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A symmetry-based approach to the heterobicyclic core of the zaragozic acids—model studies in the C_2-symmetric series

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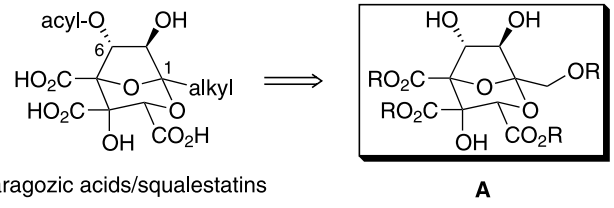
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 70th birthday

Abstract—A conceptually novel access to models for the title structures has been achieved by rapid enantioselective construction of polyhydroxy diketones in a two-directional or convergent fashion and group-selective intramolecular acetalization.

The zaragozic acids/squalestatins are a family of naturally occurring fungal metabolites isolated independently by three groups in 1991/1992.[1] These natural products are potent inhibitors of squalene synthase and *ras*-farnesyl protein transferase and additionally display significant activities toward a wide spectrum of yeast and fungal pathogens. All zaragozic acids have a densely oxygenated hydrophilic 2,8-dioxabicyclo[3.2.1]octane core differing only in the C(1) alkyl and C(6) acyl side chains (Scheme 1). Due to their structural complexity and their biological activities, they have stimulated enormous synthetic efforts. Thus, the total synthesis of several zaragozic acids has been accomplished, and many synthetic studies toward the heterobicyclic core as well as detailed investigations on structure–activity relationships have been carried out.[1]



zaragozic acids/squalestatins

A

Scheme 1. A general building block (**A**) for zaragozic acids/squalestatins.

We reasoned that compound **A** (Scheme 1) would represent a suitably functionalized general building block for the synthesis of naturally occurring zaragozic acids/squalestatins as well as unnatural analogs. A conceptually novel symmetry-based approach[2] to this heterobicyclic system is depicted in Scheme 2. Retrosynthetic disconnection of the acetal moiety of **A** leads to polyhydroxy ketone **B** featuring regions with local *meso* and C_2 symmetry. Expansion of the C_2 region within **B** by addition of a two-carbon unit to the ester terminus enhances molecular complexity, however, a pseudo C_2-symmetric diketone **C** is attained, which should be accessible by two-directional synthesis,[3] e.g. starting from a *meso* compound.[4] Diketone **C** might serve as a substitute for **B**, provided its intramolecular acetalization occurs chemoselectively and with simultaneous differentiation[5] of the two diastereotopic γ,ε-dihydroxy ketone moieties to give **D**. Finally, the superfluous appendage in **D** can be removed via a chemoselective oxidative cleavage to generate building block **A**.

For initial studies in line with the concept described above, we focused on the synthesis of the C_2-symmetric linear model compound **5** (Scheme 3). Whereas this higher symmetry assures the formation of a single acetal from the two equivalent γ,ε-dihydroxy ketone moieties, the question of chemoselectivity still remains. Indeed, prior work toward the heterobicyclic core of the zaragozic acids/squalestatins indicated that intramolecular acetalization could also proceed with participation of a δ,ε-dihydroxy ketone subunit.[1]

Keywords: zaragozic acids; heterocycles; dihydroxylation; metathesis; acetalization.
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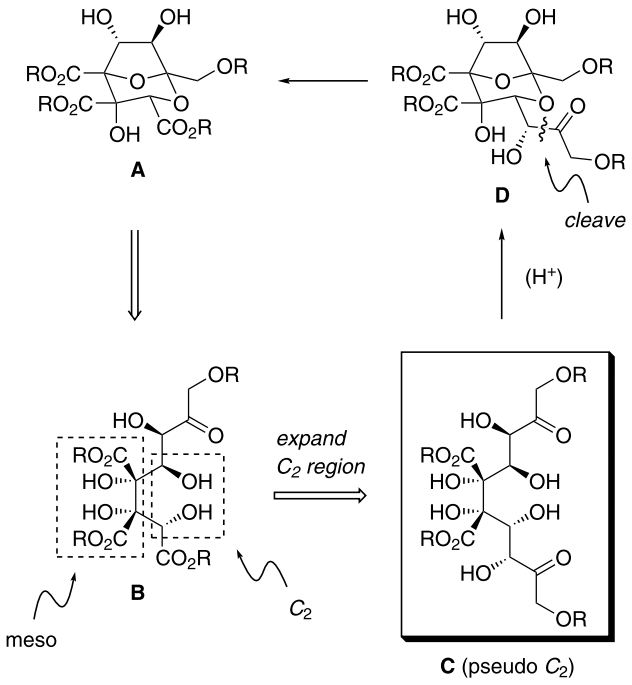


Scheme 2. Symmetry-based concept for the preparation of **A**.

