Synthesis of a Novel Spirocyclic Lactone in a Potential Route to Squalestatin 1

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The isomeric butenolides **1** and **2** have been converted into the spiro-lactone derivative **20** *via* sequential ring contraction–rearrangement processes. X-Ray crystal data have been obtained on compound **12b**.

In a recent communication[1] we described the conversion of (D)-(+)-1,6-anhydrogalactose into the butenolides **1** and **2** and the manipulation of compound **1** to give the crystalline derivative **3** (Fig. 1). In a second communication[2] we described the conversion of butenolides **1** and **2** into the dioxabicyclo-[3.2.1]octane core **4**, a late-stage intermediate for the preparation of squalestatin 1 **5**.[3] Two syntheses of simple model core structures have also been published recently.[4] Herein, we describe that the method of dihydroxylation reported by Sharpless and co-workers[5] gives a high degree of selectivity in favour of the desired diastereoisomer used in a second approach to the total synthesis of squalestatin 1.[6]

The butenolides **1** and **2** were converted into the unsaturated diol **6** by reduction with diisobutylaluminium hydride (DIBAL-H) (82%) (Scheme 1).[7] Treatment of this diol **6** with trimethylacetyl chloride and triethylamine afforded the di-pivaloylated compound **7** (99%). This compound was then bis-hydroxylated using conditions described by Sharpless[5] to afford the diol **8** (62%) almost exclusively (ratio 30:1) in favour of the diastereoisomer with the desired *S* and *R* configurations at C-4′ and C-5′, respectively.

The diol **8** was treated with 2-methoxypropene under acid catalysis to afford the protected isopropylidene derivative **9** (97%). The benzyl ether at 4-C of the tetracyclic compound **9** was removed by catalytic hydrogenolysis affording the corresponding alcohol **10** (86%), which was then treated with benzoyl chloride and triethylamine to give the fully protected compound **11** (86%). The 1,6-anhydro-bridge was then cleaved using 72% aq. perchloric acid in acetic anhydride to give the diacetate as a mixture of anomers **12a** and **12b** (32%, ratio 1:3) which were both purified by chromatography. To confirm the stereochemistry resulting from the dihydroxylation reaction, crystals of **12b** (from methanol) were analysed by X-ray crystallography (Fig. 2).

The 4-hydroxy compound **10** was treated with pivaloyl chloride to provide the stable ester derivative **13** (Scheme 2). Under our standard conditions used for the opening of the 1,6-anhydro bridge, the tripivaloate **13** gave the ring-opened compound **14** in a yield of 64%. Selective removal of the acetate protecting group at the anomeric centre was achieved using ammonia in aq. methanol, to afford the lactol **15** in a quantitative yield. Subsequent oxidation with Jones' reagent gave the lactone **16**, albeit in disappointing yield. However, using the perruthenate oxidation procedure reported by Ley and co-workers,[8] the lactone **16** was obtained in a much improved yield of 80%.

On treating lactone **16** with guanidine,[9] in a mixture of ethanol and dichloromethane, a ring-contraction was observed, producing compound **17** in 97% yield. We believe this contraction occurred due to a facile three-step process involving: (i) removal of the acetate group, (ii) intramolecular migration of the 4-pivaloyl group to the primary position, and (iii) ring contraction brought about by the newly created 4-hydroxy group attacking the anomeric centre. The 5-hydroxy group of

