A Synthetic Approach to Squalestatin 1

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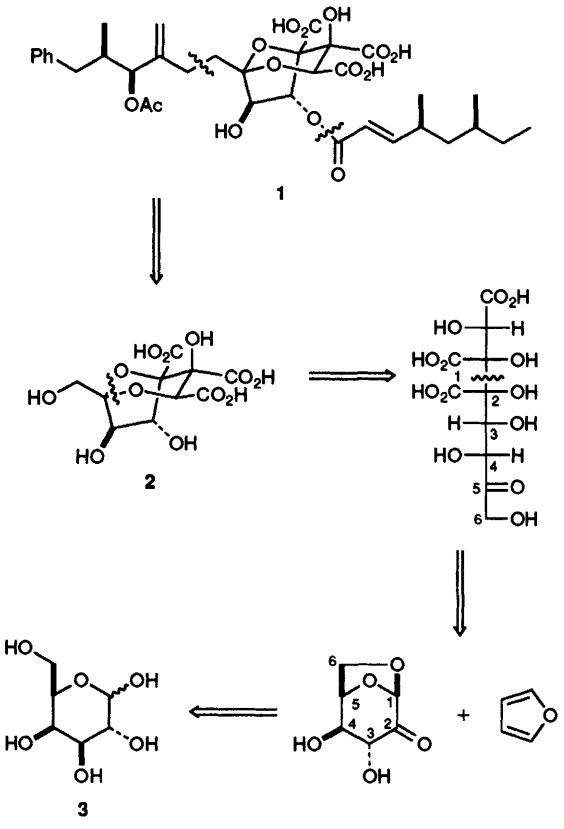
D-(+)-1,6-Anhydrogalactose **4** has been converted into the γ-lactone **16** *en route* to squalestatin 1.

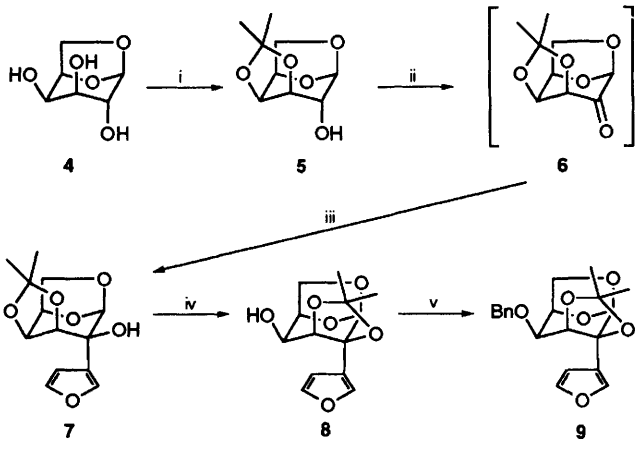
Elevated serum cholesterol levels have been shown to be a high risk factor for atherosclerosis.[1] Inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, such as lovastatin, are effective therapeutic agents for the lowering of cholesterol in man.[2] Recently inhibitors of the enzyme squalene synthase, which is responsible for the conversion of farnesyl diphosphate into squalene *via* presqualene diphosphate, have come under scrutiny as another potential route for controlling cholesterol levels.

Researchers at Glaxo Group Research have isolated a novel series of fermentation products, designated the squalestatins, which are potent selective inhibitors of squalene synthase enzymes.[3] This communication will deal with our initial results for the synthesis of the novel 2,8-dioxabicyclo[3.2.1]octane core of squalestatin 1 (**1**).

Our retrosynthetic analysis of the core **2** of squalestatin 1 which contains six contiguous stereogenic centres (two of which are quaternary) immediately suggested a convergent

