

## Total Synthesis of Papulacandin D

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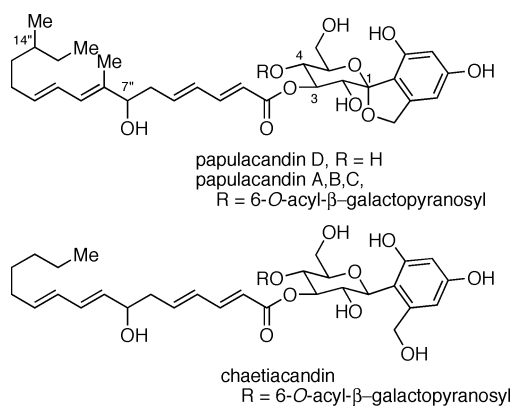
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The papulacandins and chaetiaccandins constitute a family of glycolipids that have shown potent *in vitro* antifungal activity against *Candida albicans*, *C. tropicalis*, *Pneumocystis carinii*, and related microorganisms (Chart 1).<sup>1</sup> Opportunistic infections arising from these pathogens are responsible for increased mortality among immunocompromised patients.<sup>2</sup>

Papulacandins A–E were isolated and structurally characterized by Traxler in 1977<sup>1</sup> from the fermentation broth of *Papularia sphaerosperma*. All of the papulacandins contain a 1,7-dioxaspiro-[5.4]decane skeleton with an aryl- $\beta$ -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. The papulacandin structures A–C bear different *O*-C(6)-acyl- $\beta$ -galactoside subunits at the *O*-C(4) position of papulacandin D (Chart 1).

Chart 1



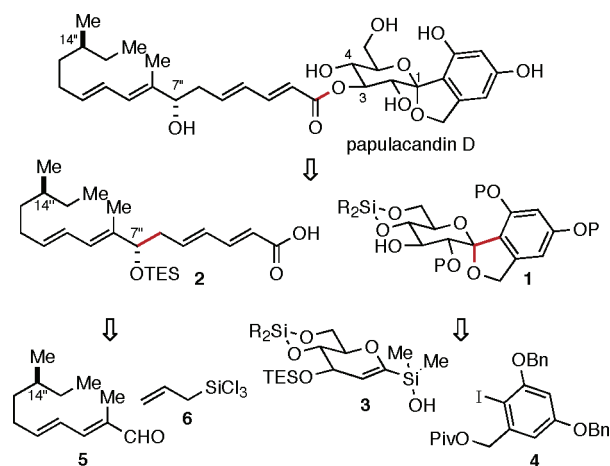
The antibiotic and antifungal properties along with the structural complexity of these spiro *C*-arylated glycopyranosides have stimulated the development of creative solutions for the construction of the tricyclic spiro ketal ring system. Recent representative examples include a synthesis of a racemic-spiro ketal unit via a hetero-Diels–Alder<sup>3</sup> reaction and dihydroxylation of 5-aryl-2-vinylfurans followed by Achmatowicz rearrangement.<sup>4</sup> The majority of work has focused on condensation of functionalized organolithium reagents with cyclic or acyclic derivatives of D-gluconolactone.<sup>5–9</sup> These methods provided rapid access to the spiro ketal core but suffer from moderate to low yields. Alternatively, nucleophilic addition of a lithiated hexenopyranose to a functionalized quinone has been utilized to access the aryl- $\beta$ -D-C-glycopyranoside.<sup>10</sup> Finally, Pd(0)-catalyzed cross-coupling reactions of a protected (tributylstannyl)-hexenopyranose with aryl bromides have been reported. Unfortunately, excess of the toxic tin reagent is required because of dimerization of the donor.<sup>11,12</sup>

Barrett and co-workers reported the first and only total synthesis of any member of the papulacandin family, papulacandin D.<sup>13</sup> Their approach features a condensation of an aryllithium reagent into a protected D-gluconolactone to assemble the spiro ketal moiety. The

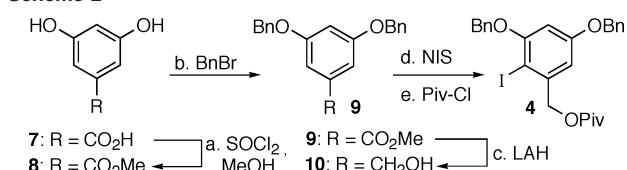
side-chain carboxylic acid was prepared from L-isoleucine using kinetic resolution to separate the C(7'') epimers. The two fragments were coupled by acylation using a mixed anhydride of the side chain.

