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Studies towards a stereocontrolled synthesis of the tricarboxylate core of the zaragozic acids–squalestatins by a cycloaddition–rearrangement strategy

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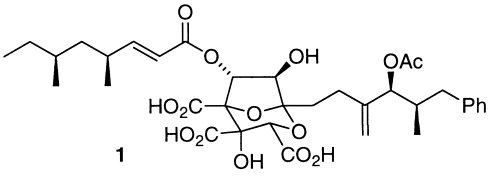
Abstract

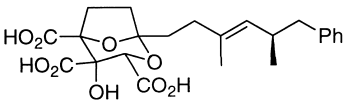
Reaction of diazoketodiester **11** with methyl glyoxylate in toluene in the presence of catalytic rhodium(II) acetate gives predominantly the 6,8-dioxabicyclo[3.2.1]octane **13**. Acid-catalysed rearrangement of the corresponding alcohol **14** favours at equilibrium the 2,8-dioxabicyclo[3.2.1]octane skeleton **15** of the zaragozic acids–squalestatins. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: zaragozic acids; cycloaddition; rearrangement; ylide.

The zaragozic acids–squalestatins [e.g. **1** (zaragozic acid A/squalestatin S1) and **2** (6,7-dideoxysqualestatin H5)] have attracted considerable attention from the synthetic community due to their novel structure combined with their biological activity (potent inhibitors of squalene synthase and farnesyl-protein transferase).[1]



1



2

In 1996 we reported an approach to the 2,8-dioxabicyclo[3.2.1]octane core of these natural products based on cycloaddition between a carbonyl ylide **4** from an α-diazo-β,ε-diketoester **3** and methyl glyoxylate (Eq. (1)).[2,3] The cycloadduct **5** was converted to a substrate which underwent acid-catalysed rearrangement to a 2,8-dioxabicyclo[3.2.1]octane **6** in which, however, incorrect relative stereochemistry (at C4 for zaragozic acid/squalestatin synthesis) originating from *endo* (with respect to the ylide-containing ring) cycloaddition had been preserved. As γ,δ-dialkoxy- (or

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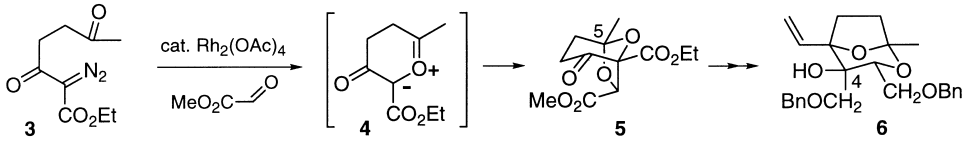
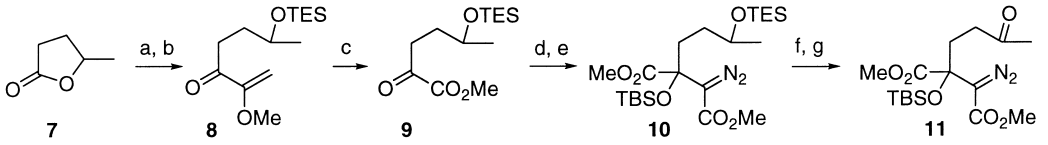
γ,δ-disilyloxy-) substituted variants of **3** failed to alter the propensity for undesired *endo* cycloaddition,[4] which, in the original system we suggested was due to preferred secondary orbital overlap between the ester carbonyl of the glyoxylate (in the *s-trans* conformation) and the ketone group of the ylide **4**,[2] we have examined modification of the ketone group of the ylide and report here our preliminary studies with such a system.



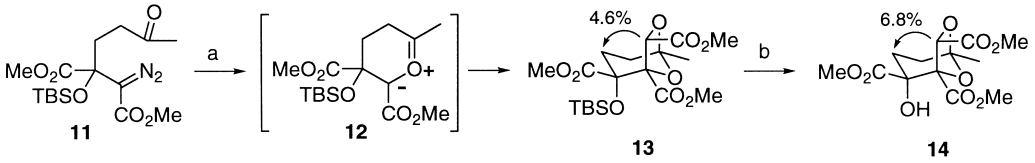
(1)

Cycloaddition substrate diazoketodiester **11**, designed to examine facial and *exo–endo* selectivity issues, was synthesised in seven steps from γ-valerolactone **7** (Scheme 1). Thus, reaction of lactone **7** with lithiated methyl vinyl ether[5] gave, following TES protection, enone **8**. Ozonolysis[6] of enone **8** gave α-ketoester **9** which was treated with lithiated methyl diazoacetate[7] to give the ether **10** (1:1 mixture of diastereomers) after tertiary alcohol protection. Selective deprotection and PCC oxidation of the intermediate secondary alcohol gave diazoketodiester **11**.



