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Studies Towards the Synthesis of the Zaragozic Acids: A Novel Epoxide Cyclisation Approach to the Formation of the Bicyclic Acetal Core.

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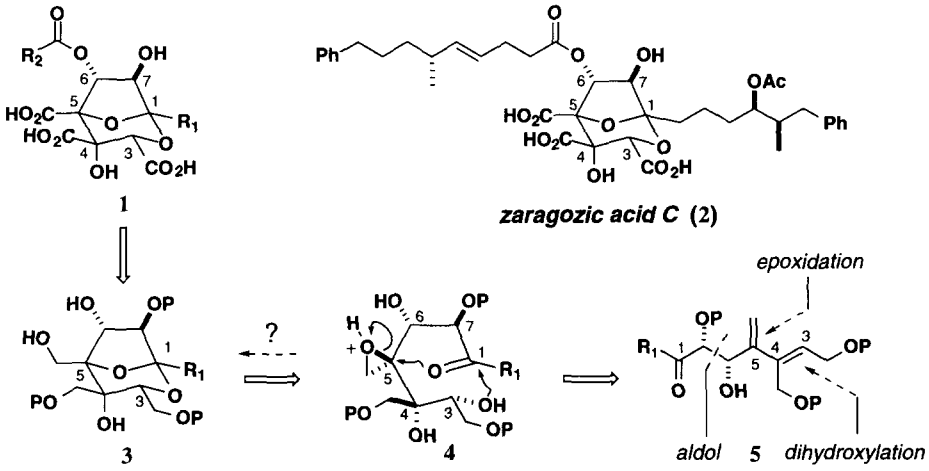
Abstract: Model studies towards the bicyclic acetal core **1** of the zaragozic acids, based on the epoxide cyclisation reaction **4** → **3**, are described. Epoxide **14** provides the desired bicyclic acetal skeleton **16**, while epoxide **27** leads through **28** to an isomeric acetal **30**.

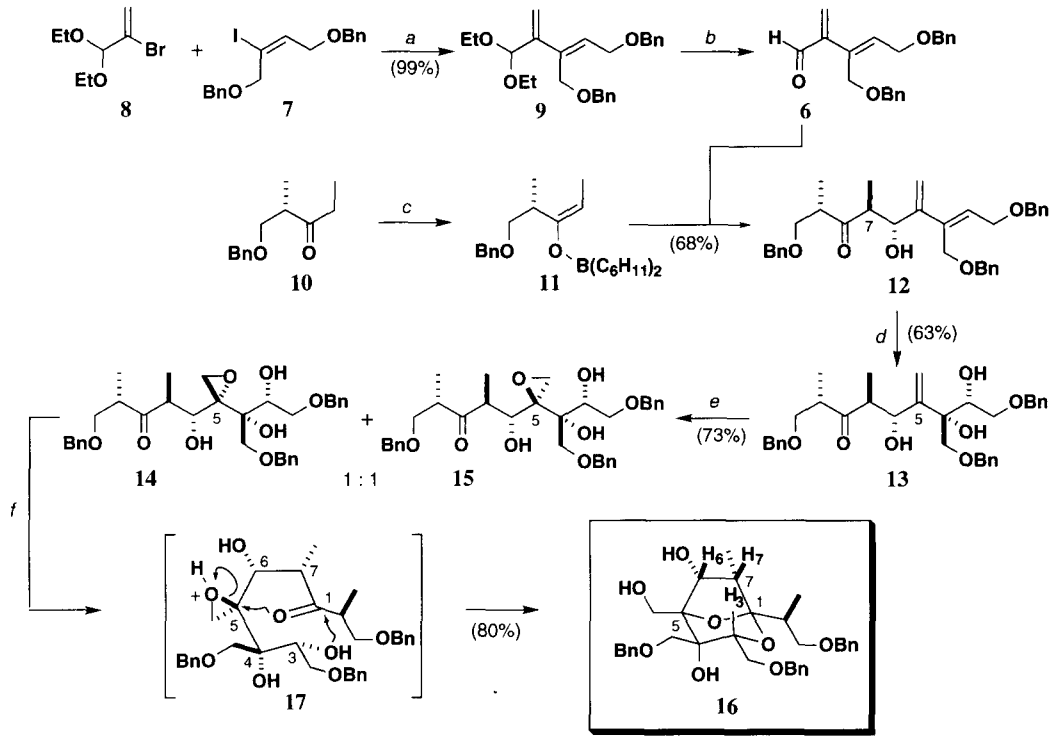
During the screening of fungal fermentation broths for potential inhibitors of cholesterol biosynthesis, research groups at Merck[1] and Glaxo[2] independently reported the isolation of a group of novel polyketide metabolites. These compounds, termed zaragozic acids by Merck and squalestatins by Glaxo, were found to be potent inhibitors of mammalian squalene synthase and thus potential therapeutic agents for treatment of hypercholesterolaemia. All the zaragozic acids contain the highly functionalised 2,8-dioxabicyclo[3.2.1]octane core **1**, which has attracted intense synthetic interest,[3] culminating in the recently reported total syntheses of zaragozic acids A[4a] and C (**2**).[4b,c] As part of our own synthetic studies in this area, we now describe a novel epoxide cyclisation approach to the formation of the bicyclic acetal skeleton of the zaragozic acids.