Our synthetic plan for papulacandin D makes the obvious disconnection at the *O*-C(3) ester linkage to acid **2** and glycopyranoside **1** (Scheme 1). The major challenges in the synthesis resided in these independent units, namely, (1) the construction of the arylglycoside bond and (2) control of the C(7'') and C(14'') stereogenic centers. Moreover, potential solutions to these problems could be identified in ongoing methodological studies in these laboratories. First, disconnection of **1** at C(1) reduced the problem to a palladium-catalyzed cross-coupling of glucal silanol **3** and aryl iodide **4**.<sup>14</sup> Although we had already reported the synthesis *C*-aryl-2-*H*-pyrans from 2-pyranylsilanols,<sup>15</sup> this transformation failed with complex substrates and the fluoride activation was incompatible with silicon protecting groups. Thus, the first challenge was to determine whether the newly developed, fluoride-free variant<sup>16</sup> could be adapted to generate the spirocyclic *C*-aryl glycopyranoside. Second, inspection of **2** suggested that the C(6'')–C(7'') bond could arise from enantioselective addition of allyltrichlorosilane (**6**) to conjugated aldehyde **5**. We have previously described in detail the chiral bisphosphoramidate-catalyzed addition of allylic trichlorosilanes into aldehydes.<sup>17</sup> Herein, we report an efficient, enantioselective total synthesis of papulacandin D in which these methods serve as the key strategic steps.

Scheme 1

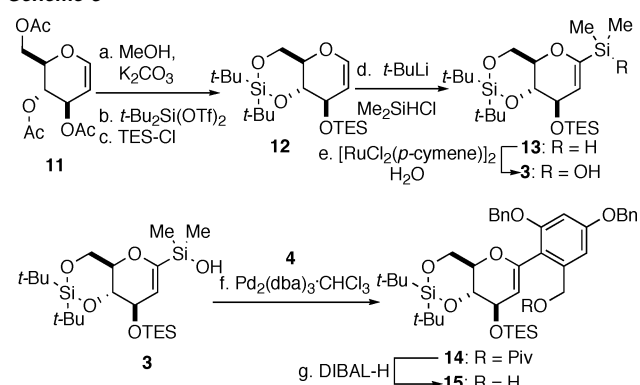


The synthetic plan began with the preparation of aromatic iodide **4**. Esterification of commercially available 3,5-dihydroxybenzoic acid to afford methyl ester **8** was followed by protection of the resorcinol hydroxyl groups with benzyl bromide and reduction of the ester with lithium aluminum hydride to afford benzyl alcohol **10** in near quantitative yield (three steps). Finally, iodination of **10** with *N*-iodosuccinimide provided the aromatic iodide, which was protected as the pivaloyl ester (**4**) in excellent yield (93%, two steps) (Scheme 2).

Scheme 2<sup>a</sup>

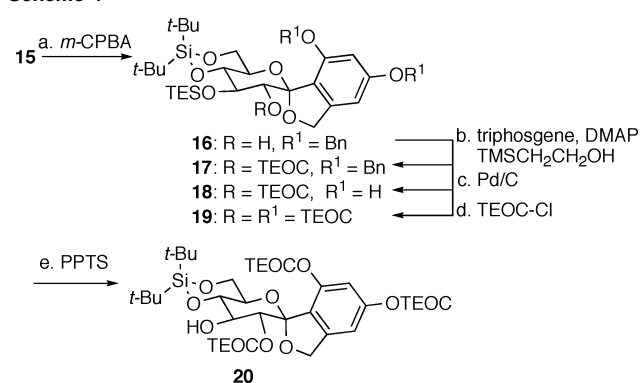
<sup>a</sup> Conditions: (a) SOCl<sub>2</sub>, MeOH, reflux, 2 h, >99%; (b) BnBr, K<sub>2</sub>CO<sub>3</sub>, acetone, room temp, 24 h, >99%; (c) LiAlH<sub>4</sub>, THF, 0 °C to room temp, 3 h, 98%; (d) *N*-iodosuccinimide, CHCl<sub>3</sub>, room temp, 24 h, 91%; (e) pivaloyl chloride, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, room temp, 3 h, 94%.

