Synthesis of the Bicyclic Core Structure of Squalestatin 1

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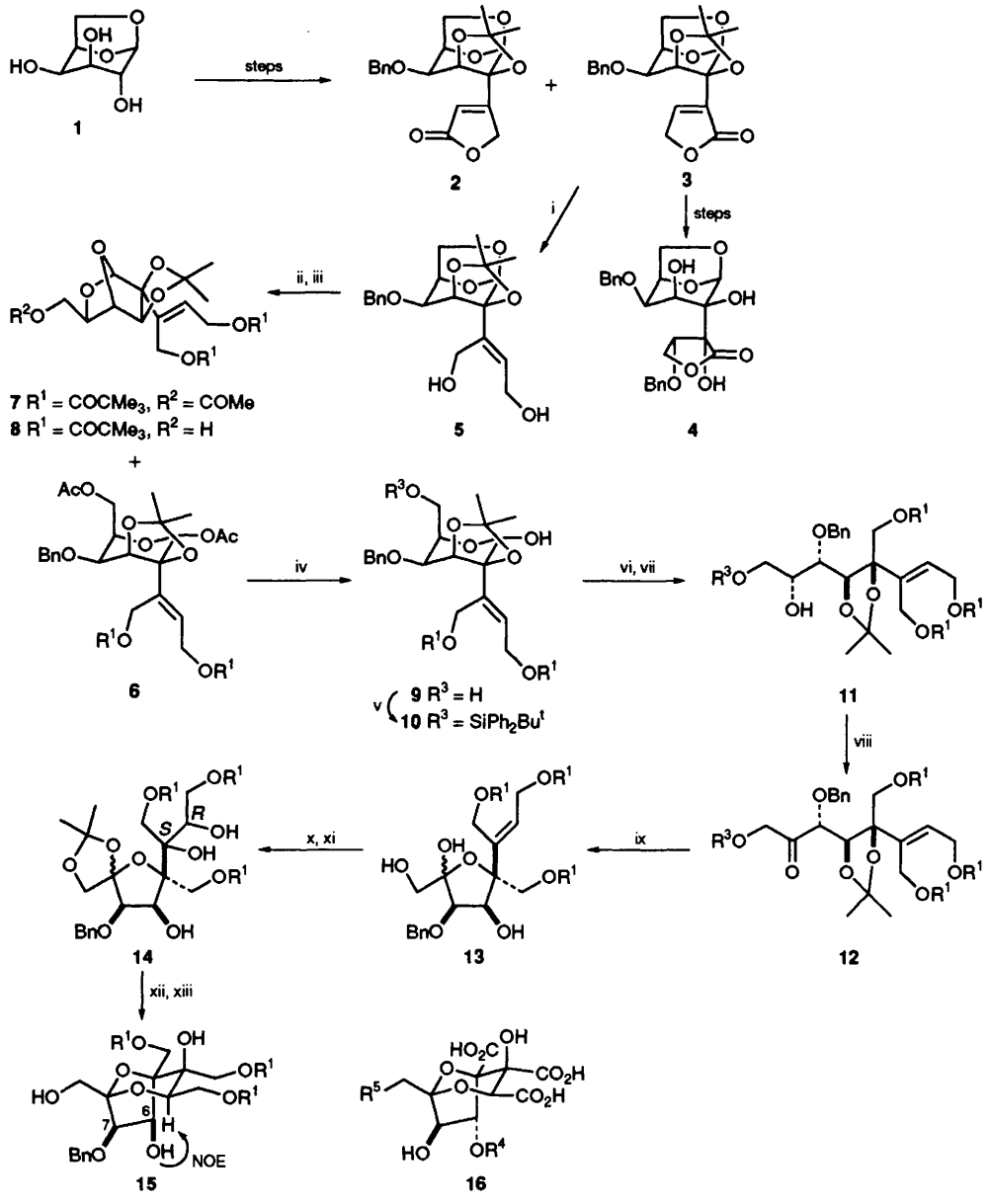
The butenolides **2** and **3** have been converted into the dioxabicyclo[3.2.1]octane derivative **15**, a late-stage precursor to squalestatin 1 **16**.

In the preceding communication[1] we described the conversion of D-(+)-1,6-anhydrogalactose **1** into the butenolides **2** and **3** (Scheme 1). The butenolide **3** was converted into the crystalline triol **4**; the stereochemical assignments for the latter compound were confirmed by X-ray crystallography.[2] In this paper we report the conversion of the butenolides **2** and **3** into a bicyclic compound very closely related to squalestatin 1 (zaragozic acid A).

Reduction of the mixture of **2** and **3** with diisobutylaluminium hydride (DIBAL-H)[3] in toluene gave the diol **5** as a



For **6**–**15**, R^1 = $COCMe_3$
For **10**–**12** R^3 = Bu^tPh_2Si
For **16**, R^4 = $COCH{=}CHCH(Me)CH_2CH(Me)CH_2Me$
R^5 = $CH_2C(CH_2)CH(OCOMe)CH(Me)CH_2Ph$

