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Synthetic Studies Towards the Squalestatins and Zaragozic Acids.

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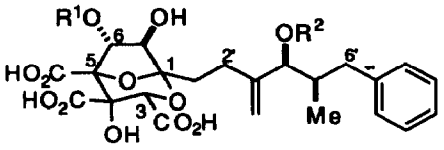
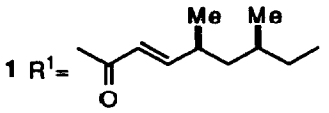
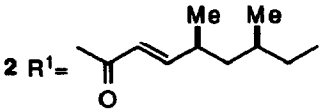
Abstract: *A synthesis of a model core system (18) of the squalestatins and zaragozic acids has been achieved from D-mannose. The key steps involve an Ireland-Claisen rearrangement of the allyl ester 5 and a stereoselective epoxidation of the furanoid glycal 12 with 2,2-dimethyldioxirane.*

A number of structurally related compounds have been isolated by two independent groups in screening programs for inhibitors of squalene synthase, the enzyme which catalyses the first pathway-specific step in sterol biosynthesis. These agents were named the squalestatins-1 (**1**), -2 (**2**) and -3 (**3**) (isolated from the fungus *Phoma* sp. C2932)[1] and the zaragozic acids A (**1**), B and C (isolated from the two fungal cultures *Sporormiella intermedia* and *Leptodonitium elatius*).[2] The structures were assigned by a combination of chemical degradation and NMR spectroscopy and finally confirmed by X-ray crystallographic analysis of various derivatives.[1,2,3] Squalestatin-1 (**1**) inhibits squalene synthesis *in vivo*[4] and therefore shows potential for use as a cholesterol lowering agent in humans.



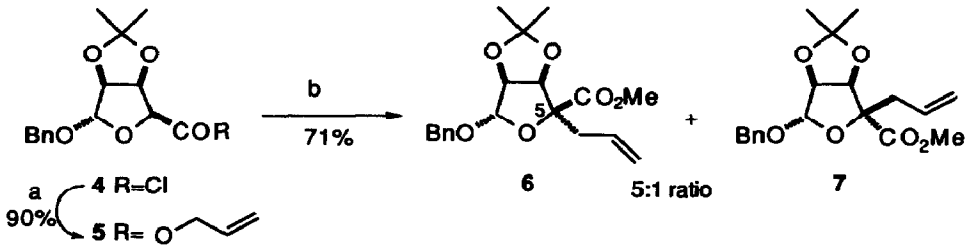




3 R^1=H R^2=Ac

The 2,8-dioxabicyclo[3.2.1]octane core common to all these compounds is rare in nature[5] and is highly substituted. Our synthetic approach to the core begins with the known acid chloride **4**, (Scheme I) available in 6 steps from D-mannose.[6] It was our intention to first set the C-5 stereochemistry by an ester enolate Claisen rearrangement[7] and towards this goal the derived allyl ester (**5**)[8] of **4** was subjected to an

Ireland-Claisen rearrangement under slightly modified conditions.[9] Methylation of the crude mixture of acids and flash chromatography provided the ester **6**[10] and the C-5[11] epimer **7** in a 5:1 ratio in 71% yield. The structures of these compounds were tentatively assigned on the basis of their ^{1}H NMR spectra and this assignment was supported by the conversion of the major ester **6** into the 2,8-dioxabicyclo[3.2.1]octane **18** (*vide infra*).