The preparation of the spirocyclic *C*-aryl glycopyranoside began by saponification of triacetate **11**<sup>18</sup> to give the free hexenopyranose which was immediately protected as its di(*tert*-butyl)silylene acetal (Scheme 3).<sup>19</sup> Protection of the C(3)-hydroxyl group with TES-Cl provided fully silyl protected hexenopyranose **12** in 91% yield (two steps). With **12** in hand, the stage was set for implementation of the key cross-coupling reaction. Thus, lithiation and silylation of **12** with chlorodimethylsilane provided **13**, which was subjected to oxidative hydrolysis catalyzed by bis[chloro(*p*-cymene)ruthenium(II)]<sup>20</sup> in the presence of 2.0 equiv of water to provide silanol **3** in 84% yield. Gratifyingly, the combination of aryl iodide **4** and the silanol **3** proceeded smoothly to afford aryl-hexenopyranose **14** in 82% yield. The vital cross-coupling reaction was carried out with 5 mol % Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> as the catalyst and 2.0 equiv of NaO*t*-Bu as the activator at 50 °C for 5 h. Removal of the pivaloyl group set the stage to elaborate the aryl-hexenopyranose.

Scheme 3<sup>a</sup>

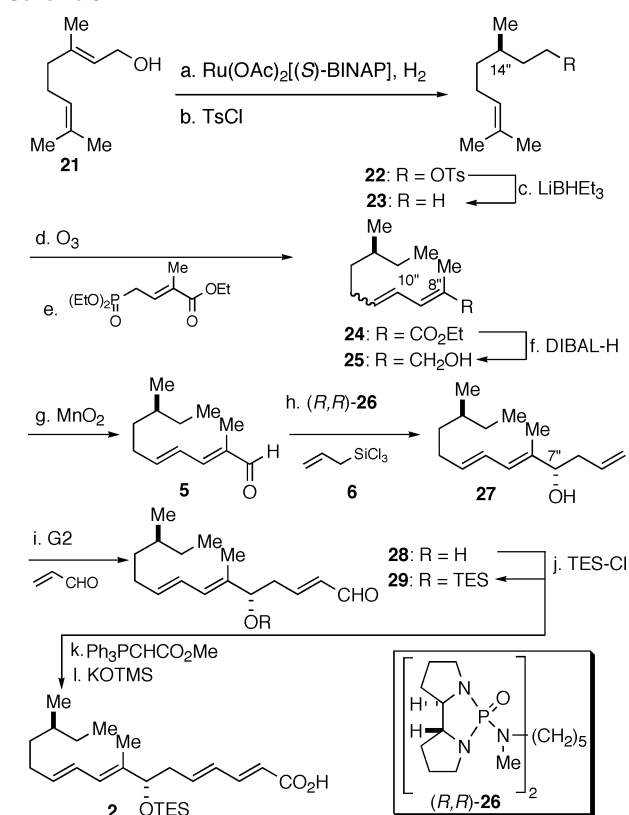
<sup>a</sup> Conditions: (a) K<sub>2</sub>CO<sub>3</sub> (0.01 equiv), MeOH, room temp, 1 h; *t*-Bu<sub>2</sub>Si(OTf)<sub>2</sub>, 2,6-lutidine, DMF, 0 °C to room temp, 2 h, 89%; (b) TES-Cl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, room temp, 4 h, 92%; (c) *t*-BuLi, Me<sub>2</sub>SiHCl, THF, -78 °C to room temp, 1 h, 89%; (d) [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (3.0 mol %), H<sub>2</sub>O (2.0 equiv), 1:1 benzene/CH<sub>3</sub>CN, room temp, 1 h, 84%; (f) Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, NaO*t*-Bu (2.0 equiv), toluene, 50 °C, 5 h, 82%; (g) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to room temp, 1 h, 98%.