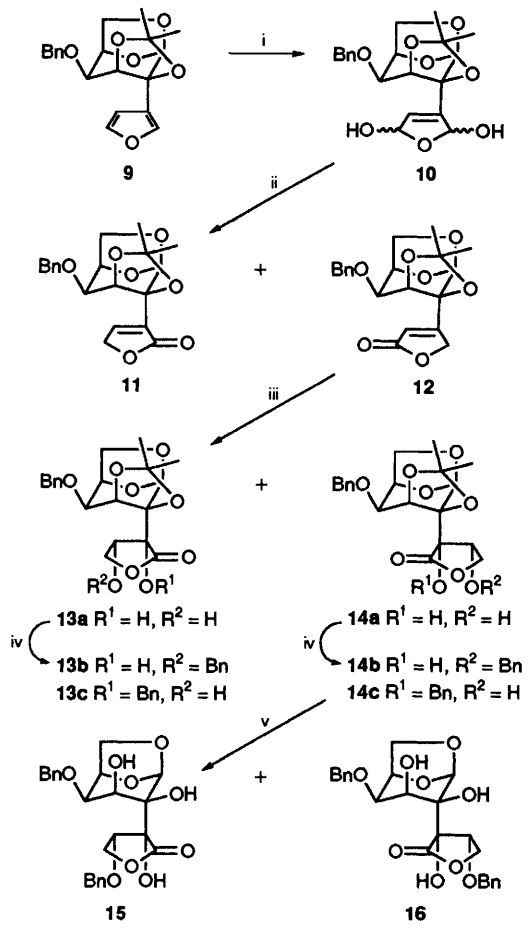


Scheme 1



Scheme 2 *Reagents and conditions*: i, Me_2CO, *p*-TsOH; ii, THF, $(COCl)_2$, DMSO, −60 °C, add **5** then warm to −20 °C cool to −78 °C then add Et_3N, warm to 0 °C; iii, 3-bromofuran, Bu^nLi, THF, −78 °C (ii and iii, 93%); iv, Me_2CO, *p*-TsOH (97%); v, DMF, NaH, BnBr (93%) (*p*-TsOH = *p*-$MeC_6H_4SO_3H$; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; DMF = dimethylformamide; Bn = $PhCH_2$)

synthesis utilising a carbohydrate moiety together with a four-carbon fragment. The four-carbon fragment could be introduced using a furan derivative, which would lend itself to further synthetic manipulation. The required carbohydrate could be a derivative of either D-(+)-gulose or D-(+)-idose as both have the required configurations at the C-3, C-4 and C-5 positions. However, we envisaged that D-(+)-galactose **3** offered a better starting point since 1,6-anhydro-D-(+)-galac-



Scheme 3 *Reagents and conditions*: i, Me_2CO, pyridine, H_2O, Br_2, −20 °C (72%); ii, 10% HCl(aq), Me_2CO (**11**, 73%; **12**, 22%); iii, OsO_4, pyridine (95%); iv, DMF, Ag_2O, BnBr (**13b** and **14b**, 47%; **13c** and **14c**, 15%); v, HCl(aq), MeOH, reflux (**15**, 46%; **16**, 52%).

tose **4** (which possesses considerable steric bulk on the β-face) would allow greater control during the nucleophilic addition of the furan fragment. The stereochemistry at C-3 could be inverted at a later stage.

D-(+)-1,6-Anhydrogalactose **4** is commerically available, but it was found to be more economic to prepare it from D-(+)-galactose **3** using the methodology outlined by Kloosterman.[4] The C-3 and C-4 hydroxy groups were protected as the 3,4-*O*-isopropylidene derivative **5**. The furan ring was introduced using 3-lithiofuran, which was itself prepared from furan *via* 3-bromofuran.[5] Swern oxidation of the C-2 hydroxy group proceeded smoothly. On isolating the ketone **6** it was found that the hydrated form of the ketone was preferred and therefore a one-pot procedure for oxidation–addition was adopted similar to that used by Ireland in synthetic studies towards polyether ionophore antibiotics.[6] Hence, slow addition of the reaction mixture obtained after Swern oxidation (cooled to −78 °C, transferred *via* cannula) to 3-lithiofuran at −78 °C resulted in the furan adduct **7** being isolated cleanly and in high yield. Care was taken to ensure that the 3-lithiofuran solution did not warm to above −40 °C, as at this temperature rearrangement to 2-lithiofuran could occur. It was found to be most efficient to remove the THF *in vacuo* and redissolve the reaction mixture in acetone in the presence of a trace of toluene-*p*-sulfonic acid. This caused a migration of the isopropylidene moiety to the C-2, C-3 positions to give compound **8**. The C-4 hydroxy group was protected to afford the corresponding benzyl ether **9**.

