The First Synthesis of the Novel 2,8-Dioxabicyclo[3.2.1]octane Ring System: a Key Feature of the Squalestatins

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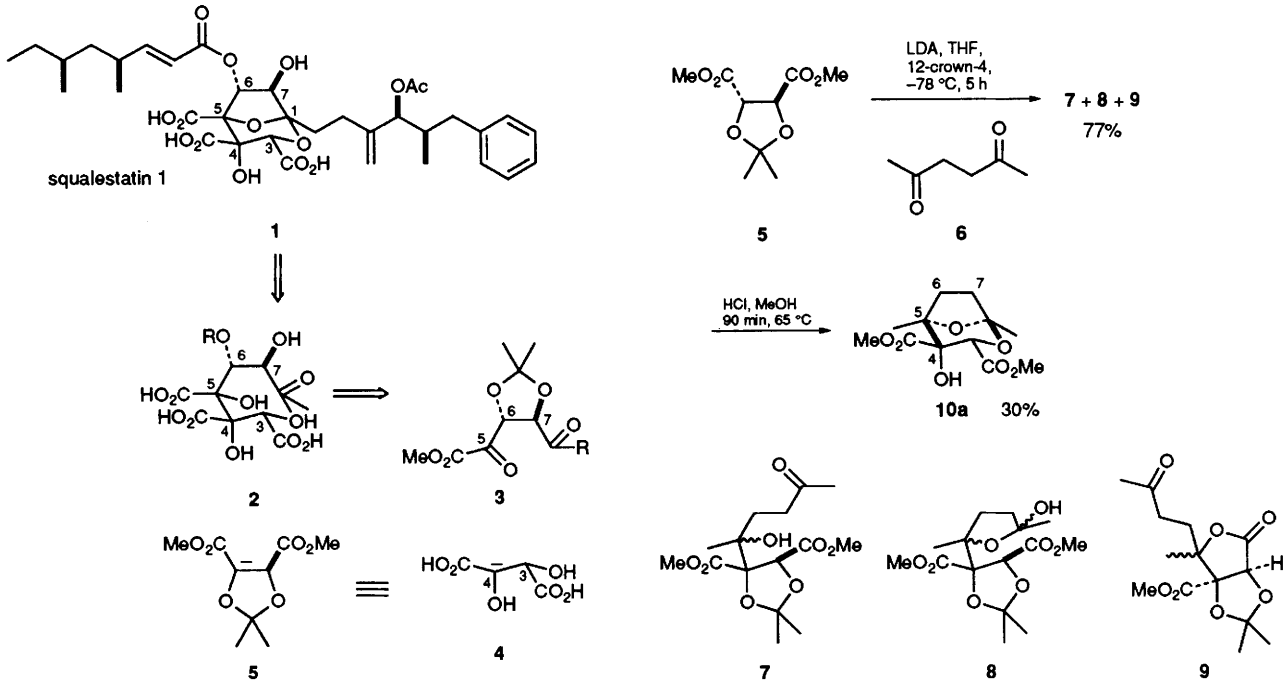
The lithium enolate of the acetonide of (*S,S*)-dimethyl tartrate **5** was prepared by treatment with lithium diisopropylamide in the presence of 12-crown-4, and added to acetonylacetone **6**; reaction of the product with acid gave a mixture of cyclised adducts from which a single diastereoisomer was isolated and shown to have a structure consistent with the core of squalestatin.