As starting material, we chose diethyl tartrate derivative **1**.[6] The bis-Weinreb amide[7] **2** was efficiently secured in a one-pot process by two-directional chain elongation via sequential reduction/HWE[8] olefination.[9] In order to achieve high *anti* selectivity in the subsequent double dihydroxylation, TBDMS protection of the diol proved to be beneficial.[10] Thus, after conversion of the Weinreb amides to methyl ketones,[11] dihydroxylation of **3** with potassium osmate and potassium chlorate[12] afforded tetraol **4** efficiently. Fluoride-induced deblocking of the silyl ethers in **4** liberated the C_2-symmetric hexahydroxy diketone **5**. To our delight, stirring crude **5** (0.04 M) in concentrated HCl/THF (1/23) at ambient temperature for 80 min followed by peracetylation gave the desired model 2,8-dioxabicyclo[3.2.1]octane **9** with complete selectivity in excellent overall yield from **4**. Unambiguous proof of the structure **9** was accomplished by X-ray diffraction analysis of its enantiomer *ent*-**9** prepared from *ent*-**1** using exactly the same reaction sequence (Fig. 1).[13] Interestingly, treatment of diketone *ent*-**5** (0.1 M) derived from *ent*-**1** under conditions similar to those that were successful in generating the heterobicyclic core of the zaragozic acids/squalestatins from polyhydroxy monoketones (0.4 N HCl in MeOH, 21 h rt)[1] led instead to the pyrano[3,2-*b*]pyran **7** as a single stereoisomer after peracetylation in high yield. Structural elucidation of **7** was based on extensive 2D NMR experiments.

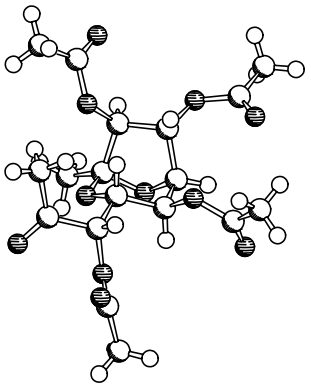
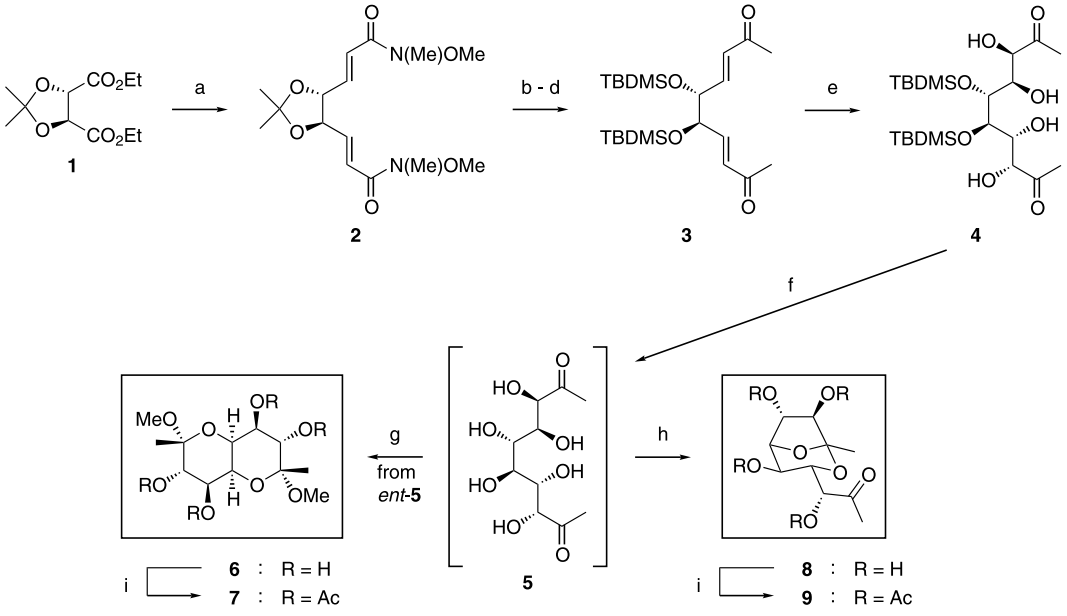
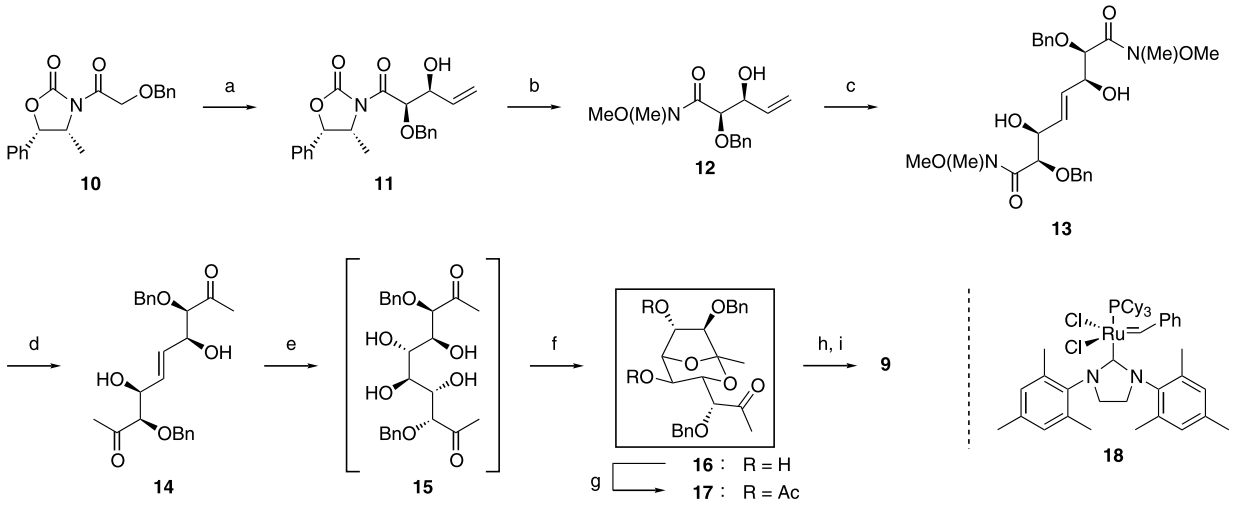


