Total Synthesis of the Antifungal Agent Papulacandin D

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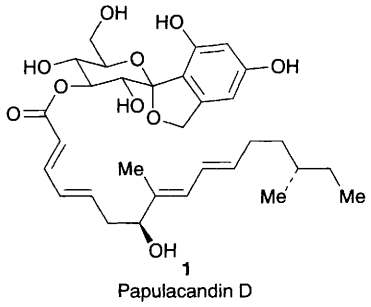
Condensation of 2,3,4,6-tetra-*O*-(trimethylsilyl)-D-gluconolactone with *tert*-butyl[2-lithio-3,5-di-(triisopropylsilyloxy)benzyloxy]dimethylsilane, protection of the resultant spiroketal with di(*tert*-butyl)silyl di(trifluoromethanesulfonate), selective *O*-3′-esterification and deprotection gives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

In the preceding communication[1] 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. Danishefsky[10] elaborated the spiroketal in racemic modification using Diels–Alder chemistry. Friesen[11] and Beau[12,13] independently reported the use of palladium(0) catalysed coupling of a 1-(tributylstannyl)-D-glucal derivative with an aryl bromide and oxidative spirocyclization to produce the papulacandin D core. Schmidt[14] utilised the condensation of an aryllithium reagent with 2,3,4,5,6-penta-*O*-benzyl-D-glucose as a key step in the synthesis of the papulacandin D spiroketal. Finally Bihovsky,[15] Barrett[8,9] and Czernecki[16] have reported that the spiroketal can be elaborated from D-gluconolactone derivatives. Herein we report an adaptation of our earlier work[8,9] which leads to the first total synthesis of papulacandin D.

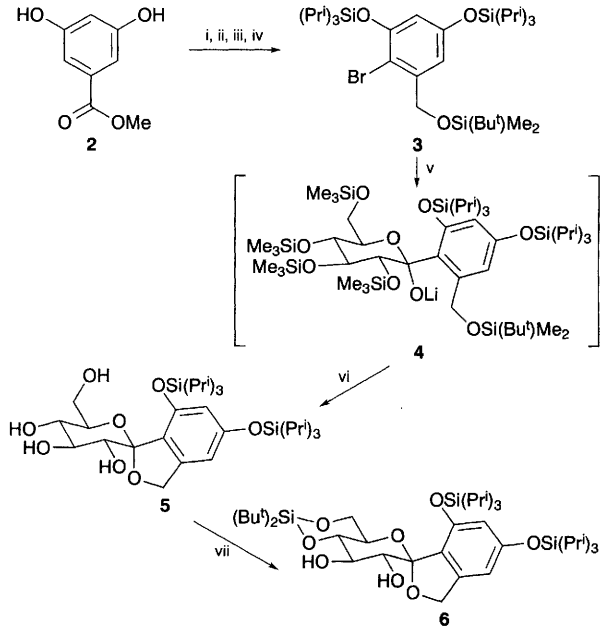
Methyl 3,5-dihydroxybenzoate **2** was protected as the bis(triisopropylsilyl ether)† and reduced to provide the corresponding benzyl alcohol. Electrophilic bromination and subsequent protection of the corresponding alcohol as the *tert*-butyldimethylsilyl ether gave the desired bromide **3** in excellent yields (Scheme 1). Generation of the aryllithium reagent followed by addition of the readily available 2,3,4,6-tetra-*O*-(trimethylsilyl)-D-gluconolactone[17] **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.

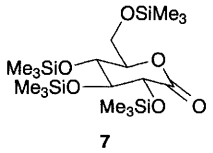


1 Papulacandin D

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 D **12** (57%) and the *O*-2 ester **13** (14%). Global deprotection of **12** was accomplished by treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (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 ± 1 (MeOH)[2] and +7 ± 1 ($CHCl_3$, 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 μg) 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, $(Pr^i)_3SiCl$, imidazole, DMAP, DMF, 90%; ii, $LiAlH_4$, Et_2O; iii, NBS, CCl_4 84% (two steps); iv, Bu^tMe_2SiCl, imidazole, DMAP, CH_2Cl_2, 92%; v, (a) Bu^tLi, Et_2O, −78 °C, (b) **7**, Et_2O, −78 °C; vi, Amberlite IR-120 (H^+ form), MeOH, 29% (three steps); vii, $(Bu^t)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 85%



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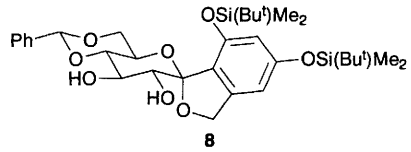