Scheme 1

As summarised in **Scheme 1**, our approach to constructing a reduced version **3** of the bicyclic acetal core **1** centred on the epoxide cyclisation reaction, **4** → **3**. We envisaged that the protonated epoxide **4** should allow nucleophilic opening at C_5 by the ketone with concomitant attack by the C_3–OH to generate the required bicyclic acetal. If successful, this simple process would serve to convert an open-chain system, containing all of the stereochemistry, into the highly functionalised 2,8-dioxabicyclo[3.2.1]octane core. We planned that this epoxide would be derived from **5** *via* hydroxyl-directed epoxidation at C_5 of the diene unit and dihydroxylation at C_3 / C_4. The adjacent oxygenated stereocentres (at C_6 and C_7) in this β-hydroxy ketone precursor **5** might then be installed together by a suitable aldol reaction.

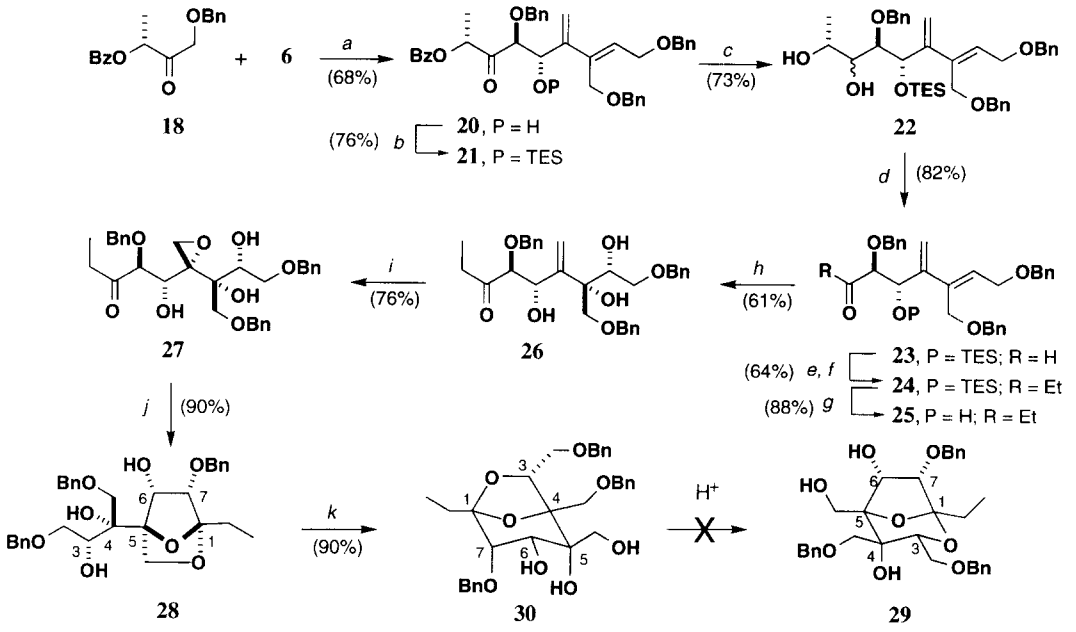
Before embarking on the synthesis of **4** with the correct R_1 sidechain for zaragozic acid C (**2**), we thought it prudent to first establish the viability of our cyclisation strategy on some model systems. As shown in **Scheme 2**,[5] the aldehyde **6** was prepared from the vinyl iodide **7**[6] by a high-yielding, Negishi-type coupling[7] (*n*-BuLi, $ZnBr_2$; $Pd(MeCN)_2Cl_2$, 10 mol%) with **8** to give the diene **9** (99%), followed by mild acetal hydrolysis. The ethyl ketone (*S*)-**10**[8] was initially selected to explore stereoregulated aldol additions with **6**. Due to the sensitive nature of aldehyde **6** (which required handling in Et_2O solution), a *syn* aldol with the Sn(II) enolate[8a] derived from **10** proved impractical. However, a boron-mediated aldol addition between the derived *E*-enol borinate **11** ($(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O)[8] and aldehyde **6** was successful, providing the *anti* isomer **12** with >97% ds in 68% yield from **9**. Although this model C_7-methylated adduct is now epimeric to that required for the acetal core **3**, it was anticipated that this stereocentre would play little or no part in the crucial cyclisation step.