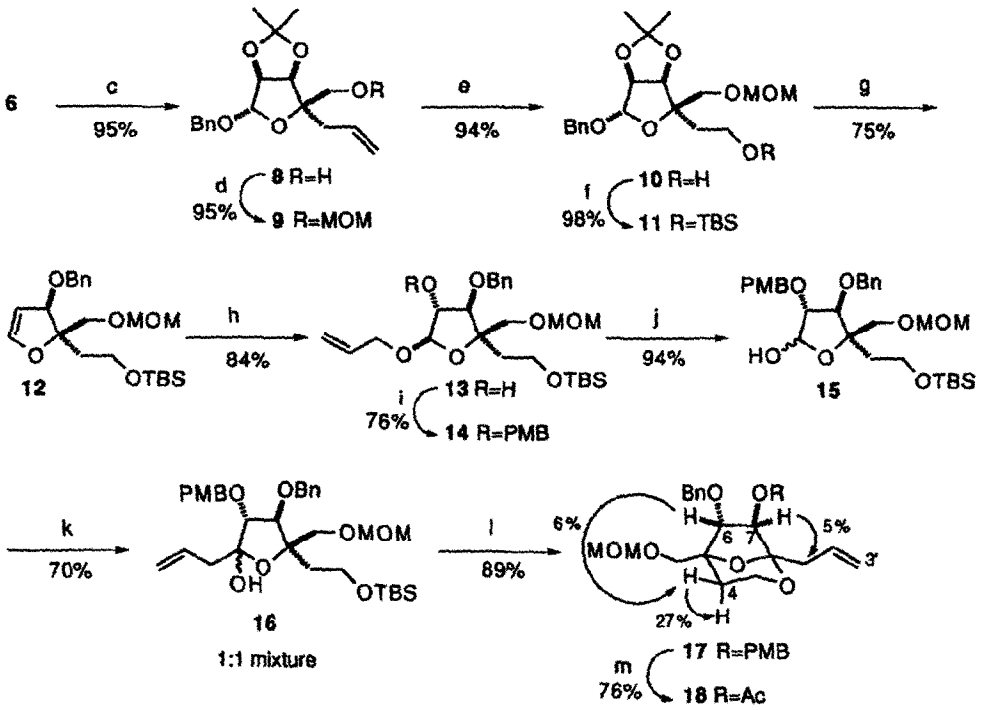
Scheme I[a]

[a]Key: (a) Allyl alcohol, DMAP, CH_2Cl_2 (b) LDA, TMSCl, HMPA/THF, -100°C-RT; CH_2N_2

With ester **6** in hand we then conducted a study towards the synthesis of a model core system (Scheme II). Reduction of **6** with $LiAlH_4$ gave the alcohol **8** which was protected to afford the MOM ether **9**. Oxidative cleavage of the terminal double bond and reduction provided alcohol **10** which on silylation yielded the ether **11**. Debenzylation then gave a lactol which was transformed into the furanoid glycal **12** by chlorination, reductive elimination[6] and benzylation. To our delight, treatment of the glycal **12** with anhydrous 2,2-dimethyldioxirane[12] at 0°C and facile regioselective ring-opening of the resulting epoxide with neat allyl alcohol at room temperature gave the alcohol **13** as the major diastereoisomer (9:1 ratio by ^{1}H NMR spectroscopy) which was converted into the *p*-methoxybenzyl ether **14**. It is postulated that epoxidation of **12** occurs from the face of the enol ether opposite the benzyloxy group and similar selectivity has been observed upon treatment of pyranoid glycals with 2,2-dimethyldioxirane.[13]

Cleavage of the allyl acetal *via* isomerisation[14] and hydrolysis with aqueous mercuric acetate in THF provided the lactol **15** as a 3:1 mixture of anomers. Treatment of this mixture with an excess of allyl magnesium chloride and oxidation[15] of the resulting crude diol then gave the hemiacetal **16** which on exposure to aqueous HF in acetonitrile afforded the model 2,8-dioxabicyclo[3.2.1]octane **17** in excellent yield. The ether **17** was finally converted into the acetate **18**[16] the structure of which followed from ^{1}H decoupling, 2D PS-NOESY, 2D COSY and NOE difference experiments. Signals due to H-6 and -7 were well separated and the observed coupling constant (J=2.4 Hz) provides a strong argument for the stereochemistry depicted. Evidence for the assigned configuration at C-5 and -1 arose from the significant nOe that was observed between H-4_{eq} and -6 (see structure) and another nOe observed between H-7 and the allylic methylene protons compares well with a similar interaction to that reported for the natural products.[3]

It is envisaged that this route will provide the natural compounds as well as interesting analogues for biological testing. Experiments to introduce the functionality at C-3 and -4 of the core and extension of the aliphatic side chain are in progress and will be reported in due course.



