

Total Synthesis of the Antifungal Agent Papulacandin D

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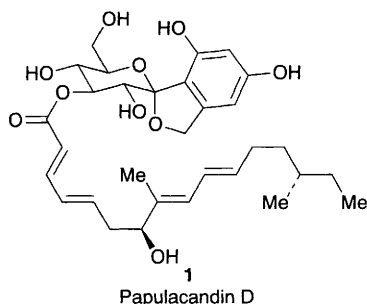
Condensation of 2,3,4,6-tetra-*O*-(trimethylsilyl)- β -D-gluconolactone with *tert*-butyl[2-lithio-3,5-di-(triisopropylsilyloxy)benzyloxy]dimethylsilane, protection of the resultant spiroketal with di(*tert*-butyl)silyl di(trifluoromethanesulfonate), selective *O*-3'-esterification and deprotection gives papulacandin D.

In the preceding communication¹ we described the synthesis and stereochemical elucidation of the fatty acyl side chain of the antifungal agent papulacandin D **1**.^{2,3} Herein we report the completion of the total synthesis of **1**. Previous work within our group has shown that condensation reactions between β -diketone dianions and lactones readily provides spiroketal arrays.^{4–9} Following this early work we sought to use similar methodology to construct the spiroketal core of **1**.

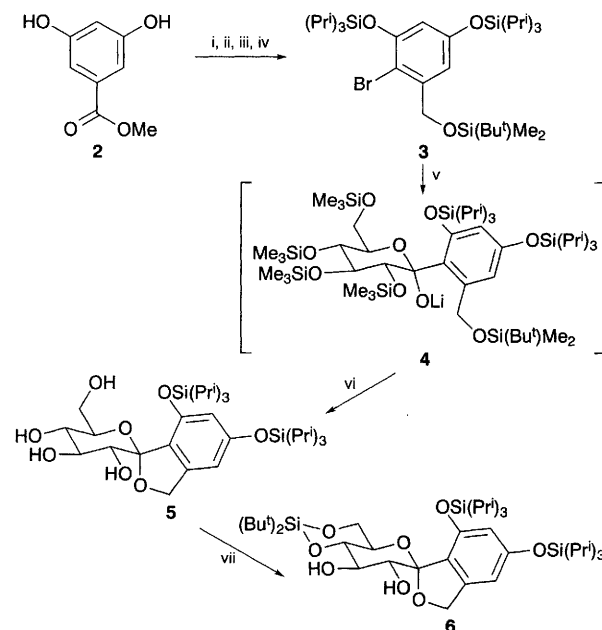
There have been several strategies used to assemble the spirocyclic unit of papulacandin D. Danishefsky¹⁰ elaborated the spiroketal in racemic modification using Diels–Alder chemistry. Friesen¹¹ and Beau^{12,13} independently reported the use of palladium(0) catalysed coupling of a 1-(tributylstannyl)- β -D-glucal derivative with an aryl bromide and oxidative spirocyclization to produce the papulacandin D core. Schmidt¹⁴ utilised the condensation of an aryllithium reagent with 2,3,4,5,6-penta-*O*-benzyl- β -D-glucose as a key step in the synthesis of the papulacandin D spiroketal. Finally Bihovsky,¹⁵ Barrett^{8,9} and Czernecki¹⁶ have reported that the spiroketal can be elaborated from β -D-gluconolactone derivatives. Herein we report an adaptation of our earlier work^{8,9} which leads to the first total synthesis of papulacandin D.

Methyl 3,5-dihydroxybenzoate **2** was protected as the bis(triisopropylsilyl ether)[†] and reduced to provide the corresponding benzyl alcohol. Electrophilic bromination and subsequent protection of the corresponding alcohol as the *tert*-butyldimethylsilyl ether gave the desired bromide **3** in excellent yields (Scheme 1). Generation of the aryllithium reagent followed by addition of the readily available 2,3,4,6-tetra-*O*-(trimethylsilyl)- β -D-gluconolactone¹⁷ **7** yielded an intermediate, presumably **4**. Direct acidification resulted in partial desilylation and cyclization to give the desired spiroketal **5** as a single anomer (29%). It is reasonable to speculate that this key spirocyclization reaction was controlled by the anomeric effect.^{18,19}

