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Synthesis of the C-1 Sidechain of the Squalestatins and Zaragozic Acid A.

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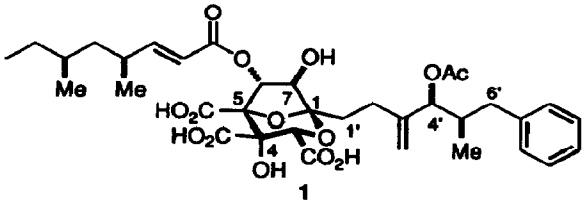
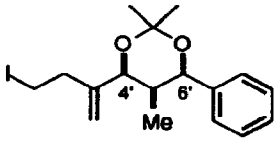
Abstract: *A synthesis of a protected C-1 side chain precursor (2) of the anti-cholesteremic agents the squalestatins and zaragozic acid A has been achieved in 9 steps from 1,4-butanediol. The key transformations involve a one pot oxidation/α-methylenation sequence to provide the α,β-unsaturated aldehyde 4 and subsequent asymmetric aldol reaction to introduce the C-4' and C-5' stereocentres.*

Squalestatin-1[1] (zaragozic acid A)[2] (**1**) is representative of a group of fungal metabolites that have been identified as inhibitors of squalene synthetase, the enzyme which catalyses the dimerisation of farnesyl diphosphate to squalene in steroid biosynthesis.[3] These compounds possess *in vivo* activity[4] and show potential for use in the treatment of hypercholesteremia in humans. In an overall plan to synthesise the squalestatins and analogues, we envisage a convergent approach in which the anion derived from a suitably protected C-1 sidechain precursor, such as iodide **2**, is coupled to a γ-lactone followed by subsequent mild acid promoted ring closure. In analogy to a synthesis of the C-1 sidechain reported by Evans,[5] dissolving metal reduction would then effect removal of the benzylic oxygen and acetonide protecting group. We have recently described a synthetic approach to the bicyclic core in which the C-5 stereocentre is set by an ester-enolate Claisen rearrangement conducted on a D-mannose derivative.[6,7] Acid hydrolysis of a silyl ether and concomitant ring closure gave a bicycle in which the model sidechain utilised was an allyl group.[6] Other synthetic studies on the bicyclic core system have also been reported.[8,9,10]



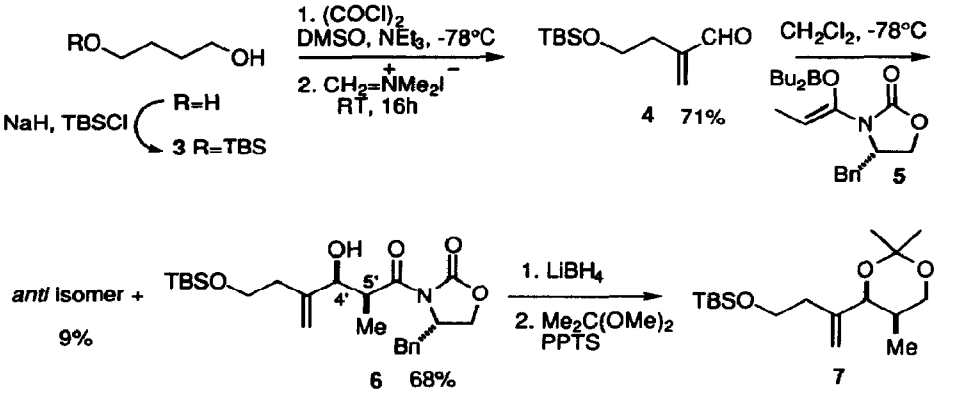
1



2

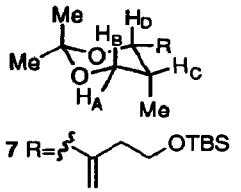
Our approach to the required precursor **2** began with the monosilyl ether **3**[11] derived from 1,4-butanediol (Scheme I). Swern oxidation followed by *in situ* methylenation[12] using Eschenmoser's salt gave the α,β-unsaturated aldehyde **4**[13] in good yield after flash chromatography. An Evans aldol reaction between the aldehyde **4** and the boron enolate **5**[14] then gave the desired 4',5'-*syn* adduct **6** (d.e. 76%) along with a small amount of the *anti* isomer.

