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The squalestatins: tricyclic 3,4-β-lactone and 3,4-oxetane systems

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Abstract

Squalestatin 3,4-β-lactone-4,5-dimethyl ester (**8**) was reductively ring-opened to yield squalestatin 3-hydroxymethyl-4,5-dimethyl ester (**6**) using mild reducing conditions (sodium borohydride). Similarly, squalestatin 3,4-oxetane-4,5-dimethyl ester (**10**) was found to ring-open to 3-iodomethyl squalestatin (**15**) under the conditions used to cleave the methyl ester functions (lithium iodide/2,4,6-trimethylpyridine).

Squalestatin **1**, a member of a family of novel fungal metabolites, is a potent inhibitor of squalene synthase (SQS), with an IC_{50} value of 12 nM against rat enzyme.[1] Workers at Merck isolated zaragozic acid A, which is identical to squalestatin **1**.[1] Extensive studies have been undertaken in order to identify the structural features necessary for SQS inhibitory activity and a number of reports have detailed chemistry undertaken around the 3 and 4 positions of the ring,[1] including the synthesis and biological evaluation of the 3-hydroxymethyl derivative of **1** and a series of close analogues.[2,3] We report herein some interesting findings around the formation and reactivity of β-lactones and oxetanes with potential application to other systems.

The 3-hydroxymethyl compound **2** is routinely prepared in a four-step process from **1**,[2] by esterification (to **3**), selective methyl ester hydrolysis at the 3-position (to **4**), activation as the 3-*N*-hydroxysuccinimidyl ester **5** and selective reduction of the 3-carboxylate function by in situ treatment with sodium borohydride to give **6** (55% yield **5** to **6**) (Scheme 1). Alternatively, the 3-*N*-hydroxysuccinimidyl ester **5** can be isolated, purified by column chromatography and then treated with sodium borohydride. Selective cleavage of the methyl ester groups within **6** is achieved under very mild conditions by treatment with lithium iodide in 2,4,6-trimethylpyridine at 45°C under a stream of nitrogen, resulting in the desired dicarboxylic acid **2**.[4] An alternative