The crucial spiro ketalization was effected by treatment of **15** with *m*-CPBA in the presence of NaHCO<sub>3</sub> to afford a mixture of chromatographically separable anomers **16** $\alpha$  (77%) and **16** $\beta$  (15%) (Scheme 4).<sup>21</sup> Initially, protection of the C(2) hydroxyl group was problematic; however, treatment of **16** with a preformed acylpyridinium species followed by addition of 2-(trimethylsilyl)ethanol gave 2-(trimethylsilyl)ethyl carbonate (TEOC)-protected spiro ketal in 92% yield. Debenzylation of **17** with Pd/C proceeded quantitatively. Subsequent TEOC protection of the resorcinol portion was achieved using TEOC-Cl<sup>22</sup> in the presence of 2,6-lutidine to produce the fully silylated spiro ketal **19** in 96% yield overall. Selective removal of the *O*-C(3) TES group with PPTS/EtOH afforded **20** in 93% yield.

Scheme 4<sup>a</sup>

<sup>a</sup> Conditions: (a) *m*-CPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h (dr 5:1, 77%  $\alpha$ , 15%  $\beta$ ); (b) triphosgene, DMAP, CHCl<sub>3</sub>, -56 °C to room temp; *i*-Pr<sub>2</sub>EtN, **16**, CHCl<sub>3</sub>, -56 °C to room temp, 2-(trimethylsilyl) ethanol, room temp, 12 h, 92%; (c) Pd/C, NaHCO<sub>3</sub>, H<sub>2</sub>, THF, room temp, 5 h, >99%; (d) TEOC-Cl, *i*-Pr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, room temp, 9 h, 96%; (e) PPTS, EtOH, room temp, 4 h, 92%.

Synthesis of the side-chain unsaturated acid **2** began by asymmetric hydrogenation of geraniol<sup>23</sup> with Ru(OAc)<sub>2</sub>[(*S*)-BINAP] to provide (*S*)-citronellol (99%, 97:3 er) (Scheme 5).<sup>24</sup>

Scheme 5<sup>a</sup>

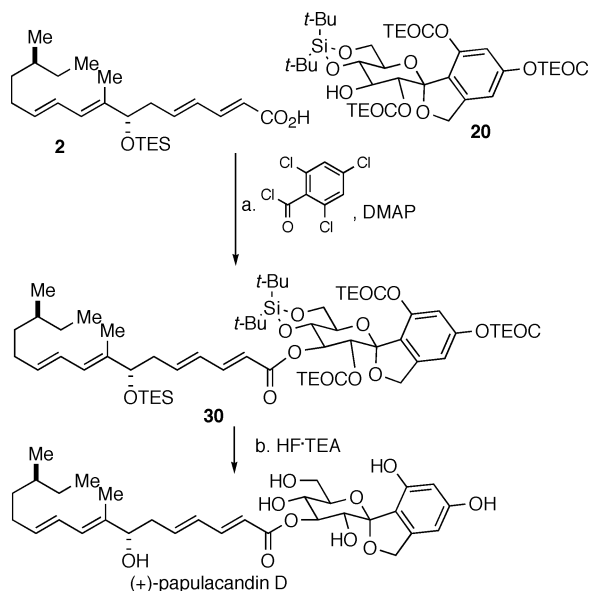
<sup>a</sup> Conditions: (a) Ru(OAc)<sub>2</sub>[(*S*)-BINAP] (0.7 mol %), H<sub>2</sub> (1500 psi), 95% MeOH, room temp, 20 h, 99% (97:3 er); (b) Ts-Cl, pyridine, room temp, 10 h, 89%; (c) LiHBEt<sub>3</sub>, THF, NaOH-H<sub>2</sub>O<sub>2</sub>, room temp, 1 h, 86%; (d) O<sub>3</sub>, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, -78 °C to room temp, DMS, 2.5 h; (e) (EtO)<sub>2</sub>POCH<sub>2</sub>C=C(CH<sub>3</sub>)CO<sub>2</sub>Et, LiOH, MS 4 Å, THF, reflux, 2 h, 78% (two steps) (*E,E/E,Z* 91:9); (f) DIBAL-H, THF, 0 °C, 0.5 h, 85% (pure *E,E*); (g) MnO<sub>2</sub>, CHCl<sub>3</sub>, reflux, 4 h, 89%; (h) (*R,R*)-**26** (10 mol %), **6**, CH<sub>2</sub>Cl<sub>2</sub>, *i*-Pr<sub>2</sub>EtN, -78 °C, 8 h, 88% (96:4 dr); (i) Grubbs' second generation catalysts (5.0 mol %), acrolein (13 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 90%; (j) TES-Cl, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, room temp, 4 h, 92%; (k) Ph<sub>3</sub>P=CCO<sub>2</sub>Me, ClCH<sub>2</sub>CH<sub>2</sub>Cl, reflux, 18 h, 90% (*E/Z* 90:10); (l) TMSOK, THF, room temp, 4 h, >99%.