Scheme 1 *Reagents and conditions*: i, Bu^i_2AlH (2.6 equiv.), toluene, 0 °C, ½ h then room temp., 2 h (78%); ii, Me_3CCOCl (6 equiv.), Et_3N, CH_2Cl_2, reflux, 24 h (89%); iii, CF_3CO_2H, $(MeCO)_2O$ (1:10), 6 h, room temp., iv, 33% aqueous NH_3–methanol (1:1), room temp., 3 h; v, Bu^tPh_2SiCl, imidazole, DMF, room temp., 7 h (42% for **5** to **10**); vi, $NaBH_4$, EtOH, 1½ h, room temp., (87%); vii, Me_3CCOCl, pyridine, DMAP (cat.), CH_2Cl_2, reflux 48 h (72%); viii, Jones' reagent (2.7 equiv.), acetone, 3 h, room temp., (91%); ix, CF_3CO_2H–H_2O (9:1), 0 °C, 8 h, (89%); x, Me_2CO, anhydrous $CuSO_4$, (±)-camphorsulfonic acid (92%); xi, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, Bu^tOH–H_2O (1:1), hydroquinidine 4-chlorobenzoate, room temp., 3½ days (60%); xii, CF_3CO_2H–H_2O–THF (1:1:4), room temp., 24 h, (60%); xiii, $CuSO_4$ (anhydrous), (±)-camphorsulfonic acid (cat.), CH_2Cl_2, room temp., 72 h (41%) (DMF = dimethylformamide; DMAP = 4-dimethylaminopyridine; THF = tetrahydrofuran; Bn = $PhCH_2$)

white foam. Protection of the diol as the dipivaloyl ester followed by treatment with trifluoroacetic acid in acetic anhydride furnished the desired diacetate **6**† and the tricyclic compound **7** in the ratio 2.2:1. The formation of the bicyclic acetal **7** is obviously due to participation of the neighbouring benzyloxy group after formation of the relatively stable carbocation at C-1 (sugar numbering).

† Compounds **6**, **9** and **10** probably exist to some extent in the $^4C_1$ conformation; conformational preferences will be discussed in the full paper.

Treatment of the mixture of **6** and **7** with 33% aqueous ammonia in methanol afforded the required diol **9** as a single anomer (59%) and the alcohol **8** (33%). Compound **9** was converted into the silyl ether **10** in high yield. Sodium borohydride reduction of **10** followed by esterification gave the alcohol **11** which was oxidised with Jones' reagent to give the ketone **12**; cold aqueous trifluoroacetic acid treatment of **12** gave the furanose **13** (ratio of anomers 8:1; 89% yield over two steps). Attempted osmylation of alkene **13** was unsuccessful, necessitating protection of the vicinal diol moiety. Formation of the corresponding acetonide and bis-hydroxyla-

tion under conditions prescribed by Sharpless[4] gave the diastereoisomerically pure triol **14** which, when treated with aqueous trifluoroacetic acid, in tetrahydrofuran followed by dichloromethane containing anhydrous copper(II) sulfate and (±)-camphorsulfonic acid, provided the requisite bicyclic compound **15**, a late-stage precursor to squalestatin 1 **16**.

The structure of the triol **15** was proved by mass spectrometry, [found: $[M + H]^+$ *m/z* 625.3249. $C_{32}H_{48}O_{12}$ requires $[M + H]^+$ 625.3224] and by NMR. The ^1H NMR data were as follows: δ_H (500 MHz; C_6D_6); 7.21 (1 H, dd, *J* 7 and 2 Hz, Ar-H), 7.18 (2 H, t, *J* 7 Hz, Ar-H), 7.11 (1 H, tt, *J* 7 and 2 Hz, Ar-H), 4.92 (1 H, ½ABX, *J* 12 and 2.5 Hz, 3-CH_2O), 4.85 (1 H, ½AB, *J* 12.5 Hz, 4-CH_2O), 4.72 (1 H, dd, *J* 7.5 and 2.5 Hz, 3-H), 4.63 (1 H, ½ABX, *J* 12 and 7.5 Hz, 3-CH_2O), 4.62 (1 H, ½AB, *J* 12.5 Hz, 4-CH_2O), 4.60 (2 H, s, 5-CH_2O), 4.51 and 4.28 (2 H, AB, *J* 11.5 Hz, CH_2Ph), 4.23 (1 H, dd, *J* 9.5 and 3 Hz, 6-H), 3.83 (1 H, d, *J* 9.5 Hz, 7-H), 3.61 and 3.49 (2 H, AB, *J* 12 Hz, 1-CH_2O), 3.55 (1 H, br s, OH), 2.46 (1 H, d, *J* 3 Hz, 6-OH), 1.24 (18 H, s, 2 × CMe_3), 1.17 (9H, s, CMe_3). The ^{13}C NMR spectrum included the following signals: δ_C (125 MHz; C_6D_6) 177.8 (C), 177.3 (2 × C), 137.2 (C), 103.8 (C), 86.0 (C), 75.3 (CH), 74.4 (CH), 73.7 (CH_2), 71.5 (C), 69.3 (CH), 64.3 (CH_2), 63.9 (CH_2), 63.1 (CH_2), 62.9 (CH_2), 38.7 (C), 38.6 (2 × C), 27.1 (3 × CH_3), 27.0 (6 × CH_3). The coupling constant J_{H6H7} = 9.5 Hz clearly indicates the dioxabicyclo[3.2.1]octane ring system and an observed NOE for the proton 3-H on irradiating the hydroxy group at C-6 confirms the stereochemistry of the Sharpless dihydroxylation reaction and the relative configurations of the various functional groups. Extensive two- and three-bond ^1H–^{13}C correlations observed in the heteronuclear multiple bond correlation spectrum[5] are also consistent with the structure **15**.

Further progress towards the synthesis of the natural product will be reported in due course.

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