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# De novo synthesis of a *galacto*-papulacandin moiety via an iterative dihydroxylation strategy

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**Abstract**—A short and highly efficient route to both the pyranose and furanose forms of a *galacto*-papulacandin ring system has been developed. The key to the overall transformation is the sequential two osmium-catalyzed dihydroxylation reactions of substituted 2,4-dienone. The resulting tetrol can be efficiently transformed into the two spiroketal moieties of *galacto*-papulacandin, which can also be inter-converted via acid catalyzed equilibration.


The papulacandins are a class of naturally occurring glycolipids with potent antifungal activity against *Candida albicans* and several other yeasts.[1] They are also found to be active against *P. carinii pneumonia*, a most prevalent opportunistic infection that is a frequent cause of death in AIDS patients.[1] The papulacandins were isolated from the fermentation broths of *Papularia sphero-sperma*[2] and *Dictyochaeta simplex*.[3] The mechanism of action for the papulacandins is believed to be the inhibition of 1,3-α-D-glucan synthase, which is essential for cell wall construction in fungal cells but not exist in human cells.[4]

Of the papulacandins A–D, papulacandin C is the most active member (Fig. 1). Papulacandin C contains a lactose disaccharide with the *gluco*-sugar converted to a spirocyclic arylglycoside. On each sugar there is an unsaturated fatty acid, linked at the *C*-3 and *C*-6′ hydroxyl groups. The simplest member, papulacandin D, lacks the *C*-4 galactose with the *C*-6′ acyl group.

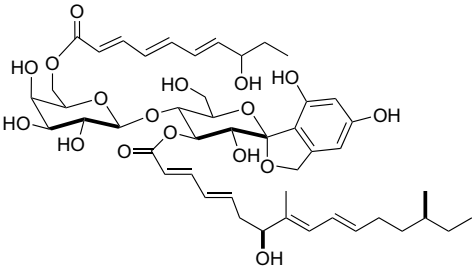

**Figure 1.** Papulacandin C.

The high degree of selective toxicity and the fascinating molecular structure of the papulacandins have stimulated a significant amount of both biological[5] and synthetic research by a number of research groups.[6] So far, only one member of the papulacandins has ceded to total synthesis that being by the efforts of Barrett et al.[7] Hitchcock and his group at Lilly have completed a semi-synthesis of papulacandin D by attaching the more readily available papulacandin A side chain to the papulacandin D ring system.[8] These two routes, when taken together, can be used to assign the absolute stereochemistry of the *C*-3 acyl side chain for both papulacandin A and papulacandin D.

With the exception of the work from the Danishefsky group[6a] and our own,[9] all other routes to the papulacandins derived their asymmetry from D-glucose. Danishefsky used a Diels–Alder strategy to construct the spiroketal portion of the papulacandins, in which the asymmetry was derived from a combination of chiral auxiliary and chiral Lewis acid.[6a] Our group has developed an approach to the mannose, allose and glucose stereoisomers of the papulacandin ring system via an asymmetric dihydroxylation of 5-aryl-2-vinyl furans (**1a**–**c** from **2**, Scheme 1), followed by an Achmatowicz rearrangement.[10] The route initially generated a mixture

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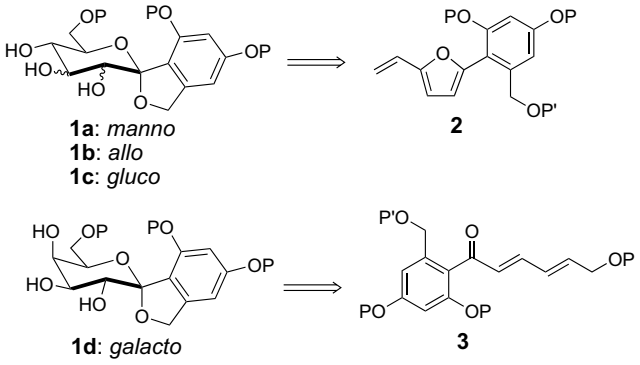