Figure 1. Crystal structure of heterobicyclic ketone *ent*-**9**.[13,14]



Scheme 3. *Reagents and conditions*: a: (i) DIBAL-H, toluene, −78°C, (ii) $(EtO)_2PO$-CH(Na)-CON(Me)OMe, DME, −78°C–rt, 80%; b: HOAc, H_2O, 60°C, 92%; c: TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C–rt, 96%; d: MeLi·LiBr, THF, 0°C, 94%; e: $K_2OsO_4{\cdot}2H_2O$, $KClO_3$, MeOH, H_2O, HOAc, rt, 88%; f: Bu_4NF, THF, rt; g: 0.4 N HCl, MeOH, rt; h: conc. HCl, THF, rt; i: Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 70% **7** from *ent*-**4**, 90% **9** from **4**.



Scheme 4. *Reagents and conditions*: a: (i) Bu_2BOTf, Et_3N, CH_2Cl_2, 0°C, (ii) acrolein, −78°C, (iii) buffer pH 7, MeOH, H_2O_2, 0°C, 92%; b: Me_3Al, MeONHMe·HCl, CH_2Cl_2, 0°C–rt, 81%; c: 2 mol% **18**, CH_2Cl_2, reflux, 89%; d: MeMgBr, THF, 0°C, 83%; e: $K_2OsO_4{\cdot}2H_2O$, $NaClO_3$, MeOH, H_2O, HOAc, rt; f: conc. HCl, THF, rt; g: Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 61% **17** from **14**; h: 1 atm H_2, 10% Pd/C, THF, rt; i: Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 72% **9** from **17**.

A strategically related access to a dibenzylated derivative of **8** is depicted in Scheme 4. In this alternative approach, the C_2-symmetric polyhydroxy ketone **15** is constructed in a convergent fashion using molecular duplication via olefin self-metathesis.[15] Evans aldol reaction[16a] of oxazolidinone **10**[16b] with acrolein[17] provided **11** as a single stereoisomer in excellent yield, the relative configuration of which was confirmed by X-ray diffraction analysis (Fig. 2).[13] Conversion of **11** to give the Weinreb amide **12** and subsequent treatment of **12** with the second generation Grubbs catalyst **18** smoothly furnished the homodimer **13** with complete *E* selectivity. Two-directional generation of the methyl ketone termini followed by dihydroxylation of the resulting olefin **14** and intramolecular acetalization of crude **15** using HCl in THF as before led to 2,8-dioxabicyclo[3.2.1]octane derivative **16**, which was isolated as diacetate **17**. The good overall yield of **17** from **14** indicates a pronounced *anti* selectivity for the dihydroxylation step. The structure of **17** was verified by detailed 2D NMR experiments and was additionally proven by debenzylation and acetylation to give tetraacetate **9**.

