synthesis vindicates our strategy as well as confirming the stereochemical assignment of the key double asymmetric dihydroxylation process.[15] Ongoing work is aimed at improving the stereoselectivity of the formation of the C7-stereocentre, and in the preparation of other members of the natural product family.

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19. Subsequent to these model ketalisation studies, Hashimoto (ref. 12) also suggested that formation of a mixture of ketal isomers could be due to differential rates of protecting group hydrolysis.
20. Data for **15**: Colourless oil, R_f 0.61 (50% EtOAc-petrol); $[\alpha]_D^{21}$ +12.6 (*c* 0.92, CH_2Cl_2); ν_{max}(film) 3458, 3062, 3028, 2927, 2875, 1730, 1603, 1496, 1454, 1370, 1248, 1208, 1098, 1027, 959, 910, 796, 738, 699 and 666 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31-7.23 (15H, m, Ph), 7.17-7.15 (3H, m, Ph), 7.10-7.09 (2H, m, Ph), 4.85-4.83 (1H, m, C*H*(OAc)), 4.76 (1H, br s, H6), 4.54-4.43 (4H, m, 2xOCH_2Ph), 4.38 (1H, m, H3), 4.32-4.27 (2H, m, OCH_2Ph), 3.98 (1H, br s, H7), 3.90 (1H, d, *J* 9.6 Hz, one of CH_2OBn at C4 or C5), 3.77 (1H, dd, *J* 10.7, 3.0 Hz, one of CH_2OBn at C3), 3.59-3.56 (3H, m, one of CH_2OBn at C3 and CH_2OBn at C4 or C5), 3.46-3.45 (2H, m, one of CH_2OBn at C4 or C5 and 7-O*H*), 3.32 (1H, s, 4-O*H*), 2.71 (1H, dd, *J* 13.4, 4.8 Hz, one of H6'), 2.30 (1H, br s, 6-O*H*), 2.28 (1H, dd, *J* 13.2, 9.6 Hz, one of H6'), 2.02 (3H, s, COCH_3), 1.95 (1H, m, H5'), 1.82-1.45 (6H, m, CH_2CH_2CH_2CH(OAc)), 0.82 (3H, d, *J* 6.7 Hz, H13'); δ_C (68 MHz, $CDCl_3$) 170.9 (s), 140.5 (s), 138.0 (s), 137.6 (s), 136.7 (s), 129.0 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.8 (d), 127.6 (d), 127.5 (d), 125.8 (d), 105.1 (s), 86.6 (s), 83.5 (d), 79.4 (d), 76.8 (d), 73.8 (t), 73.4 (t), 73.1 (t), 72.8 (d), 70.9 (s), 69.5 (t), 69.3 (t), 68.4 (t), 39.3 (t), 38.2 (d), 35.2 (t), 31.0 (t), 21.1 (q), 19.1 (t), 13.9 (q); *m/z* (FAB+) 777 (M+Na), 755 (M+H), 695, 665, 605, 509, 359, 329, 269, 133, 91; observed: 755.3850. $C_{45}H_{55}O_{10}$. (M+H) requires 755.3795.
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