**Scheme 1.** De novo approaches to various papulacandins.

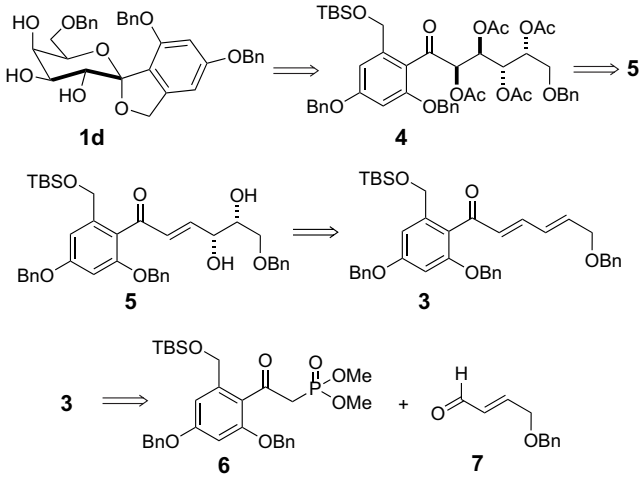
of *manno*- and *allo*-papulacandins (**1a/b**) and using an oxidation/reduction strategy, converted the *manno*-isomer to the *gluco*-isomer (**1a** to **1c**).[9]

In the context of a research program aimed at the synthesis and biological study of the papulacandins and various analogues, we have been looking for an easy entry into the spiroketal moiety of a *galacto*-papulacandin. In particular, we desired a *galacto*-papulacandin **1d** to examine it as both a potential glycosidase and a glycosyl transferase inhibitor. While in theory **1d** could be prepared from the *gluco*-isomer **1c**, in practice this would require too many additional steps. Thus we decided to investigate an alternative de novo approach to a *galacto*-papulacandin **1d**. Ultimately we hoped that a *galacto*-isomer like **1d** would lead to the formation of disaccaride papulacandins via an $S_N2$-type inversion at *C*-4.

For some time, we have been exploiting the efficiency of the Sharpless asymmetric dihydroxylation of various 2,4-dienoates for synthesis.[11] Quite recently we disclosed our discovery that various *galacto*-sugars can be easily prepared from 2,4-dienoates iteratively using the Sharpless asymmetric dihydroxylation.[12] Herein we would like to describe a new strategy for construction of the spiroketal moiety of *galacto*-papulacandin **1d** via a similar iterative osmium-catalyzed dihydroxylation reaction of substituted 2,4-dienone **3** (Scheme 2).

Retrosynthetically, we envisioned constructing the desired dienone **3** by an HWE-olefination of β-keto phosphonate **6** with the known aldehyde **7**. The β-keto phosphonate **6** was easily prepared from the 3,5-dibenzyloxy benzyl alcohol **8** in four steps and excellent overall yield 56% (Scheme 3). The benzylic alcohol **8** was selectively iodinated with NIS and then protected to form TBS ether **9** in excellent overall yield (91%). Carbonylation of **9** with catalytic palladium in methanol gave **10** in 82% yield, which upon exposure to a lithiated trimethylphosphate gave β-keto phosphonate **6** in 75% yield.

With ample supplies of phosphonate **6**, we next investigated the synthesis of dienone **3** and its subsequent bis-dihydroxylation (Scheme 4). Exposure of **6** and **7** to $Cs_2CO_3$ in *i*-propanol gave a good yield of the desired dienone **3** (70% yield). [13,14] The 2,4-dienone **3** was