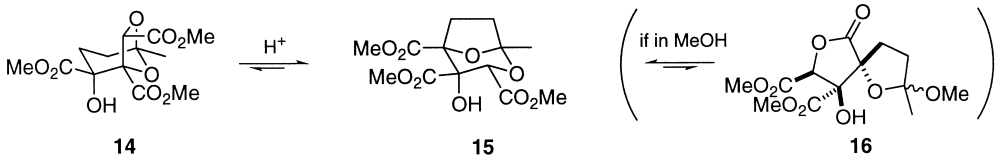
Scheme 1. *Reagents and conditions*: (a) methyl vinyl ether, Bu^{t}Li, THF, –78°C, 18 h (86%); (b) TESOTf, 2,6-lutidine, CH_2Cl_2, –78°C, 5 min (67%); (c) O_3, CH_2Cl_2:py (100:1), –78°C, 40 min, then Ph_3P (57%); (d) methyl diazoacetate, LDA, THF, –78°C, 30 min (62%); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 25°C, 4 days (72%); (f) AcOH:THF:H_2O (2:4:1), 25°C, 1 h (76%); (g) PCC, NaOAc, CH_2Cl_2, 25°C, 16 h (90%)

Diazoketodiester **11** underwent $Rh_2(OAc)_4$-catalysed cycloaddition with methyl glyoxylate to give a major cycloadduct **13** (65%, Scheme 2) and two minor cycloadducts [ratio of major (**13**) to minor isomers: 12:1:1]. The stereochemistry of the major isomer **13** was assigned as that required for zaragozic acid/squalestatin synthesis. Data supporting the cycloaddition regioselectivity in cycloadduct **13** are ketal carbon C5 [δ_C 110.2 (δ_C 111.0 for C5 in **5** of established[2] structure)] HMBC connectivities with C4–H_2 and C5–Me. The facial selectivity was initially assigned on the basis of similar facial selectivity in related cycloadditions described by Hashimoto and co-workers,[8] and the fact that cycloaddition of the corresponding (less sterically demanding) TMS ether (**11**, TBDMS = TMS) showed lower facial selectivity (8:1:1). For cycloadduct **13** an NOE between C7–H and one H of C3–H_2 (4.6%) indicated the desired *exo* orientation of the glyoxylate-derived ester group. The predominant stereochemical outcome of the cycloaddition of methyl glyoxylate with diazoketodiester **11** can be tentatively rationalised as follows: Replacement of the β-keto group found in α-diazo-β,ε-diketoester **3** with the comparatively bulky α-silyloxy ester functionality in diazoketodiester **11** leads to an ylide **12** where cycloaddition preferentially occurs on the less-hindered face (opposite to the silyloxy group), with the methyl glyoxylate orienting itself to avoid steric interactions between its ester group and the ester group of the α-silyloxy ester functionality. Deprotection of cycloadduct **13** gave alcohol **14** for studying the acid-catalysed isomerisation.



Scheme 2. *Reagents and conditions*: (a) methyl glyoxylate, cat. $Rh_2(OAc)_4$, toluene, reflux, 1 h (65%); (b) TBAF, THF, 25°C, 15 min (74%)

No reaction of alcohol **14** was observed with 2% HCl in $CHCl_3$ (reflux, 15 h), or with triflic acid in d_6-DMSO (25°C, 4 days).[9] Using CSA in MeOH (reflux, 24 h) or 2% HCl in MeOH[10] (reflux, 15 h) gave the first signs of isomerisation to the core **15**, although spirolactone **16** was also observed[11] in both cases (**14**:**15**:**16**, 83:13:4 and 69:21:10, respectively, Eq. (2)). Triflic acid in $CDCl_3$ (25°C, 4 days) gave a 75:25 ratio of alcohol **14** to core **15**; however, prolonged exposure (68 h) to Evans' conditions (CH_2Cl_2:TFA:H_2O, 20:10:1)[12] at reflux were found to favour the core structure (**14**:**15**, 33:64, 54% of **15** isolated, 83% based on recovered **14**). That true equilibrium had been reached was established by subjecting core **15** to these latter reaction conditions, which resulted in the same ratio of alcohols **14**:**15**. For **15**, NOEs between C3–H and one H of C6–H_2 and one H of C7–H_2 (5.8 and 6.9%, respectively) served to confirm the facial selectivity in the *exo* cycloaddition step.



(2)

Molecular mechanics calculations for **14** and **15** using the MM2* force field[13] lead to the prediction that **15** should not be observed at equilibrium (the computed energy difference between global minima is 27 kJ mol^{-1}). However, it is known that the MM2* force field underestimates the energy of 1,3-dioxolanes (such as the bridged 1,3-dioxolane in **13**) compared to 1,3-dioxanes (such as **15**), because it ignores important transannular O,C-destabilising electrostatic interactions in 1,3-dioxolanes; such interactions are included in the calculations for 1,3-dioxanes because the relevant atoms are now in a 1,4 relationship.[9] Interestingly, the experimentally observed 33:64 ratio of **14** and **15** is correctly predicted (1:2, **14**:**15**) using the MM2* with the 1,4-electrostatic interactions scaled to 70% (this scaling factor was used since it leads to agreement between the computed and experimentally observed ratio for a simple 2,8- 6,8-dioxabicyclo[3.2.1]octanol equilibrium,[9] where the 6,8- system is favoured).

Extension of the studies to the fully oxygenated (6,7-dioxy) core of the zaragozic acids-squalestatins and to 6,7-dideoxysqualestatin H5 will be reported in due course.

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