Scheme 2: (*a*) **7**, *n*-BuLi, THF, –78 °C, 30 min; $ZnBr_2$, 2.5 h; **8**, DMF, $Pd(MeCN)_2Cl_2$ (10 mol%), –78 → 20 °C, 2 h; (*b*) 1 *M* HCl / THF (1:10), 20 °C, 4 h; (*c*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 3 h; **6**, –78 → –18 °C, 18 h; H_2O_2, MeOH, pH 7 buffer; (*d*) AD-mix-β [$(DHQD)_2PHAL$ (4 mol%), $K_2OsO_4.2H_2O$ (1 mol%)], *t*-BuOH / H_2O (1:1), 20 °C, 14 h; (*e*) $VO(acac)_2$ (20 mol%), TBHP, CH_2Cl_2, 20 °C, 20 min; (*f*) PPTS, MeOH, 20 °C, 14 h.

Attention was now focused on the regio- and diastereoselective introduction of the three oxygens into the diene portion of **12** using Sharpless asymmetric dihydroxylation (AD)[9,10] followed by epoxidation. By employing freshly prepared, enriched AD-mix-β[10a,b] (containing 4 mol% of $(DHQD)_2PHAL$ + 1 mol% of $K_2OsO_4.2H_2O$), triol **13** was obtained in 63% yield with >95% ds. This dihydroxylation reaction occurred only at the trisubstituted alkene.[10c] Completion of the synthesis of the first model substrate for cyclisation simply required hydroxyl-directed epoxidation of the remaining disubstituted alkene. Treatment of **13** with $VO(acac)_2$ / TBHP[11] in CH_2Cl_2 provided an equimolar mixture of epimeric epoxides **14** and **15** in 73% yield.

These were chromatographically separated and cyclisation conditions were then screened for each epoxide. Gratifyingly, treatment of **14** with PPTS in anhydrous MeOH provided the required bicyclic acetal **16** in 80% yield. The structure and stereochemistry of **16** were established by detailed 1-D and 2-D ^{1}H NMR experiments. In particular, $J_{6,7}$ = 7.7 Hz and strong NOEs were observed between H_3, H_6 and H_7, as required by the zaragozic acid core structure. Interestingly, the epimeric epoxide **15** proved to be inert under these mild cyclisation conditions.



Scheme 3: (*a*) (*c*-C_6H_{11})$_2$BCl, Me_2NEt, Et_2O, 0 °C, 3 h; **6**, −78 → −18 °C, 18 h; H_2O_2, MeOH, pH 7 buffer; (*b*) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 30 min; (*c*) $LiBH_4$, THF, −78 → 20 °C, 36 h; (*d*) $NaIO_4$, MeOH / pH 6.5 buffer (2:1), 20 °C, 1 h; (*e*) EtMgBr, THF, −78 → 0 °C, 2 h; (*f*) TPAP, NMO, CH_2Cl_2, 20 °C, 6 h; (*g*) HF.py, pyridine, THF; (*h*) AD-mix-β [(DHQD)$_2$PHAL (4 mol%), $K_2OsO_4.2H_2O$ (1 mol%)], $NaHCO_3$, *t*-BuOH / H_2O (1:1), 20 °C, 14 h; (*i*) $VO(acac)_2$ (20 mol%), TBHP, CH_2Cl_2, 20 °C, 20 min; (*j*) PPTS, MeOH, 20 °C, 2 h; (*k*) PPTS, $CHCl_3$, 60 °C, 12 h.