The furan ring was subsequently oxidized using bromine in acetone–water to give **10**.[7] Treatment of an acetone solution of **10** with 10% hydrochloric acid gave the α- and β-butenolides, **11** and **12**, in the ratio of 3 : 1 respectively. It was later found that treatment of the furan derivative with *N*-bromosuccinimide in water–THF gave the diol **10** after 5 min, whereupon removal of the THF *in vacuo* followed by dilution of the residue with diethyl ether–acetone and treatment with hydrochloric acid (2 mol l^{-1}) provided the α- and β-butenolides in highly satisfactory yields of 63 and 24% respectively.

cis-Dihydroxylation of the α-butenolide **11** was achieved using a stoichiometric amount of osmium tetroxide in pyridine[8] [reactions using catalytic amounts of osmium tetroxide in the presence of NMO (*N*-methylmorpholine *N*-oxide) were unfruitful]. Two inseparable diastereoisomers, **13a** and **14a**, were obtained in a 1 : 1 ratio. The mixture of diastereoisomers was treated with benzyl bromide in the presence of silver(I) oxide to give four products, namely the tertiary alcohols, **13b** and **14b** (47%), and the secondary alcohols, **13c** and **14c** (15%). The two inseparable diastereoisomers, **13b** and **14b**, were treated with 10% hydrochloric acid (2 mol l^{-1}) in methanol and boiled at reflux to remove the isopropylidene protecting group and afford the isomers **15** and **16** (98%)† which were separated by flash chromatography. The triol **15** was crystallised from methanol to give needle-like crystals which were suitable for single crystal X-ray analysis.[9] It was found that **15** has the *R* configuration at C-3′ and the *S* configuration at C-4′, hence **16** possesses the desired *S* and *R* configurations at C-3′ and C-4′ respectively.

The strategy of utilising D-(+)-galactose **3** to build the core structure of squalestatin 1 has led to the advanced intermediates **11**, **12** (see next communication) and **16** with the latter having the correct absolute stereochemistry in all but one of the stereogenic centres.

† Mp 109 °C (MeOH) {Found *m/z* (CI, NH_3) $[M + H]^+$ 459.1655. $C_{24}H_{26}O_9$ requires $[M + H]^+$ 459.1646}; $[\alpha]_D^{35}$ −32.9 (*c* 0.70, $CHCl_3$); ν_{max}/cm^{-1} 3529 (OH), 3005, 2979, 2908, 1784 (CO_2R), 1453, 1370, 1334, 1138, 1096, 1030, 992 and 974; δ_H (250 MHz; $CDCl_3$ + D_2O) 7.40–7.20 (10 H, m), 5.26 (1 H, d, *J* 1.2 Hz), 5.16 (1 H, dt, *J* 5.0 Hz, 1.2 Hz), 4.80–4.55 (4 H, 2 × ABq, *J* 11.9, 11.5 Hz), 4.49 (1 H, t, *J* 6.0 Hz), 4.44 (1 H, br. apparent t, *J* 5.2 Hz), 4.35–4.26 (2 H, m), 4.14–4.01 (2 H, m), 3.59 (1 H, br. dd, *J* 7.2 and 5.2 Hz); δ_H (250 MHz; $CDCl_3$) 4.15–4.08 (2 H, m, 4 H and OH), 3.54 (1 H, s, OH), 3.19 (1 H, d, *J* 1.8 Hz, OH); δ_C (62.9 MHz; $CDCl_3$) 172.77 (C), 137.63 (C), 136.44 (C), 128.66 (CH), 128.62 (CH), 128.18 (CH), 128.10 (CH), 127.95 (CH), 101.93 (CH), 76.42 (C), 74.40 (CH), 73.61 (CH), 73.03 (CH), 72.99 (C), 72.43 (CH_2), 72.00 (CH_2), 68.83 (CH_2), 65.48 (CH), 64.54 (CH_2).

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9 The X-ray crystallographic data for **15** will be published elsewhere.