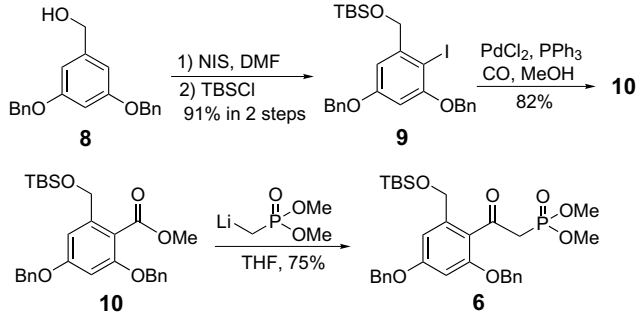



**Scheme 2.** Retrosynthetic analysis of *galacto*-papulacandin.

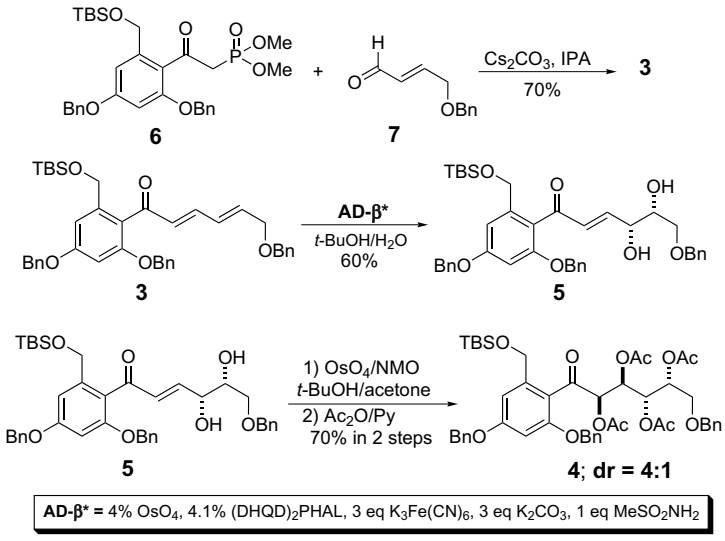
exposed to the typical Sharpless AD-mix procedure (4% $OsO_4$/4.1% $(DHQD)_2$ PHAL, 3 equiv of $K_3Fe(CN)_6/K_2CO_3$, 1 equiv of $MeSO_2NH_2$) to give diol **5** in a good yield (60%) and high enantiomeric excess (90% ee).[15] As we found with the dienoates,[12] this double bond selectivity in the dihydroxylation of dienone **3** can be explained in terms of electron density of the π-system; where as, the second double bond does not react under the reaction conditions because of a mismatch between the reagent ($(DHQD)_2PHAL/OsO_4$) and substrate (**5**).[12]

The mismatch between the substrate and reagent was also seen when the ligand ($(DHQD)_2PHAL$) was removed from the AD-mix reaction condition (Scheme 4).[16] Thus, when diol **5** were exposed to the typical Upjohn procedure ($OsO_4$/NMO in *t*-BuOH/acetone), it reacted with achiral $OsO_4$ to afford tetrol product with good conversion, which was isolated as their corresponding tetra-acetate **4** (70% yield in two steps) with 4:1 diastereomeric ratio.[17] Once the minor diastereomer was removed by silica gel chromatography the tetra-acetate **4** was obtained with essentially complete enantiomeric and diastereomeric purity.

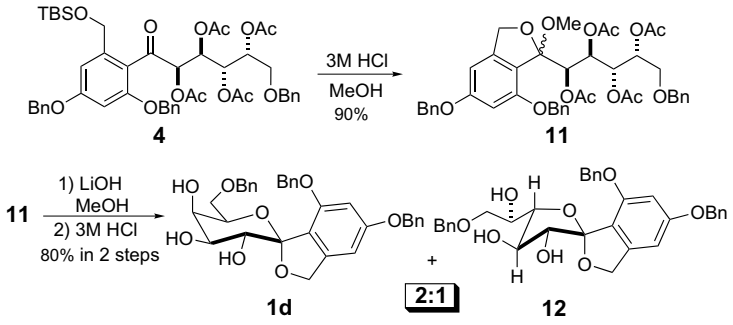
Deprotection of TBS group from tetra-acetate **4** using 3 M HCl/MeOH afforded the mixed ketal **11** in excellent yield (90%). Exposure of **11** to the global acetate deprotection (5 equiv LiOH/MeOH), followed by spiro-




