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Reductive Aromatization of Quinols: Synthesis of the *C*-Arylglycoside Nucleus of the Papulacandins and Chaetiacandin

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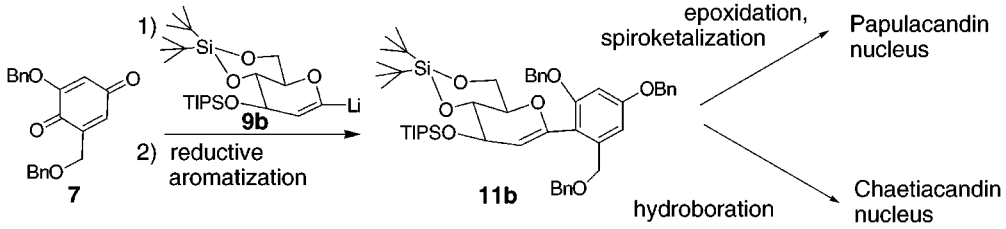
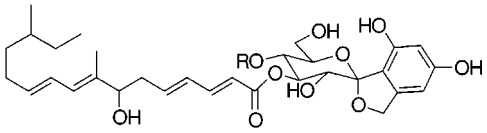
ABSTRACT



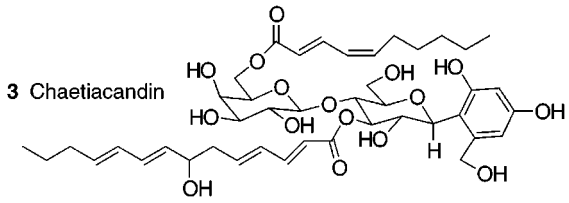
Nucleophilic 1,2-addition of lithiated glycal 9b to functionalized quinone 7 provided, after reductive aromatization, *C*-arylglycoside 11b. Treatment with mCPBA afforded the tricyclic papulacandin framework. Alternatively, hydroboration gave the chaetiacandin nucleus.

Papulacandins A−D, **1** and **2**,[1] are antifungal antibiotics isolated from *Papularia sphaerosperma*.



1 Papulacandin A, B, C R= 6-O-acyl-β-D-galactopyranosyl
2 Papulacandin D R= H

Although their structures were fully elucidated more than 20 years ago, serious attention to these compounds as synthetic targets only followed the more recent discovery of their strong activity against clinical isolates of *Candida albicans* and other fungi. Papulacandins inhibit the enzymes involved in the biosynthesis of 1,3-β-D-glucan, a vital constituent of fungal cell walls.[2] By inhibiting these synthases, the papulacandins pose a major threat to the life cycle of *Pneumocystis carinii*, an opportunistic infection responsible for *P. carinii*-induced pneumonia in AIDS patients.[3] Chaetiacandin **3**, more recently isolated from *Monochaetia dimorphospora*,[4] demonstrates similar biological activity.



Successful preparations of the *C*-arylglycosidic nuclei of the papulacandins and chaetiacandin include as key steps a

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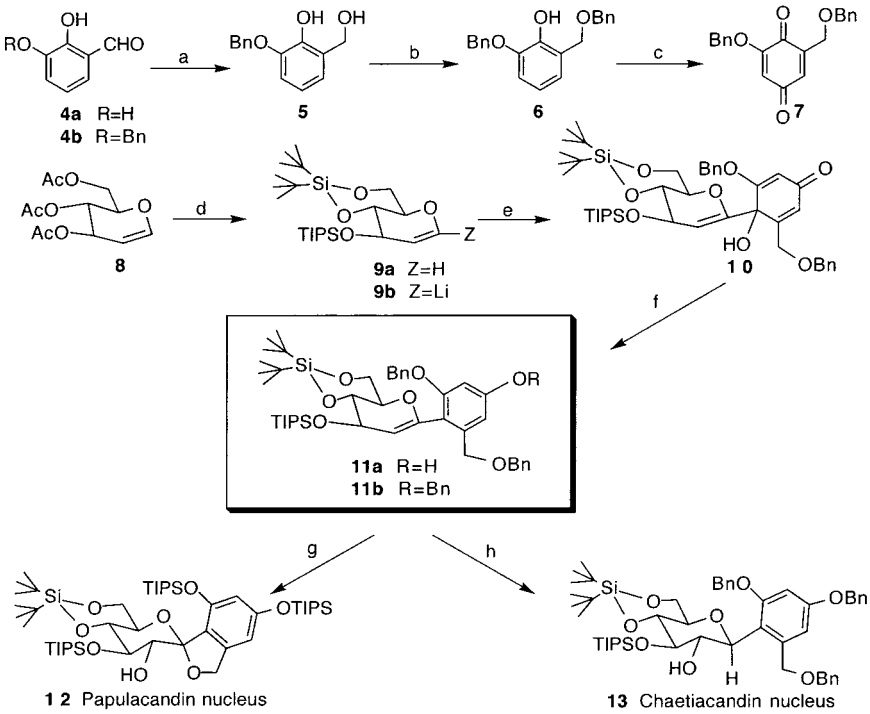
Scheme 1[a]



a) BnBr, NaH, THF (73%); $NaBH_4$, MeOH (98%) b) BnBr, NaH, DMSO (68%) c) O_2, salcomine, DMF, 72 h (64%) d) K_2CO_3, MeOH (98%); $(t\text{-Bu})_2Si(OTf)_2$, 2,6- lutidine, DMF, -50°C, 10 h (91%); TIPSCl, Imidazole, 45°C, 24 h (96%); 2 eq. t-BuLi, THF, -78°C->0°C, 2 h e) addition of **9** to **7**, BF_3-Et_2O, THF, -78°C, 8 h (33%) f) 5 eq. $Na_2S_2O_4$, THF/H2O (5:2), 8 h; BnBr, NaH, THF (85% for two steps) g) mCPBA, 10:1 MeOH/THF, 2 days (84%); H_2, Pd/C, EtOAc/MeOH; TIPSCl, 2.2 eq. Et_3N, CH_2Cl_2 (86% for two steps); h) BH_3-THF, H_2O_2, aq. NaOH (81%)

