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A Cycloaddition–Rearrangement Approach to the Squalestatins

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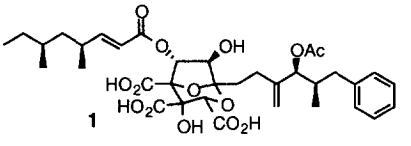
Abstract: Reaction of diazodiketoester **4** with methyl glyoxylate in toluene in the presence of catalytic rhodium(II) acetate generates the 6,8-dioxabicyclo[3.2.1]octane **5** as a single regio- and stereo-isomer in good yield. Elaboration provides a suitable alcohol **7** for acid-catalysed rearrangement to give the 2,8-dioxabicyclo-[3.2.1]octane skeleton **8** of the squalestatins. Copyright © 1996 Elsevier Science Ltd

First reported in 1992, the squalestatins / zaragozic acids [*e.g.* **1** (squalestatin S1 / zaragozic acid A)] have since become the focus of intense synthetic interest.[2] These natural products are important therapeutic leads for the treatment of hypercholesterolemia and fungal infections and, in addition, possess a structurally novel and synthetically challenging densely functionalised 2,8-dioxabicyclo[3.2.1]octane core.



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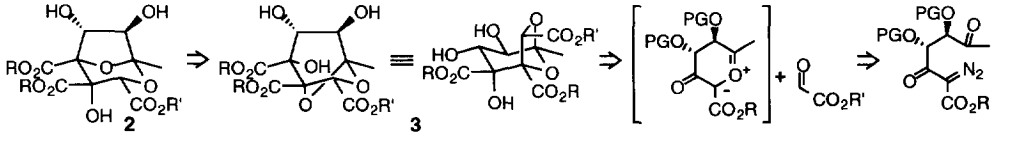
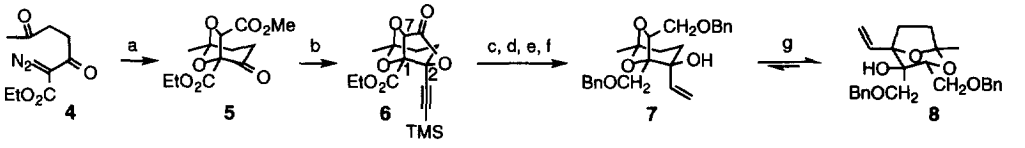
Analysis of the anhydrofuranose core **2** suggested that it might be formed by acid-catalysed rearrangement of anhydropyranose **3** (Scheme 1, PG = protecting group). We envisaged that the anhydropyranose **3** could arise from a 1,3-dipolar cycloaddition,[3] followed by a ketone to hydroxy acid conversion.



Scheme 1

In order to examine this chemistry, initially in a racemic model study,[4] the known and readily prepared diazodiketoester **4**[3] was reacted with freshly distilled methyl glyoxylate[5] in the presence of catalytic $Rh_2(OAc)_4$ in refluxing toluene (Scheme 2). We were delighted to find that under these conditions clean cycloaddition took place to give a single cycloadduct **5** (60%).[6] X-ray crystallographic analysis[7] of the cycloadduct **5** indicated that cycloaddition had occurred in the desired regiochemical sense, but that the *endo*

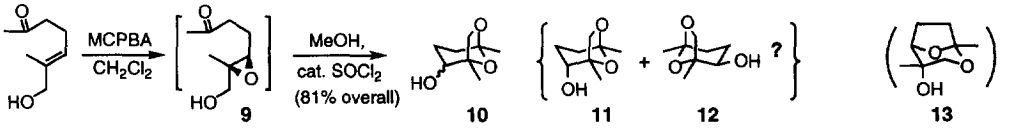
isomer (with respect to the ylid-containing ring) had been produced. Reproducibly good yields for this step contrast with recently reported work using the same diazodiketoester **4** with aromatic aldehydes.[8] Good yields in the present case may be due to the use of a highly electron deficient aldehyde which could result in an energetically favourable LUMO (dipolarophile) - HOMO (dipole) interaction.[9] We attribute the *endo* selectivity observed with a glyoxylate to preferred secondary orbital overlap[9] between the ester carbonyl of the glyoxylate (in the *s-trans* conformation) and the ketone group of the ylid; overlap with the side-chain ester group of the ylid is less effective.