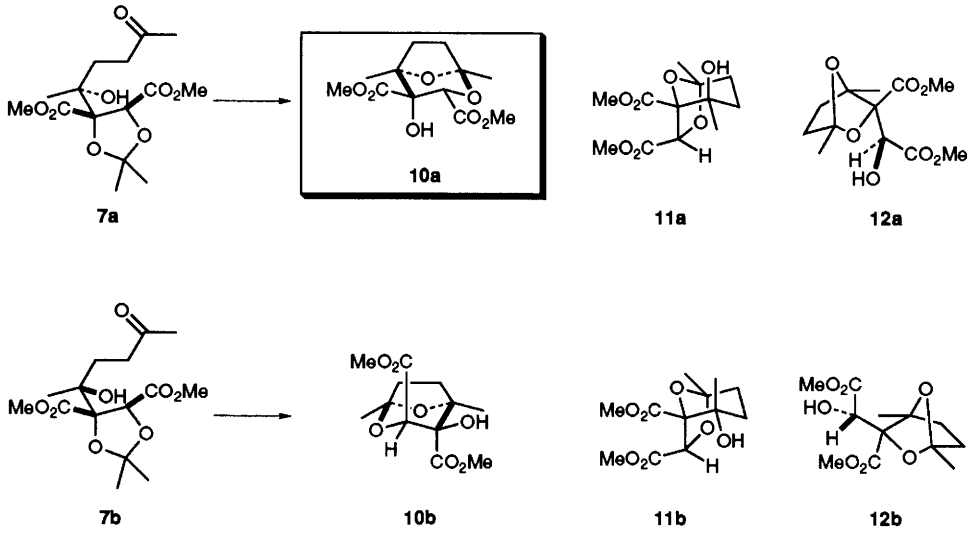
The squalestatins are a newly discovered class of fungal metabolites that exhibit very high levels of activity against the enzyme squalene synthetase.[1–5] The absolute stereochemistry of squalestatin 1 has recently been determined[2,3] and is as shown (**1**). A common distinguishing feature of this family of compounds is the highly functionalised, novel 2,8-dioxabicyclo[3.2.1]octane ring system. This unique, highly oxidised, bicyclic ring system make this novel structural class a formidable challenge to the synthetic chemist. In considering a total synthesis of squalestatin 1 we considered initial disconnection of the ketal at position 1 to give **2** followed by a disconnection that would require the addition of synthon **4** to the α-keto ester **3**. A potential reagent that could correspond to synthon **4** could be the enolate of the acetonide of (*S,S*)-dimethyl tartrate **5**. In order to test the feasibility of this approach we decided to carry out an analogous anion reaction with a simpler ketone (**6**) but one which retained sufficient functionality to allow formation of the bicyclic core of the squalestatins.

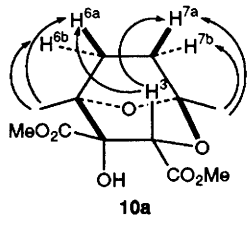
Anion reactions of the tartaric acid derivative **5** have been studied by Seebach[6,7] and he found that alkylations and aldol reactions with symmetrical ketones (*e.g.* acetone) worked well giving good ratios of adducts in reasonable yield provided hexamethylphosphoric triamide (HMPA) or dimethylpyrrolidineurea (1,3-dimethyl pyrrolidin-2-one, DMPU)[8] was used as cosolvent.

We have carried out a similar reaction between the anion of **5** and acetonylacetone **6**. Under similar conditions to those described in the literature [lithium diisopropylamide (LDA), HMPA or DMPU][6–8] we obtained only low yields of adducts (5–10%). Even varying the base resulted in little improvement in yield. It was not clear whether the problem lay in formation of the lithium enolate or the reactivity of the enolate or indeed both. As the role of HMPA in reactions of lithiated anions is thought to be to help solvate the lithium counter-ion and generate more ionic and therefore more reactive species (and not to break up aggregates)[9] we reasoned that such promotion of LDA reactivity or enolate reactivity could also be obtained using 12-crown-4. There is surprisingly little in the literature on the use of 12-crown-4 to facilitate reactions of lithiated anions and yet such use would obviate the need for using the highly carcinogenic HMPA.

In the event, reaction between the anion of **5** and acetonylacetone **6** in the presence of 12-crown-4 gave a 24% yield of a mixture of isomeric adducts. Using an excess of the tartrate anion (5 equiv.) this yield rose to 77%. There were at least four isomers present: possibly various diastereoisomers of **7**, **8** and **9**, but it was not possible to determine the relative ratios of these products at this stage. This mixture was treated with acid and cyclisation ensued to give the bicyclic core of squalestatin **10a**.† It was found that heating for intermediate periods of time (1–3 h; 2 h was optimum) gave the highest yield (30% from the mixture of **7**, **8** and **9**) of essentially a single diastereoisomer. Shorter periods did not allow complete equilibration to occur; presumably **10a**, **11a** and **12a** are formed but only slowly equilibrate to the thermodynamically more stable product **10a**. Prolonged heating resulted in lower yields of mixtures of cyclised adducts. This latter observation can be easily rationalised by assuming that, of the mixture of diastereoisomers at C-5 (obtained in the anion reaction), one of them (**7a**) cyclises rapidly to give the all-equatorial cyclised adduct whereas the other diastereoisomer (**7b**) cyclises more slowly to give the less stable adducts **10b** or **11b**.