**Scheme 3.** Synthesis of β-keto phosphonate.




**Scheme 4.** Regio- and diastereoselective dihydroxylation.

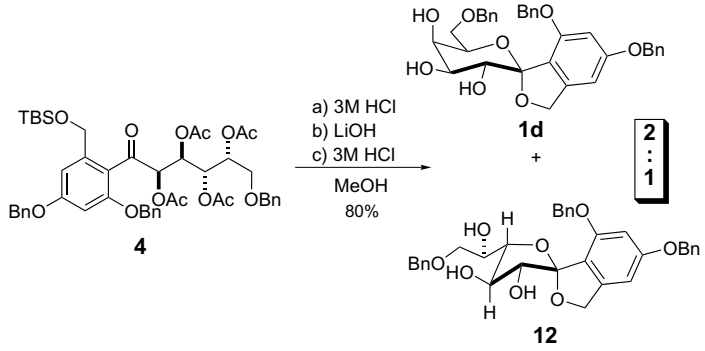



**Scheme 5.** Deprotection and spiroketalization.

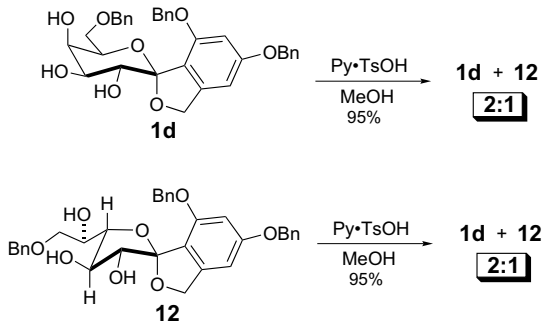
ketalization of the crude material using 3 M HCl afforded *galacto*-pyrano papulacandin **1d** and *galacto*-furano papulacandin **12** as 2:1 ratio and good yield (80%; Scheme 5).[18]

By simply keeping track of the exact amounts of acid and base used in the deprotection/spiroketalization steps an improved one-pot procedure was achieved (Scheme 6). Thus exposing a MeOH solution of tetra-acetate **4** to 1 equiv of HCl (3 M), then 5 equiv of LiOH, followed by 6 equiv of HCl (3 M) gave the same 2:1 mixture of **1d** and **12** in an improved overall yield (80%).

To establish whether **1d** and **12** were formed via thermodynamically controlled process the two isomers were separately equilibrated under mildly acidic conditions until identical ratios were achieved. Thus, the *galacto*-pyrano-papulacandin **1d** and *galacto*-furano-papulacandin **12** were separately exposed to a catalytic amount of Py·TsOH (10%) in methanol. After 36 h, crude $^1$H NMR




**Scheme 6.** One-pot deprotection and spiroketalization.




**Scheme 7.** Spiroketal equilibration.

analysis indicated that both solutions had equilibrated to the original 2:1 ratio. It is important to note that these equilibrated mixtures of isomers were re-isolated in excellent yields (95% yield, Scheme 7); therefore, indicated that neither isomer was being selectively destroyed under the reaction conditions.

In summary, we have developed a concise de novo approach to both the pyranose and furanose forms of a *galacto*-papulacandin (**1d** and **12**) from 2,4-dienone **3** in four steps and 33% overall yield. The complete synthesis requires only nine total steps from commercially available 3,5-dibenzyloxybenzyl alcohol **8**, which has provided significant quantities (~500 mg in three batch) of material for both biological study and further synthetic efforts toward papulacandin C.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.073.

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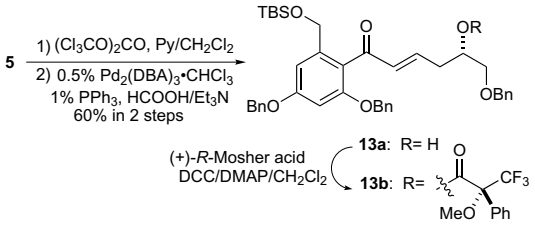