(a) methyl glyoxylate, cat. $Rh_2(OAc)_4$, toluene, reflux, 0.5 h (60%); (b) TMSC≡CLi, THF, –78 °C, 1 h (80%); (c) K_2CO_3, wet DMF, 25 °C, 3 h (98%); (d) H_2 (1 atm.), Pd/C, 25 °C, 2 h (quant.); (e) $LiAlH_4$, Et_2O, 25 °C, 24 h (67%); (f) NaH, BnCl, cat. NaI, DME, 0 °C to 25 °C (52%); (g) 2% HCl in MeOH, 25 °C, 0.25 h.

Scheme 2

Although the incorrect relative stereochemistry (for squalestatin / zaragozic acid synthesis) had been set up in this step, the excellent selectivity in this cycloaddition encouraged us to pursue a modified strategy with cycloadduct **5**. This first involved using the *endo* ester substituent in the cycloadduct **5** to effectively block the upper face of the ketone to external nucleophiles. This aspect, together with the normal propensity for axial attack by sterically small nucleophiles in conformationally biased cyclohexanones, resulted in reaction of the cycloadduct **5** with lithium trimethysilylacetylide (to introduce a masked form of the remaining carboxylic acid unit) to give exclusive formation of the lactone **6** (80%). At this stage we had installed the desired relative stereochemistry at C2 and C7 in the lactone **6**, but now required an inversion of stereochemistry at the C1 position in the lactone **6**, together with the originally planned 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement. We considered that precedent for configurational instability at such a position might be found in a study by Johnston and Oehlschlager towards frontalin (Scheme 3).[10]

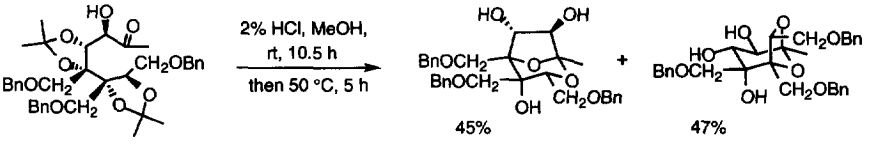


Scheme 3 (Johnston and Oehlschlager's study)[10]

On treatment of the labile epoxide **9** with MeOH / cat. $SOCl_2$, Johnston and Oehlschlager observed two products (ratio reported after 1 h at rt, 1.5:1; after 18 h at rt, 15:1) which they assigned to an isomeric axial / equatorial alcohol mixture **10** (major isomer not specified). We interpreted this mixture **10** to consist of alcohols **11** and **12**, since configurational instability (if it occurred) would have been expected at the tertiary (rather than the secondary) centre. We repeated their work but isolated only one product, which gave ^1H nmr data consistent with that published for the major isomer. We have assigned the structure of this product to the 6,8-dioxabicyclo[3.2.1]octane **11** on the basis of NOE studies.[11] This result provided a possible precedent in our system for equilibration to the desired axial alcohol (compare anhydropyranose **3** in Scheme 1). However,

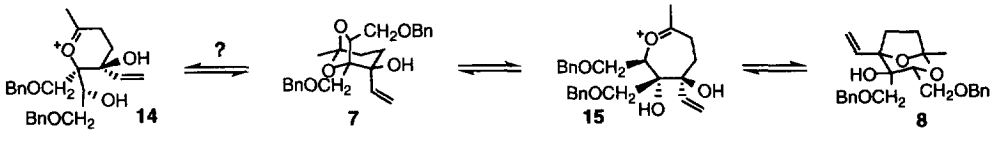
since the relative configuration between C1 and C2 in the 6,8-dioxabicyclo[3.2.1]octane **11** could arise from the epoxide **9** by a simple intramolecular 'S_N2' opening of the epoxide at the tertiary position by the ketone group, our results do not prove configurational instability at the tertiary centre in this system. Finding the 6,8- rather than the 2,8-dioxygenated skeleton was favoured in this system was an additional concern to us in the context of our squalestatin synthesis. However, Nicolaou and co-workers have reported that more functionalised / oxidised systems favour the 2,8-structure.[12]