Tosylation followed by deoxygenation with LiHBEt<sub>3</sub> afforded hydrocarbon **23** in good yield (88%, two steps). Subsequent

ozonolysis and Horner–Wadsworth–Emmons<sup>25</sup> olefination afforded unsaturated ester **24**, an inseparable mixture of isomers ( $\Delta^{10',11'}$  *E/Z*, 91:9). Subsequently, DIBAL-H reduction followed by chromatographic separation of the geometrical isomers and oxidation afforded aldehyde (*E,E*-**5** in 84% yield (four steps).

The enantioselective allylation of **5** using chiral bisphosphoramidate (*R,R*)-**26**<sup>17</sup> smoothly provided **27** in good yield and excellent diastereomeric selectivity (88%, dr 96/4). The expected C(7'') *S* configuration was confirmed by analysis of Mosher esters.<sup>26</sup> Olefin metathesis with acrolein using Grubbs' second generation catalyst,<sup>27</sup> and protection of the C(7'') hydroxyl group with TES-Cl gave **29** (91%, two steps). The synthesis of **2** was completed by Wittig olefination and saponification with potassium trimethylsilanoate<sup>28</sup> in excellent yield (90%, two steps).

The coupling of fragments **2** and **20** was achieved via the mixed anhydride of acid **1** from 2,4,6-trichlorobenzoyl chloride<sup>29</sup> and DMAP in good yield (87%) (Scheme 6). Global deprotection proceeded smoothly with HF/Et<sub>3</sub>N (60:40 ratio) in DMSO to afford papulacandin D (89% yield). Synthetic papulacandin D exhibited spectroscopic and physical properties identical to those reported for the natural and synthetic material (<sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS, optical rotation, UV–vis).<sup>1,13</sup>

Scheme 6<sup>a</sup>

<sup>a</sup> Conditions: (a) 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl, Et<sub>3</sub>N, room temp, 1 h, **20**, toluene, room temp, 3 h, 87%; (b) HF·Et<sub>3</sub>N (60:40 ratio), DMSO, 60 °C, 15 h, 89%.

In conclusion, papulacandin D has been synthesized by a convergent synthetic strategy that features a silicon-based, cross-coupling reaction to construct the key spirocyclic C-aryl glycopyranoside **16** and an enantioselective allylation reaction using a chiral bisphosphoramidate for the construction of the C(7'') stereocenter. The application of palladium-catalyzed, silicon-based, cross-coupling reactions in the synthesis of more complex molecules is currently under investigation.

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**Supporting Information Available:** Detailed experimental procedures, full characterization of all products, and comparison NMR

spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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