The crucial homodimerization was also investigated with oxazolidinone **11** and methyl ketone **20** that was readily secured from Weinreb amide **12** (Scheme 5). Whereas the bis-oxazolidinone **19** was formed with complete *E* selectivity, thus opening another avenue to isomerically pure **14**, self-metathesis of **20** turned out to be less stereoselective.

Finally, cleavage of the superfluous two-carbon appendage present in **9** was addressed (Scheme 6). Reduction of **9** with lithium aluminum hydride afforded a pentaol **21** that was subjected to chemoselective periodate cleavage[18] followed by Pinnick oxidation[19] of the resulting aldehyde **22** to give acid **23**. After peracetylation and treatment with 3-methyl-1-*p*-tolyltriazene,[20] methyl ester **24** was isolated in good overall yield from **9**.

In summary, we have developed two short and highly stereoselective symmetry-based routes to models for the heterobicyclic core of the zaragozic acids/squalestatins. Corresponding studies in the pseudo C_2-symmetric series are currently being performed in our laboratories.

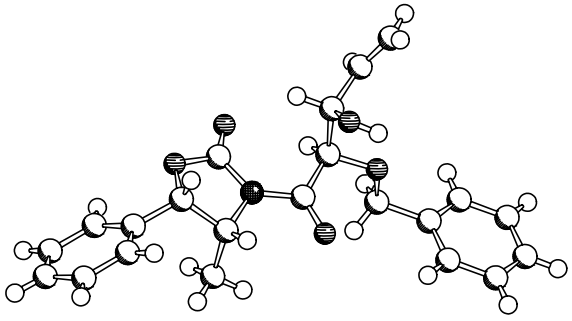
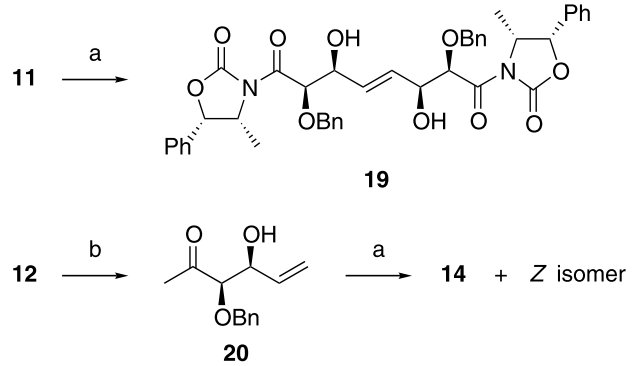
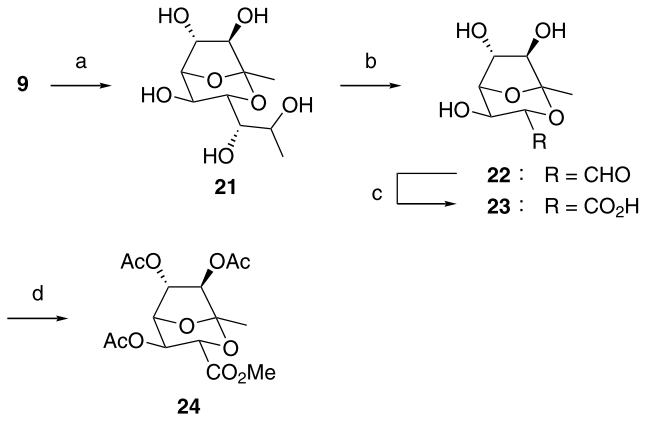


Figure 2. Crystal structure of aldol adduct **11**.[13,14]



Scheme 5. *Reagents and conditions*: a: 2 mol% **18**, CH_2Cl_2, reflux, 90% **19** from **11**, 94% **14** ($E/Z = 82/18$–$93/7$) based on 68% conversion from **20**; b: MeMgBr, THF, 0°C, 92%.



Scheme 6. *Reagents and conditions*: a: $LiAlH_4$, THF, reflux; b: $NaIO_4$, MeOH, H_2O, rt; c: $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, rt; d: (i) Ac_2O, DMAP, pyridine, rt, (ii) 3-methyl-1-*p*-tolyltriazene, EtOAc, rt, 29% **24** from **9**.

Acknowledgements

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13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 214333 (*ent*-**9**) and CCDC 214334 (**11**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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