In the event, subjecting the alcohol **7** (Scheme 2), chosen to be capable of stabilising a potential carbocation at C1, to the rearrangement conditions in Scheme 3 gave no scrambling of stereochemistry at C1 but instead reproducibly gave the rearranged alcohol **8** (60%), along with recovered starting alcohol **7** (**7**:**8**, 1:3). The stucture of **8** was assigned on the basis of an extensive ^{1}H nmr study.[13] That true equilibrium had been reached was established by subjecting alcohol **8** to the reaction conditions, which resulted in the same ratio of alcohols **7**:**8**. In another recently reported study towards the squalestatins, configurational instability does not seem to have been observed in a system where potentially it might occur (Scheme 4).[14]



Scheme 4 (Armstrong and Barsanti's study)[14]

The results obtained in our system are most simply explained by equilibration through the seven-membered ring oxonium ion **15** (Scheme 5).[12b,15] The six-membered ring oxonium ion **14** must not, if formed, proceed to undergo the desired epimerisation. The evidence brought together in the present paper also suggests that the minor isomer observed by Johnston and Oehlschlager is unlikely to be the alcohol **12**, but more likely the unepimerised alcohol **13** (Scheme 3).[16,17]



Scheme 5

Assessment of the factors which are significant in controlling formation of a 2,8- or 6,8-dioxabicylo[3.2.1]octane where both can exist in principle under equilibrating conditions is not straightforward.[18] Efforts to understand these factors and to manipulate the stereochemistry obtained in carbonyl ylid cycloadditions are currently underway.

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10. Johnston, B. D.; Oehlschlager, A. C. *Can. J. Chem.* **1984**, *62*, 2148-2154.
11. The 3,5-dinitrobenzoate derivative of **11** showed an NOE between C2-H and one H of C7-H_2.
12. (a) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467-494; (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim. 1996: pp. 673-709.
13. In the dimethylene unit of alcohol **8**, the *trans* ^3J values (5.0 and 4.5 Hz) are consistent with this unit residing in a five- (rather than six-) membered ring (*e.g.* Aggarwal, V. K.; Wang, M. F.; Zaparucha, A. *J. Chem. Soc., Chem. Commun.* **1994**, 87-88). In a NOESY spectrum of alcohol **8**, no cross-peaks were observed between either of the two CH_2OBn groups and the dimethylene unit. However, cross-peaks were observed between the dimethylene unit and C3-H, and between CH_2=C*H* and one H of C4-CH_2OBn.
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15. Equilibration *via* a (comparatively strained) 2,7-dioxabicyclo[2.2.1]heptane formed from ion **14** is also possible in our system.
16. δ_H 3.51 (1H, dd, *J* 12, 2), 3.67 (1H, d, *J* 12) and 4.07 (1H, dd, *J* 7, 2) reported for the minor isomer[10] are consistent with C3-H_{eq}, C3-H_{ax} and C5-H respectively in alcohol **13** [w-coupling (2 Hz) between C3-H_{eq} and C5-H; ^3J coupling (7 Hz) between C5-H and C6-H_{exo}]. These data are inconsistent, however, with equatorial alcohol **12**.
17. The change in the major : minor isomer ratio after 1 h and 18 h reported in this earlier study (and inversion at the tertiary centre only) is consistent with the epoxide **9** initially forming a six-membered ring oxonium ion (similar to **14**) which then partitions between alcohols **11** and [*via* a 2,7-dioxabicyclo[2.2.1]heptane (Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267-2268)] **13**. Alcohols **11** and **13** may prefer to interconvert by a seven-membered ring oxonium ion similar to **15**.
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