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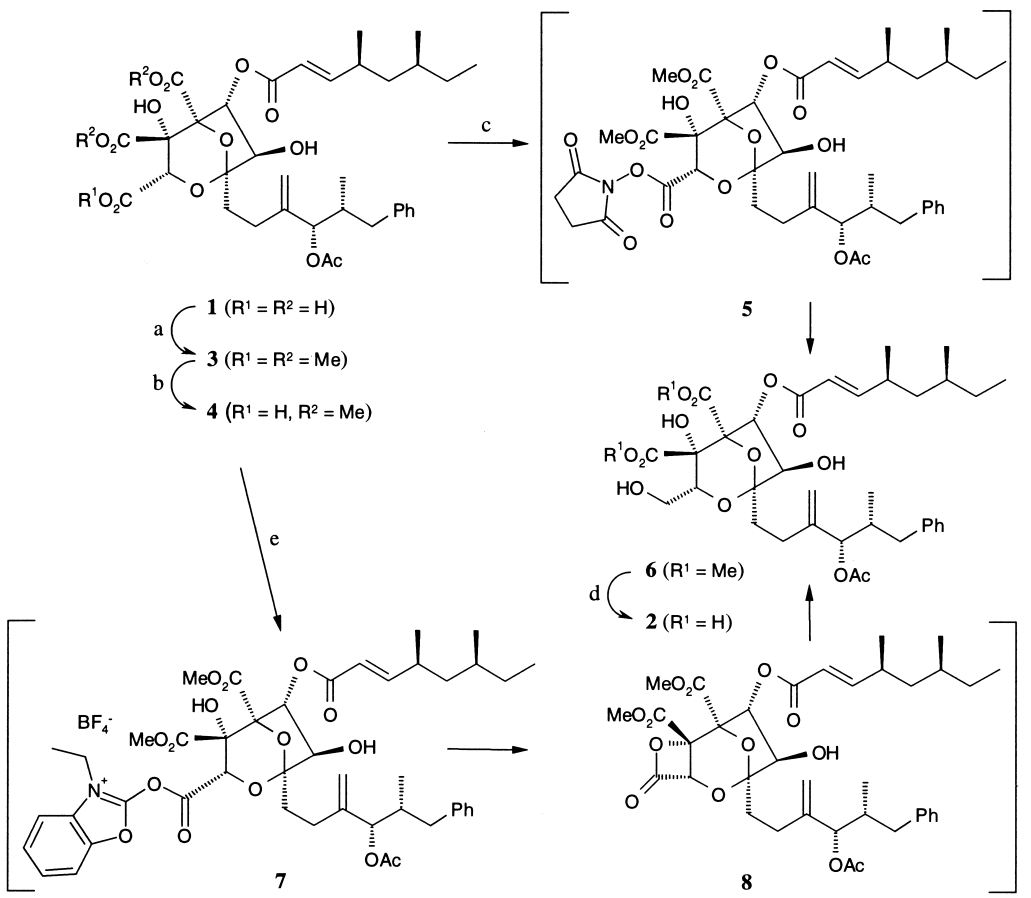
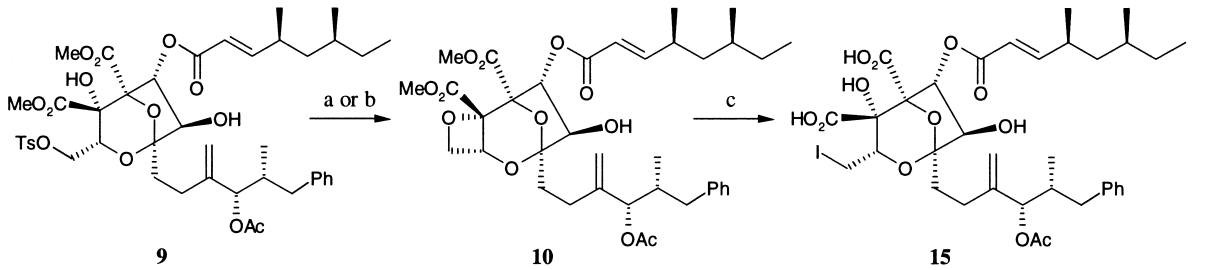
method for reduction of the 3-carboxylic acid **4** involves its activation using 2-chloro-3-ethylbenzoxazonium tetrafluoroborate, followed by addition of sodium borohydride in THF, to give **6** in ~25% yield. Interestingly, during the formation of the presumed carboxylate species **7**, prior to the addition of the sodium borohydride, the generation of a less-polar product was observed on TLC. Repeating the procedure with work-up after the first stage allowed the isolation and structural elucidation of this product, which was found to be the 3,4-β-lactone **8**.[5,6] Treatment of the β-lactone **8** with sodium borohydride resulted in the formation of the 3-hydroxymethyl compound **6**. This suggests that the β-lactone is formed as an intermediate in the one-pot reduction using 2-chloro-3-ethylbenzoxazonium tetrafluoroborate. In the literature, there are only two references[7] to the use of sodium borohydride for the reduction of β-lactones to 1,3-diols, which is normally accomplished by the use of more powerful reducing agents such as lithium aluminium hydride. Workers at Merck have also described[8] the preparation of a 3,4-β-lactone employing benzene sulfonyl chloride as an activating agent.



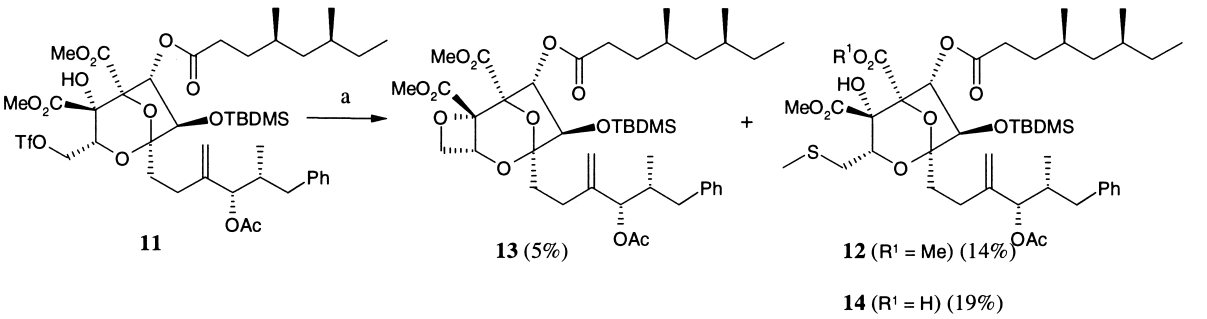
Scheme 1. (a) MeI, $NaHCO_3$, DMF, 90%; (b) 0.1 M aq. NaOH, THF, 100%; (c) (i) *N*-hydroxysuccinimide, 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-*p*-toluenesulfonate, THF, (ii) $NaBH_4$, THF, 55%; (d) LiI (anhydrous), 2,4,6-trimethylpyridine, 45°C, 48%; (e) (i) 2-chloro-3-ethylbenzoxazonium tetrafluoroborate, Et_3N, DCM, (ii) $NaBH_4$, THF, 25%