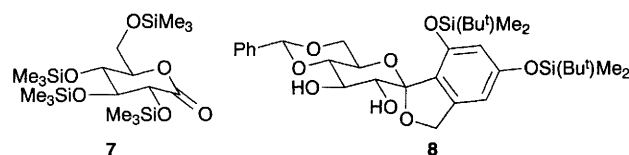
We considered that selective protection of the 4,6-diol unit of the tetrol **5** and monoesterification would provide the *O*-3-ester selectively. In preliminary studies,⁹ we sought to achieve this selectivity *via* formation of the 4,6-*O*-benzylidene derivative **8**. However, we found that this sequence of protection, mono-*O*-3-esterification and deprotection proceeded in poor yields due to degradation during cleavage of the benzylidene protecting group. In contrast we have found that a 4,6-*O*-(di-*tert*-butylsilylene) protecting strategy is much more efficient. Treatment of **5** with di(*tert*-butyl)silyl di(trifluoromethanesulfonate)²⁰ gave the silylene derivative **6** in good yield.

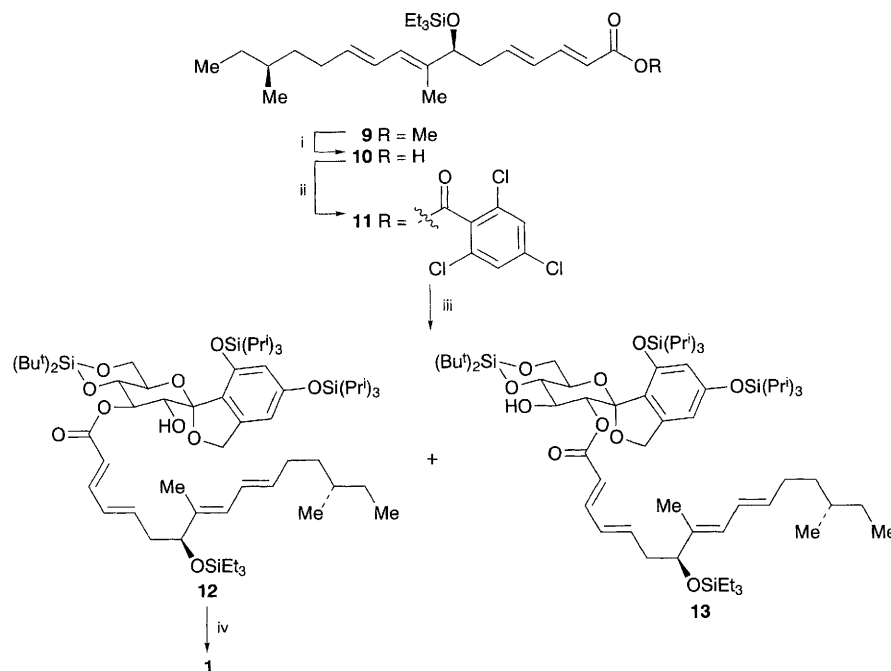


The unsaturated ester **9**¹ was cleanly hydrolysed to acid **10** (Scheme 2), using potassium trimethylsilanolate,²¹ and converted to the mixed anhydride **11** with 2,4,6-trichlorobenzoyl chloride.²² Addition of **11** to a mixture of spiroketal **6** and 4-(dimethylamino)pyridine resulted in selective *O*-3 esterification to give the protected papulacandin **12** (57%) and the *O*-2 ester **13** (14%). Global deprotection of **12** was accomplished by treatment with tris(dimethylamino)sulfonium difluoro-trimethylsilicate (TASF)²³ to yield synthetic **1** (64%) (Scheme 2). This material was spectroscopically and chromatographically identical with an authentic sample of the natural product.[‡] However, we observe a specific rotation different from that reported for the natural product. Traxler, Gruner and Auden reported an $[\alpha]_D^{20}$ value for papulacandin D of $+7 \pm 1$ (MeOH)² and $+7 \pm 1$ (CHCl₃, *c* = 0.250).²⁴ In our hands synthetic **1** is insufficiently soluble in chloroform to record an $[\alpha]_D$. In methanol solution, the synthetic compound showed $[\alpha]_D^{20} = +27.5$ (MeOH, *c* = 0.245) which is significantly greater than the literature value. Unfortunately, we have access to only very limited quantities of natural **1** (<500 μ g) and this has precluded us obtaining a reliable rotation. This sample showed $[\alpha]_D^{20} = +17$ (MeOH, *c* = 0.09) but this value is clearly of