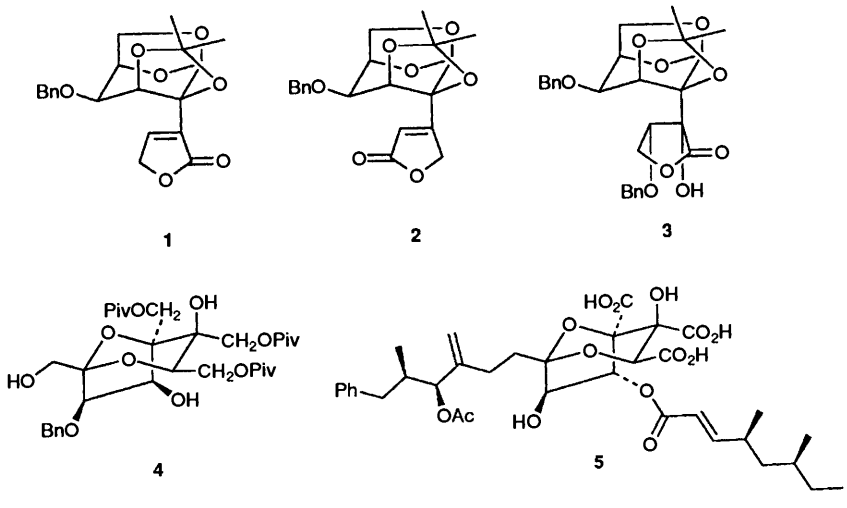
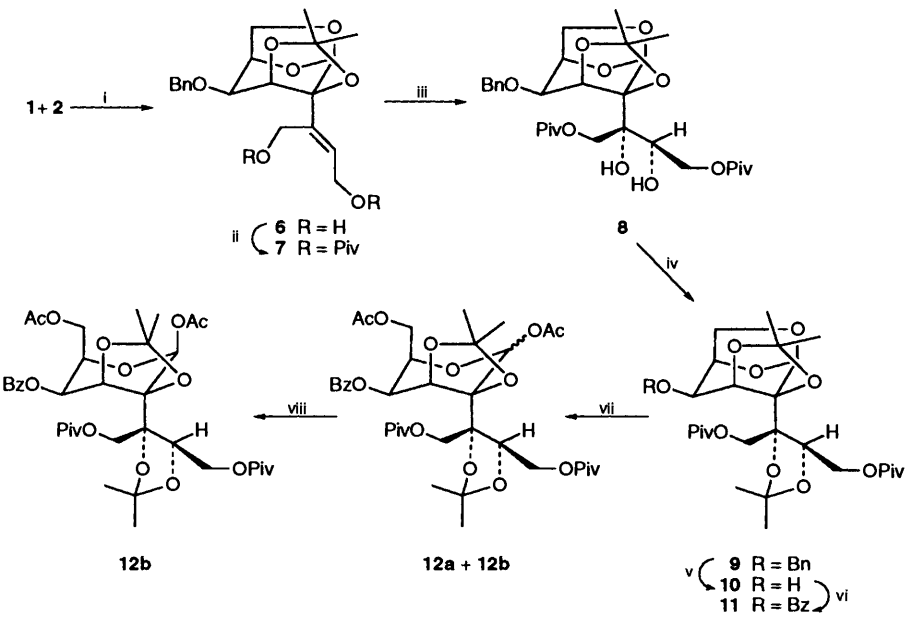


Fig. 1



Scheme 1 *Reagents and conditions:* i, Bu^i_2AlH (4.5 equiv.), THF, 0 °C, 30 min, then room temp. 4 h (82%); ii, pivaloyl chloride (6 equiv.), Et_3N, CH_2Cl_2, room temp. 18 h (99%); iii, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, Bu^tOH–H_2O (1 : 1), hydroquinidine 4-chlorobenzoate, room temp. 4 h (62%); iv, 2-methoxypropene, CH_2Cl_2, catalytic *p*-$MeC_6H_4SO_3H$, room temp. 18 h (97%); v, 10% Pd–C, H_2, ethanol, room temp., 72 h (86%); vi, benzoyl chloride (3 equiv.), Et_3N, CH_2Cl_2, reflux, 18 h (86%); vii, acetic anhydride, 72% aq. perchloric acid (cat.), −20 °C, 4 h (32% plus 34% recovered starting material); viii, chromatography and recrystallisation from methanol.