At this stage, we had demonstrated the viability of our epoxide cyclisation approach to a model zaragozic acid core. Notably, the transformation **14** → **16** proceeds under unusually mild acidic conditions, presumably occurring either directly *via* **17** or by rapid rearrangement of a kinetically generated acetal.[12] However, two problems needed to be addressed. Firstly, **16** lacks the required oxygen functionality at C_7. Secondly, the C_1 sidechain is not readily elaborated to that of zaragozic acid C (**2**). An efficient solution to both these issues presented itself by replacing **10** with the (*R*)-lactate-derived ketone **18** (**Scheme 3**).[13] Not only does **18** bear a protected oxygen for C_7, but it now also allows for the introduction of a sidechain equivalent nucleophile at C_1. Using our standard conditions,[13] a boron-mediated aldol addition of ketone **18** to aldehyde **6** gave the *anti* adduct **20** in 68% yield with >97% ds. Protection of the hydroxyl of **20** as its TES ether **21**, followed by $LiBH_4$ reduction, then gave diol **22** (73%). This glycol was readily cleaved using $NaIO_4$ (MeOH, pH 6.5 buffer) to provide aldehyde **23** in 82% yield. As a model for the zaragozic acid C sidechain, we elected to use a simple ethyl group (*i.e.* R_1 = Et in **Scheme 1**). Thus treatment of **23** with EtMgBr in THF followed by TPAP oxidation[14] afforded ethyl ketone **24** (64%). Alternatively, this same ketone could be obtained from **21** by reductive removal of the α-benzoate with SmI_2.[13] The TES group was then removed to provide alcohol **25**.

We now focused our attention on the controlled oxygenation of the diene portion of **25**. Enriched AD-mix-β was again used to dihydroxylate the trisubstituted alkene, where buffering the reaction mixture with $NaHCO_3$ was beneficial, allowing the isolation of triol **26** in 61% yield. In contrast to the earlier substrate **13**, epoxidation of **26** using $VO(acac)_2$ / TBHP was highly stereoselective and gave **27** as the only detectable isomer in 76% yield. Treatment of **27** with PPTS (MeOH, 20 °C, 2 h) promoted attack of the epoxide at C_5 by the C_1 ketone, where the resulting primary hydroxyl participated to form a kinetic acetal. On isolation, acetal **28** was only moderately stable to acidic conditions and underwent further rearrangement.[12] Upon treatment with either silica gel for 24 h, or by warming with PPTS to 60 °C in $CHCl_3$ for 12 h, **28** gave a more stable acetal. This proved not to be the required 2,8-dioxabicyclo[3.2.1]octane core **29** but the isomeric acetal **30**, whose structure was assigned by extensive NMR experiments ($J_{6,7}$ = 3.0 Hz, NOE between H_3 and H_6 but not H_7). Despite several attempts, prolonged acid treatment did not lead to any rearrangement in favour of **29**.

This competing cyclisation mode giving **30** is not unique to our approach to the zaragozic acid skeleton, having previously been encountered in model studies by both Heathcock[15] and Armstrong.[16] Clearly the factors governing which bicyclic acetal is generated are finely balanced. It is fortunate that we initially chose to explore the epoxide cyclisation chemistry of model substrate **15**, as this gave **17** without complication (*cf.* **Scheme 1**). Therefore, we conclude that a crucial factor operating is likely to be the steric demands of the C_1 sidechain. Large alkyl groups (as in **14**) tend to favour the desired bicylic acetal core, whereas smaller groups (*e.g.* Me or Et) appear to favour the isomeric acetal (*cf.* **27** → **28** → **29**). Studies to introduce the zaragozic acid C sidechain (which may be viewed as large) are currently underway.

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