Scheme II[b]

[b]Key: (c) $LiAlH_4$, Et_2O (d) MOMCl, $^iPr_2NEt$, CH_2Cl_2 (e) i. OsO_4, NMO, THF/H_2O; ii. $NaIO_4$; iii. $NaBH_4$, EtOH (f) TBSCl, imidazole, DMF (g) i. Li, liq. NH_3; ii. HMPT, CCl_4, THF; iii. Li, liq. NH_3, iv. BnBr, NaH, DMF/THF (h) i. 2,2-Dimethyldioxirane, acetone, CH_2Cl_2, 0°C; ii. Allyl alcohol, RT, 30 mins (i) PMBCl, NaH, DMF/THF; (j) i. cat. $(Ph_3P)_3RhCl$, 1,4-diazabicyclo[2.2.2]octane, EtOH reflux, 2h; ii. $Hg(OAc)_2$, THF/H_2O (k) i. 3 eq. Allylmagnesium chloride, THF; ii. Dess-Martin periodinane (l) 50%HF/MeCN (5:95)/H_2O, RT 2.5h (m) i. DDQ, CH_2Cl_2/H_2O; ii. Ac_2O, pyridine, RT, 16h.

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10. Data for compound **6**: m.p. 91-92°C (hexanes); $[\alpha]_D^{20}$ +4.2° (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1736 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.29 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.68 (1H, dd, *J*= 14.2 and 6.2 Hz, $CH_2CH=CH_2$), 2.82 (1H, dd, *J*= 14.2 and 7.6 Hz, $CH_2CH=CH_2$), 3.79 (3H, s, OCH_3), 4.52 (1H, d, *J*=11.8 Hz, $PhCH_2O$), 4.75 (ABq, *J*= 5.8 Hz, H-6 and -7), 4.82 (1H, d, *J*=11.8 Hz, $PhCH_2O$), 5.09-5.14 (2H, m, $CH_2CH=CH_2$), 5.38 (1H, s, H-1), 5.81 (1H, m, $CH_2CH=CH_2$), and 7.28-7.37 (5H, m, ArH); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 25.0, 25.9, 41.8, 52.2, 70.1, 85.3, 85.7, 92.8, 108.0, 113.2, 118.8, 127.7, 127.8, 128.4, 132.2, 137.1, 169.8. Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.36; H, 6.69.
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16. Data for compound **18**: m.p. 50-51°C (pentane); $[\alpha]_D^{20}$ -29.3° (*c* 1.3, $CHCl_3$); ν_{max} (film) 1747 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.52 (1H, dd, *J*= 13.2 and 3.6 Hz, $H\text{-}4_{eq}$), 2.11 (3H, s, $COCH_3$), 2.25 (1H, ddd, *J*= 13.2, 12.3 and 7.2 Hz, $H\text{-}4_{ax}$), 2.47 (2H, dt, *J*= 7.2 and 0.9 Hz, H-1'), 3.34 (3H, s, OMe), 3.72 (2H, ABq, *J*= 10.5 Hz, CH_2O), 3.94 (1H, d, *J*= 2.4 Hz, H-6), 3.97-4.11 (2H, m, $H\text{-}3_{ax}$ and $\text{-}3_{eq}$), 4.43 (1H, d, *J*= 11.7 Hz, $PhCH_2O$), 4.66 (2H, s, OCH_2O), 4.68 (1H, d, *J*=11.4 Hz, $PhCH_2O$), 5.09-5.17 (2H, m, H-3'), 5.33 (1H, d, *J*= 2.4 Hz, H-7), 5.83 (1H, ddt, *J*=17.1, 10.4 and 7.2 Hz, H-2'), 7.23-6.38 (7H, m, ArH); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 21.1, 30.6, 41.0, 55.3, 60.0, 68.5, 71.6, 81.0, 82.7, 85.1, 96.8, 104.2, 118.7, 127.7, 127.8, 128.4, 131.4, 137.5, 169.4. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.47; H, 7.05.

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