16. When diol **5** was dihydroxylated with the matched reagent system ($(DHQ)_2PHAL/OsO_4$) gave the same selectivity as the $OsO_4$/NMO reaction but in a lower overall yield (44%).
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18. Major Isomer (**1d**): $R_f$ (EtOAc) = 0.32; mp 151 °C; $[\alpha]_D^{25}$ 12.7 (*c* 1, $CH_2Cl_2$); IR (thin film, $cm^{-1}$) 3480, 2957, 2921, 2873, 2360, 1637, 1540, 1494, 1456, 1418, 1338, 1154, 1092, 1064, 980; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.39 (m, 15H), 6.51 (d, $J$ = 1.2 Hz, 1H), 6.42 (d, $J$ = 1.8 Hz, 1H), 5.15 (d, $J$ = 12 Hz, 1H), 5.11 (d, $J$ = 11.4 Hz, 1H), 5.09 (d, $J$ = 11.4 Hz, 1H), 5.07 (d, $J$ = 12 Hz, 1H), 5.03 (s, 2H), 4.65 (dd, $J$ = 9.0, 8.4 Hz, 1H), 4.57 (d, $J$ = 12 Hz, 1H), 4.52 (d, $J$ = 12 Hz, 1H), 4.19 (ddd, $J$ = 6.0, 4.2, 1.2 Hz, 1H), 4.14 (ddd, $J$ = 7.2, 4.2, 1.2 Hz, 1H), 3.87 (ddd, $J$ = 9.0, 4.2, 4.2 Hz, 1H), 3.80 (dd, $J$ = 10.2, 6.0 Hz, 1H), 3.73 (dd, $J$ = 10.2, 4.8 Hz, 1H), 2.83 (d, $J$ = 3.6 Hz, 1H), 2.65 (d, $J$ = 6.0 Hz, 1H), 1.89 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 162.1, 154.9, 143.4, 137.8, 136.5, 136.4, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.1, 127.8, 127.7 (2C), 127.6, 127.4 (2C), 126.9 (2C), 118.2, 110.8, 100.5, 98.4, 73.6, 73.0, 72.5, 70.9, 70.4, 70.3, 70.2, 70.0, 69.9; CIHRMS: Calculated for $[C_{34}H_{34}O_8+Na]^+$: 593.2151, found: 593.2125.
Minor Isomer (**12**): $R_f$ (EtOAc) = 0.27; $[\alpha]_D^{25}$ –9.9 (*c* 1, $CH_2Cl_2$); IR (thin film, $cm^{-1}$) 3480, 2957, 2921, 2851, 2360, 1637, 1540, 1494, 1456, 1418, 1338, 1154, 1114, 1092, 1064, 980, 731; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.39 (m, 15H), 6.51 (d, $J$ = 1.2 Hz, 1H), 6.38 (d, $J$ = 1.8 Hz, 1H), 5.18 (d, $J$ = 12.6 Hz, 1H), 5.11 (d, $J$ = 12 Hz, 1H), 5.08 (d, $J$ = 12 Hz, 1H), 5.02 (s, 2H), 4.96 (d, $J$ = 12.6 Hz, 1H), 4.77 (dd, $J$ = 9.0, 8.4 Hz, 1H), 4.56 (d, $J$ = 12.6 Hz, 1H), 4.53 (d, $J$ = 12.6 Hz, 1H), 4.29 (dd, $J$ = 8.4, 7.2 Hz, 1H), 3.95 (dd, $J$ = 7.2, 4.8 Hz, 1H), 3.91 (ddd, $J$ = 6.6, 6, 4.8 Hz, 1H), 3.60 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.53 (dd, $J$ = 9.6, 7.2 Hz, 1H), 2.93 (d, $J$ = 1.2 Hz, 1H), 2.81 (d, $J$ = 6.0 Hz, 1H), 2.49 (d, $J$ = 10.2 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 162.3, 155.1, 143.3, 137.7, 136.4, 136.2, 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.1,128.0, 127.8, 127.7 (2C), 127.4 (2C), 127.0 (2C), 116.0, 114.2, 100.4, 98.1, 81.3, 78.6, 76.2, 73.5, 72.8, 71.4, 70.4, 70.3, 69.9; CIHRMS: calculated for $[C_{34}H_{34}O_8+Na]^+$: 593.2151, found: 593.2109.