A Total Synthesis of Papulacandin D

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Papulacandin D is the simplest member of a family of *C*-arylglycosides isolated from the fermentation broth of *Papularia spherosperma*. Papulacandin D has shown potent *in vitro* antifungal activity against clinical isolates of *Candida albicans* and other fungi that are responsible for increased mortality among immunocompromised patients. The key structural features are a 1,7-dioxaspiro[5.4]decane skeleton with an aryl-β-*D*-*C*-glycopyranoside derived from 5-(hydroxymethyl)resorcinol. In addition, the *O*-C(3) position of the glucose ring is esterified with a branched 18-carbon unsaturated fatty acid.

We envisioned disconnection at *O*-C(3) ester linkage to fatty acid **2** and spirocyclic *C*-arylglycopyranoside **1**. Disconnection of **1** at C(1) reduced the problem to oxidative spiroketalization of aryl-hexenopyranose **3**. The key step in the synthesis of **1** was a palladium-catalyzed cross-coupling reaction of silanol **4** with aryl iodide **5** in the presence of an alkoxide activator. Fatty acid **2** was simplified to conjugated aldehyde **6**, elaborated from geraniol, through an enantioselective addition of allyltrichlorosilane **7** to set the C(7'') stereocenter.