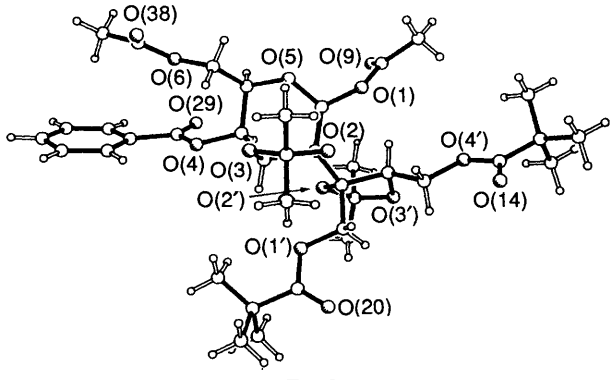


Fig. 2

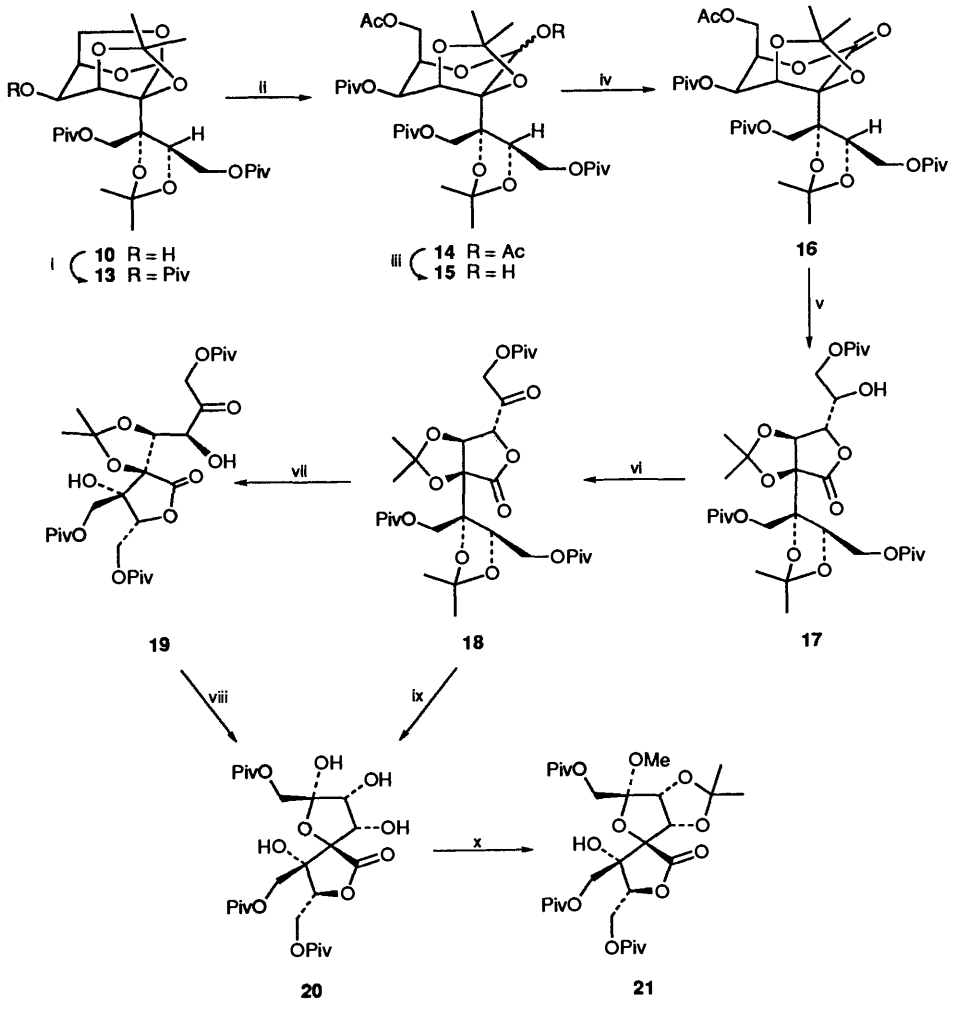
compound **17** was subsequently oxidised, using Jones' reagent, to give the ketone **18** in quantitative yield. On treating **18** with a trifluoroacetic acid–water mixture (9 : 1) at 0 °C before warming to room temp. over 30 min a second rearrangement occurred to give another five-membered lactone **19**. It was found that by treating this lactone **19** with further TFA–H_2O at room temp. (or by leaving the ketone **18** to react with TFA–H_2O for a longer period of time at room temp.) the spiro lactone **20** was obtained. The structure of this spiro lactone ring system was determined by NMR studies on the functionalised derivative **21**, formed by protection of the anomeric hydroxy group as the methyl ether and the *cis*-diol as an acetonide unit. A combination of HMBC, HECTOR and NOE studies on both compounds **20** and **21** led to the identification of the structures shown.

A comparison of the spiro compound **20** with squalestatin 1 **5** shows that ring-opening on the γ-lactone unit would allow the hydroxy group to attack the anomeric centre to provide the core structure of squalestatin with only the 6-C centre requiring inversion. Studies into the total synthesis of squalestatin 1 along these lines are continuing in our laboratories and will be reported elsewhere.