Scheme I



Evidence for the stereochemical outcome of the aldol reaction rested on ^{1}H NMR studies conducted on the acetonide **7** derived from oxazolidinone **6** by reduction and acetonisation. The small coupling constants observed between H_C and H_D (Figure 1) as well as between H_B/H_A and H_C supported the *syn* stereochemistry depicted.

Figure 1



Coupling Constants

J_{AB} = 11.6 Hz

J_{AC} = 2.8 Hz

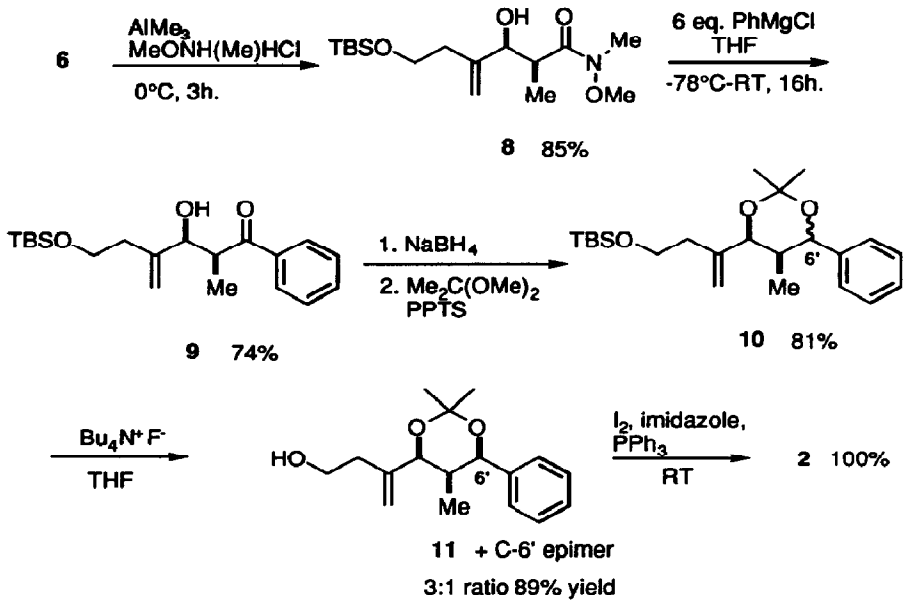
J_{CD} = 1.8 Hz

J_{BC} = 1.5 Hz

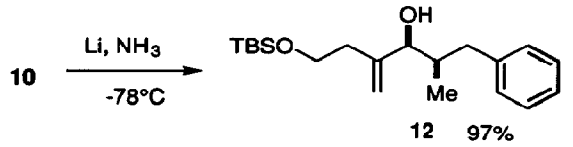
Transamidation[15] of the alcohol **6** yielded the Weinreb amide **8**[16] (Scheme II) which upon treatment with an excess of phenylmagnesium chloride at -78°C followed by warming to room temperature gave the monoadduct **9**.[17] It should be noted that under these conditions the reaction proceeded to completion without epimerisation at C-5'. In contrast, epimerisation was observed when the addition of the Grignard reagent to the hydroxyamide **8** was conducted at 0°C. Reduction of the phenyl ketone **9** followed by acetalisation gave the acetonide **10** as an inseparable 3:1 mixture at C-6'. Desilylation of the ethers **10** then provided the alcohol **11** (67%) and the C-6' (22%) epimer which were easily separable by flash chromatography. The stereochemical assignment of the major alcohol **11** was based on the ^{13}C NMR chemical shifts measured for the acetonide C(2)-methyl carbons (δ 19.5 and 29.9) and the C(2)-acetal carbon (δ 99.4). These values are in agreement with

the expected shifts for a *syn*-1,3-diol-acetonide.[18] Conversion of the alcohol **11** into the desired iodide **2** was then effected in quantitative yield by the agency of I_2, Ph_3P and imidazole in MeCN/ether.[19]

Scheme II



Reduction of the mixture of acetonides **10** with lithium in liquid ammonia at -78°C cleanly provides the correctly functionalised sidechain **12** as previously reported.[5] The iodide **2** is currently being utilised as a protected surrogate for the side chain of the squalestatins/zaragozic acid A and efforts toward coupling the derived anion with a suitable core system are currently underway.



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