Lewis acid-catalyzed hetero Diels−Alder reaction,[5] a Stille-type coupling of a stannylglycal with an aryl bromide,[6] and an aryllithium condensation with a D-glucose precursor[7] or a protected gluconolactone.[8] The stereochemistry of the chiral centers in the papulacandin D side chain was established by Barrett[9] who then completed a total synthesis of papulacandin D, the simplest member of the series.

The papulacandins and chaetiacandin are ideal candidates for illustrating our "reverse polarity" strategy for the synthesis of *C*-arylglycosides of the group I substitution pattern.[10] In this methodology, a 1,2-addition of a protected nucleophilic glycal to an electrophilic quinone followed by reductive aromatization of the resulting quinol affords phenols that bear glycals in the para position.[11] A glycal-substituted phenol of this type (see **11a**) might serve as the common synthetic intermediate to both the papulacandins and chaetiacandin. Our umpolung approach provides an attractive alternative to coupling procedures which rely on tin reagents as it does not lead to toxic or environmentally problematic byproducts.

Synthesis of the *C*-arylglycoside intermediate **11a** began with the construction of the functionalized quinone **7** (Scheme 1)**.** Regioselective benzylation (BnBr, 2.5 equiv of NaH, THF, 25 °C, 10 h)[12] of commercially available 2,3-dihydroxybenzaldehyde **(4)** followed by hydride reduction ($NaBH_4$, MeOH) of monobenzylated aldehyde **4b** afforded alcohol **5**. A second regioselective benzylation (BnBr, 3 equiv of NaH, DMSO) yielded phenol **6**. Catalytic salcomine oxidation[13] (O_2, *N*,*N*′-bis(salicylidene)ethylenediiminocobalt-(II), DMF, 48 h) furnished the appropriately substituted quinone **7**.

Preparation of differentially protected glycal **9** began with commercially available tri-*O*-acetyl-D-glucal. Removal of the acetyl groups by methanolysis (K_2CO_3, MeOH, 25 °C) followed by silylation, first with di-*tert*-butylsilyl ditriflate (2,6-lutidine, DMF, −50 °C, 10 h) and then with triisopro-

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pylsilyl chloride (DMF, 50 °C, 24 h),[14] delivered the fully protected glycal **9a**.

With the two *C*-arylglycoside precursors in hand, we were now prepared to apply our umpolung methodology to the papulacandin and chaetiacandin nuclei. Lithiation of silylated glycal[15] **9a** with t-BuLi (2 equiv of t-BuLi, THF, −78 °C, then 0 °C, 2 h) and addition of **9b** in THF at −100 °C to quinone **7** in THF at −78 °C afforded quinol **10** with a disappointing yield of 9%. Attempts to improve this key reaction by the addition of chelating ligands were unsuccessful.[16] Likewise, use of the transmetalated organocerium[17] or organocadmium[18] reagent did not lead to improvement. Examination of the effect of Lewis acids revealed that while LiCl, LiBr, and $ZnCl_2$ were ineffective, the presence of 1 equiv of $BF_3{\cdot}Et_2O$ provided a useful procedure. Chromatography of the crude reaction product afforded 33% of quinol **10**. This yield is somewhat shy of those obtained in similar systems.[19] However, 58% of quinone **7**, pure enough for use in subsequent reactions, was also recovered from the chromatography, somewhat offsetting the modest conversion.

Reductive aromatization of intermediate **10** with $Na_2S_2O_4$ (5:2 THF/ H_2O, 8 h) afforded phenol **11a** which proved to be unstable even for short periods of time at ambient temperature. Therefore, the crude **11a** was immediately benzylated (BnBr, NaH, THF) to give the more stable *C*-arylglycoside **11b**.[15]

The papulacandin nucleus was elaborated by oxidation of the glycal olefin with mCPBA.[9a] Oxidation of intermediate **11b** occurred cleanly from the α-face, a result consistent with studies on similar compounds.[20] Removal of the benzyl ethers[10] and selective silyl protection of the phenolic hydroxyl groups gave the papulacandin intermediate **12** appropriately functionalized for further elaboration to the natural product.

Alternatively, hydroboration of the glycal double bond of **11b**, also from the α-face, with oxidative workup under basic conditions (H_2O_2, aqueous NaOH)[6c] yielded the chaetiacandin nucleus **13**. Like papulacandin intermediate **12**, the differentially protected chaetiacandin nucleus **13** is set up for the appending of the side chains in preparation for total synthesis.

As described, key intermediates **12** and **13** are available by short schemes that do not employ noxious or ecologically unfriendly reagents. The stage is therefore set for the completion of a practical synthesis of one or more of the papulacandin/chaetiacandin class of natural products. Efforts to effect a fully convergent total synthesis of papulacandin D are currently underway.

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Supporting Information Available: Full experimental and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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