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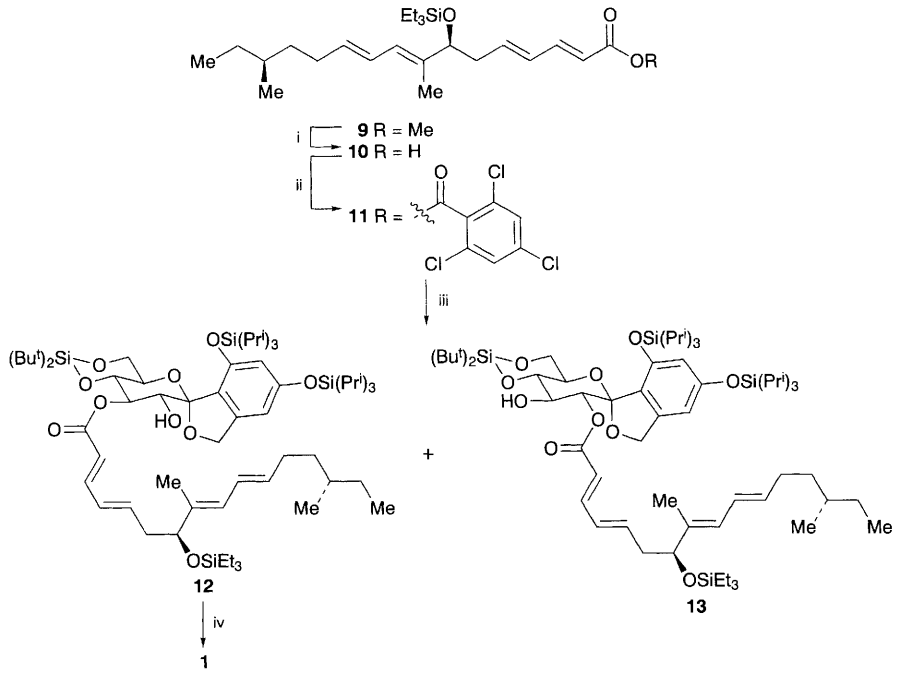

Scheme 2 *Reagents and conditions*; i, Me_3SiOK, THF; ii, Et_3N, 2,4,6-trichlorobenzoyl chloride, THF; iii, **6**, DMAP, DMF, 70% (three steps), 4 : 1 (3-ester); iv, TASF, THF, 64%

dubious accuracy. Nonetheless, we believe that an $[\alpha]_D^{20}$ 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); $[\alpha]_D^{25}$ = +27.5 (*c* = 0.25 in methanol); IR (thin film) v/cm^{-1} 3329, 2959, 2926, 2874, 1698, 1639, 1615, 1463, 1377, 1347, 1304, 1261, 1153, 1070, 1005, 977 and 838; ^{1}H 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, 1H, *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.

References

1 A. G. M. Barrett, M. Peña and J. A. Willardsen, *J. Chem. Soc., Chem. Commun.*, 1995, 1145.
2 P. Traxler, J. Gruner and J. A. L. Auden, *J. Antibiot.*, 1977, **30**, 289.
3 P. Traxler, H. Fritz, H. Fuhrer and W. Richter, *J. Antibiot.*, 1980, **33**, 967.
4 S. V. Attwood, A. G. M. Barrett and J.-C. Florent, *J. Chem. Soc., Chem. Commun.*, 1981, 556.
5 S. V. Attwood, A. G. M. Barrett, R. A. E. Carr and G. Richardson, *J. Chem. Soc., Chem. Commun.*, 1986, 479.
6 A. G. M. Barrett, R. A. E. Carr, S. V. Attwood, G. Richardson and N. D. A. Walshe, *J. Org. Chem.*, 1986, **51**, 4840.
7 A. G. M. Barrett and T. M. Raynham, *Tetrahedron Lett.*, 1987, **28**, 5615.
8 A. G. M. Barrett, D. Dhanak, S. A. Lebold, M. Peña and D. Pilipauskas, *Pestic. Sci.*, 1991, **31**, 581.
9 A. G. M. Barrett, M. Peña and J. A. Willardsen, in *Recent Advances in the Chemistry of Anti-Infective Agents*, ed. P. H. Bentley, RSC, Cambridge and London, 1993, p. 234.
10 S. Danishefsky, G. Philips and M. Ciufolini, *Carbohydr. Res.*, 1987, **171**, 317.
11 R. W. Friesen and C. F. Sturino, *J. Org. Chem.*, 1990, **55**, 5808.
12 E. Dubois and J.-M. Beau, *Tetrahedron Lett.*, 1990, **31**, 5165.
13 E. Dubois and J.-M. Beau, *Carbohydr. Res.*, 1992, **223**, 157.
14 R. R. Schmidt and W. Frick, *Tetrahedron*, 1988, **44**, 7163.
15 S. B. Rosenblum and R. Bihovsky, *J. Am. Chem. Soc.*, 1990, **112**, 2746.
16 S. Czernecki and M.-C. Perlat, *J. Org. Chem.*, 1991, **56**, 6289.
17 D. Horton and W. Priebe, *Carbohydr. Res.*, 1981, **94**, 27.
18 A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, New York, 1983.
19 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Toronto, 1983.
20 E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, 1982, **23**, 4871.
21 E. D. Laganis and B. L. Chenard, *Tetrahedron Lett.*, 1984, **25**, 5831.
22 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.
23 W. J. Middleton, *Org. Synth.*, 1985, **64**, 221.
24 P. Traxler, J. Gruner and J. Nüesch, *Ger. Offen.*, 1976, 2609611.
25 *Carbohydrates*, ed. P. M. Collins, Chapman and Hall, London, 1987, p. 312, 362.