Studies directed towards the derivatisation of the 3-hydroxymethyl compound **6** revealed further unexpected chemistry around the 3 and 4 positions. Firstly, when evaluating approaches

to the 3-methyl compound, the 3-(4-methylbezenesulfonate) **9**[9] was subjected to a variety of reducing conditions, and surprisingly the only product from these reactions was the 3,4-oxetane derivative **10** (Scheme 2). The ease of formation of this product was confirmed by treatment of **9** with base.[6] Furthermore, during the preparation of the 3-thiomethyl ether **12**, by the treatment of the 3-trifluoromethylsulfonate **11**[10] with sodium thiomethoxide, formation of the oxetane **13** was observed as a significant side product (Scheme 3). Attempts to deprotect the oxetane **10** to give the di-acid using our standard lithium iodide conditions described earlier gave another surprising product, the 3-iodomethyl, di-acid **15** resulting from the ring opening of the oxetane (Scheme 2).[11] The conditions usually associated with ether cleavage, even cyclic ethers, are relatively harsh, e.g. aq. HBr or aq. HI at elevated temperature. However, there have been several examples reported of oxetane ring opening using iodides, e.g. silyl iodides[12] (TMS iodide generated in situ from TMS chloride and sodium iodide) or by Lewis acid mediated methods[13] (tetraethylammonium iodide/BF_3 etherate).



Scheme 2. (a) Zn/NaI, DME (11% yield of **10**) or Bu_3SnH/NaI (37% yield of **10**); (b) *t*-BuOK, THF (30% yield of **10**); (c) LiI (anhydrous), 2,4,6-trimethylpyridine, 45°C, 13%



Scheme 3. (a) $NaSCH_3$, DMF

The relative ease of reduction of **8** and the ring-opening of **10**, both under mild conditions, may be attributed to the relief of strain and steric interaction associated with the 4,6,5 ring system, further studies are planned to investigate whether these findings can be extended into other systems.

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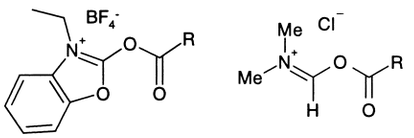
4. A modification of the method of Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1960**, *43*, 113.
5. The intermediate formed from 2-chloro-3-ethylbenzoxazonium tetrafluoroborate can be regarded as analogous to that of the Vilsmeier reagent that has also been used for ester formation (e.g. Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675) and the reduction of carboxylic acids to alcohols (e.g. Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* **1983**, *6*, 835).



6. A key feature associated with the fused 4,6,5 ring systems in the ^{1}H NMR ($CDCl_3$) of the 3,4-β-lactone and 3,4-oxetane is the downfield shift of the 6-H; 5.81 ppm in **3**, 5.83 ppm in **6**, 6.22 ppm in **8** and 5.99 ppm in **10**. This downfield shift is presumably attributable to the intramolecular effect of the 4-methyl ester assuming a pseudo-axial position, rather than a pseudo-equatorial position in the compounds without the four membered ring.
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9. Synthesised from **6** (tosyl chloride, DCM, pyridine, 70%).
10. Synthesised in four steps from **3**: (i) 1,4-reduction of the α,β-unsaturated ester with concomitant saponification of 3-methyl ester ($NaBH_4$, $MeOH/CuSO_4$, H_2O, 61%), (see Ref. 2a); (ii) TBDMS protection of 7-hydroxy group (TBDMSCl, imidazole, DMF, 30%); (iii) reduction of 3-carboxylic acid function (*N*-hydroxysuccinimide, DCC, $DCM/NaBH_4$, THF, 41%); (v) triflate formation at 3-hydroxymethyl group (triflic anhydride, 2,4,6-trimethylpyridine, DCM, 56%).
11. ^{13}C NMR chemical shift for $-CH_2I$; $\delta = 5.5$ppm (CD_3OD).
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