Experimental

1,6-*Di*-O-*acetyl*-4-O-*benzyl*-2,3-O-*isopropylidene*-2-[(4′S,5′R)-2′,2′-*dimethyl*-*bis*(*pivaloyloxymethyl*)*dioxolan*-4′-*yl*]-α-talo-*hexopyranose* **12a** *and the* β-*Anomer* **12b**.—The substance **11** (292 mg, 0.46 mmol) was dissolved in acetic anhydride (20.0 cm^3) and cooled to −20 °C in an ice–salt bath. Perchloric acid (72% aq. solution) (0.50 cm^3) was added dropwise and the mixture was stirred between −20 and −10 °C for 4 h, at which point unwanted side products began to form. The reaction was quenched by pouring the mixture into sat. aq. sodium hydrogen carbonate (100 cm^3) at 0 °C and stirring for a further 15 min. The mixture was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The crude residue was then dissolved in toluene (20 cm^3) and concentrated under reduced pressure. Flash column chromatography, eluting with 25% ethyl acetate in cyclohexane, gave the desired product **12** as a colourless oil (100 mg, 32%) [R_f = 0.41 (25% ethyl acetate in cyclohexane)] and recovered starting material (100 mg, 34%). The product was a mixture of the anomers **12a** and **12b**. The latter recrystallised from methanol to give the *title compound* **12b**; m.p. 133–134 °C (Found: C, 60.6; H, 7.4. $C_{37}H_{52}O_{15}$ requires C, 60.31; H, 7.11%); $[\alpha]_D^{23}$ +12 (*c* 1.00 in $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 2955, 2923, 2850 (saturated C–H and aromatic) and 1726 (ester C=O); δ_H(400 MHz; $CDCl_3$) 8.06 (2 H, m, Ar), 7.60 (1 H, m, Ar), 7.46 (2 H, m, Ar), 6.16 (1 H, s, 1-H), 6.14 (1 H, dd, *J* 8.0 and 2.4, 4-H), 5.15 (1 H, d, *J* 2.4, 3-H), 4.67 (1 H, dt, *J* 6.0 and 6.0, 5-H), 4.55 (1 H, d, *J* 12.0, O-C*H*$_2$-C-4′), 4.48 (2 H, d, *J* 6.0, 6-H), 4.36 (1 H, t, *J* 8.0, 5′-H), 4.20 (2 H, m, O-C*H*$_2$-C-5′), 4.15 (1 H, d, *J* 12.0, O-C*H*$_2$-C-4′), 2.15 (3 H, s, OCOMe), 1.78 (3 H, s, OCOMe), 1.62 (3 H, s, isopropylidene Me), 1.46 (3 H, s, isopropylidene Me), 1.43 (3 H, s, isopropylidene Me), 1.41 (3 H, s, isopropylidene Me), 1.22 (9 H, s, CMe_3), 1.13 (9 H, s, CMe_3) {Found: (FAB; NH_3) $[M + NH_4]^+$ 754.3685 $C_{37}H_{52}O_{15}$ requires $[M + NH_4]^+$ 754.3650}; *m*/*z* 677 (8%), 391 (13), 329 (7), 271 (20), 185 (100) and 157 (21).

Crystal Data for Compound **12b**.—$C_{37}H_{52}O_{15}$, *M* = 736.81, monoclinic, *a* = 38.76(2), *b* = 8.343(4), *c* = 12.948(7) Å, β =



Scheme 2 *Reagents and conditions:* pivaloyl chloride, triethylamine, DMAP, reflux, 7 h, 97%; ii, acetic anhydride, 72% aq. perchloric acid (cat.), −20 °C–10 °C, 2 h, 64%; iii, 32% aq. NH_3–MeOH (1:4), −20 °C–room temp., 100%; iv, TPAP, CH_2Cl_2, 4 Å sieves, NMO, 18 h, 80%; v, guanidine, EtOH–CH_2Cl_2 (9:1), 12 min, 97%; vi, Jones' reagent, acetone, 50 min, 100%; vii, TFA–H_2O (9:1), 0 °C–room temp., 30 min, 74%; viii, TFA–H_2O (9:1), room temp., 24 h, 88%; ix, TFA–H_2O, (9:1), room temp., 36 h, 88%; x, (*a*) CH_2N_2, SiO_2, Et_2O, 15 min; (*b*) 2,2-dimethoxypropane, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2, 8 h, 40%.

104.81(4)°, V = 4048(7) Å^3, λ = 1.541 78 Å, space group $C2$, Z = 4, D_c = 1.21 g cm^{-3}, $F(000)$ = 1576 μ(Cu-Kα) = 0.75 mm^{-1}. Siemens R3m/V diffractometer, 3034 reflections measured ($3 < 2\theta < 115°$) of which 2980 were unique and 2612 had $I > 3.0\ \sigma(I)$. Full matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode with common isotropic U's applied to those which were chemically similar. Individual weights were applied according to the scheme $W = [\sigma^2(F_o) + 0.0008|F_o|^2]^{-1}$ and refinement converged at R 0.052, R_w 0.057, goodness-of-fit = 1.89. All computations were carried out using the SHELXTL PLUS[10] (μ-VAX II) system of programs.

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