Scheme 1 Reagents and conditions: i, (Pr)₃SiCl, imidazole, DMAP, DMF, 90%; ii, LiAlH₄, Et₂O; iii, NBS, CCl₄ 84% (two steps); iv, Bu^tMe₂SiCl, imidazole, DMAP, CH₂Cl₂, 92%; v, (a) Bu^tLi, Et₂O, –78 °C, (b) **7**, Et₂O, –78 °C; vi, Amberlite IR-120 (H⁺ form), MeOH, 29% (three steps); vii, (Bu^t)₂Si(OTf)₂, 2,6-lutidine, CH₂Cl₂, 85%





Scheme 2 Reagents and conditions; i, Me_3SiOK , THF; ii, Et_3N , 2,4,6-trichlorobenzoyl chloride, THF; iii, **6**, DMAP, DMF, 70% (three steps), 4 : 1 (3-ester); iv, TASF, THF, 64%

dubious accuracy. Nonetheless, we believe that an $[\alpha]_{\text{D}}^{20}$ of +27.5 is very reasonable given that the specific rotations for papulacandin A, § methyl α -D-glucopyranoside and methyl α -D-lactopyranoside are respectively 30 ± 1 ($c = 0.419$, MeOH),^{2,24} 159 (H_2O)²⁵ and 115 ($c = 1.03$, H_2O).²⁵ ¶ Finally, the synthetic side chain and natural side chain were identical by CD spectroscopy.

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Footnotes

† All new compounds were fully characterised by spectroscopic data and microanalysis and/or HRMS.

‡ Spectroscopic and physical data for synthetic papulacandin D: $R_f = 0.24$ (10% methanol in chloroform); $[\alpha]_{\text{D}}^{25} = +27.5$ ($c = 0.25$ in methanol); IR (thin film) ν/cm^{-1} 3329, 2959, 2926, 2874, 1698, 1639, 1615, 1463, 1377, 1347, 1304, 1261, 1153, 1070, 1005, 977 and 838; ^1H NMR (CD_3OD , 500 MHz) δ 7.30 (dd, 1 H, $J = 10.1, 15.2$ Hz), 6.25 (ddt, 1 H, $J = 1.3, 10.8, 15.0$ Hz), 6.23 (dd, 1 H, $J = 10.7, 14.7$ Hz), 6.20 (m, 1 H), 6.19 (m, 1 H), 6.12 (dt, 1 H, $J = 14.7, 15.2$ Hz), 6.00 (dd, 1 H, $J = 0.7, 10.8$ Hz), 5.92 (d, 1 H, $J = 15.3$ Hz), 5.66 (dt, 1 H, $J = 7.0, 15.0$ Hz), 5.34 (t, 1 H, $J = 9.7$ Hz), 5.03 (ABq, 2 H, $J = 12.6$ Hz), 4.33 (d, 1 H, $J = 10.0$ Hz), 4.07 (t, 1 H, $J = 6.6$ Hz), 3.87 (ddd, 1 H, $J = 2.3, 4.8, 10.1$ Hz), 3.66–3.70 (m, 2 H), 3.68 (t, 1 H, $J = 9.7$ Hz), 2.42 (t, 2 H, $J = 7.0$ Hz), 2.04–2.18 (m, 2 H), 1.71 (d, 3 H, $J = 0.5$ Hz), 1.29–1.49 (m, 3 H), 1.11–1.28 (m, 2 H), 0.87 (t, 3 H, $J = 7.3$ Hz) and 0.87 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR (CD_3OD , 125 MHz) δ 169.0, 161.5, 154.7, 146.4, 145.5, 141.8, 137.5, 136.2, 131.5, 127.1, 127.0, 120.9, 116.7, 112.1, 103.0, 99.9, 78.4, 77.5, 75.8, 73.8, 71.9, 69.8, 62.5, 40.0, 37.5, 35.2, 31.6, 30.4, 19.4, 12.2 and 11.7.

§ Papulacandin A is *O*-4'-[6-*O'*-(deca-2,4-dienoyl)- β -D-galactopyranosyl]papulacandin D [a lactose analogue of papulacandin D **1**].

¶ It is clear from the second two reference compounds that *O*-4-(β -D-galactopyranosylation leads to a decrease in specific rotation, not an

increase. By analogy the rotation of papulacandin D should not be significantly lower than papulacandin A but rather higher.

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