The structure and relative stereochemistry of the cyclisation product were confirmed by ^{1}H–^{13}C correlation and by NOE difference analysis (see below). Whilst the NOE confirms the relative stereochemistry of the cyclisation product (**10a** and **10b**) it does not unambiguously distinguish between **10a**, **11a** and **12a**, all of which might show similar NOEs. However, the *trans*-vicinal coupling constants [J_{6a7b} (4.5 Hz), J_{7a6b} (5.5 Hz)] are too low for diaxial protons in a six-membered ring but are consistent with coupling constants in five-membered rings. This discounts structures **11a/b**. The strong NOE from 3-H to 6a-H and 7a-H together with the complete absence of NOEs from either of the methyl ester groups to the same protons and the absence of an NOE from 3-H to one of the methyl groups suggests that **12a/b** is not the structure of the adduct. More conclusively, the NMR spectrum of the adduct recorded in $(CD_3)_2SO$ shows the OH proton as a singlet whereas the OH of methyl mandelate (an α-hydroxy ester) appears as a doublet. This evidence together with the negative NOE data allows us to discount structures **12a/b**. Thus, we conclude that the structure obtained in the cyclisation is **10a**.

In summary we have developed a short asymmetric synthesis of the bicyclic core of the squalestatins. Whilst the stereochemistry of the addition process is not very selective the commercial availability of the two starting materials coupled with ease of carrying out his chemistry make it an attractive approach to the squalestatins themselves.

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Footnote

† Data for the cyclised adduct **10a** (Found M^+ −59 *m/z* 215.0919. $C_{10}H_{15}O_5$ 215.2190); δ_H (250 MHz; $CDCl_3$) 1.25 (3 H, s, Me), 1.62 (3 H, s, Me), 1.75 (1 H, ddd, *J* 5.5, 12.5 and 13.9 Hz, 6b- or 7b-H), 2.03 (1 H, ddd, *J* 4.5, 12.5 and 14.0 Hz, 7b- or 6b-H), 2.16 (1 H, ddd, *J* 5.5, 9.5 and 14.0 Hz, 7a- or 6a-H), 2.81 (1 H, ddd, *J* 4.5, 9.5 and 13.4 Hz, 6a- or 7a-H), 3.50 (1 H, brs, OH), 3.70 (3 H, s, CO_2Me), 3.82 (3 H, s, CO_2Me) and 4.86 (1 H, s, 3-H); δ_C (62.9 MHz; $CDCl_3$) 19.91 (Me), 23.66 (Me), 31.56 (6-C or 7-C), 34.04 (7-C or 6-C), 52.58 (OMe), 52.94 (OMe), 74.99 (2-C), 75.85 (5-C or 4-C), 85.91 (4-C or 5-C), 107.34 (1-C), 168.33 (CO) and 170.64 (CO); *m/z* (EI) 215 (M^+ −59) and 115 (M^+ −159, 100%).

References

1 A. Baxter, B. J. Fitzgerald, J. L. Hutson, A. D. Mccarthy, J. M. Motteram, B. C. Ross, M. Sapra, M. A. Snowden, N. S. Watson, R. J. Williams and C. Wright, *J. Biol. Chem.*, 1992, **267**, 11705.
2 P. J. Sidebottom, R. M. Highcock, S. J. Lane, P. A. Procopiou and N. S. Watson, *J. Antibiotics*, 1992, **45**, 648.
3 K. E. Wilson, R. M. Burk, T. Biftu, R. G. Ball and K. Hoogsteen, *J. Org. Chem.*, 1992, **57**, 7151.
4 J. D. Bergstrom, M. M. Kurtz, D. J. Rew, A. M. Amend, J. D. Karkas, R. G. Bostedor, V. S. Bansal, C. Dufresne, F. L. Vanmiddlesworth, O. D. Hensens, J. M. Liesch, D. L. Zink, K. E. Wilson, J. Onishi, J. A. Milligan, G. Bills, L. Kaplan, M. N. Omstead, R. G. Jenkins, L. Huang, M. S. Meinz, L. Quinn, R. W. Burg, Y. L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M. T. Diez and A. W. Alberts, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 80.
5 C. Dufresne, K. E. Wilson, D. Zink, J. Smith, J. D. Bergstrom, M. Kurtz, D. Rew, M. Nallin, R. Jenkins, K. Bartizal, C. Trainor, G. Bills, M. Meinz, L. Y. Huang, J. Onishi, J. Milligan, M. Mojena and F. Pelaez, *Tetrahedron*, 1992, **48**, 10221.
6 R. Naef and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 1030.
7 D. Seebach, J. D. Aebi, M. Gandercoquoz and R. Naef, *Helv. Chim. Acta*, 1987, **70**, 1194.
8 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385.
9 F. E. Romesberg, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.*, 1991, **113**, 5751.