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Enantioselective Synthesis of the Papulacandin Ring System: Conversion of the Mannose Diastereoisomer into a Glucose Stereoisomer

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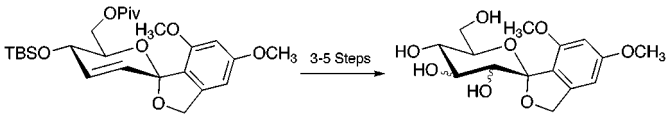
ABSTRACT



An enantioselective synthesis of three diastereoisomers of the *C*-arylglycoside tricyclic spiroketal nucleus of the papulacandins has been achieved, in which the initial asymmetry was introduced via a Sharpless dihydroxylation of substituted 5-aryl-2-vinylfurans. A selective oxidation–reduction sequence converted the mannose isomer into the glucose isomer. This sequence can conveniently produce both the papulacandin ring system along with its enantiomer and diastereomers in only 10–14 steps from 3,5-dimethoxybenzyl alcohol in 5–8% overall yield.

The discovery of antifungal agents that possess a high degree of selective toxicity against fungal cells remains an important scientific challenge. The need for antifungal agents is evident in that *Pneumocystis carinii* pneumonia is the most prevalent opportunistic infection in AIDS patients worldwide and a frequent cause of death.[1] An attractive enzyme target for the development of new antifungal agents is 1,3-β-glucan synthase, which is necessary for cell wall construction in fungi but not humans.[2] Several proposed 1,3-β-glucan synthase inhibitors were evaluated for their ability to control *P. carinii* pneumonia in vivo.[1a] Emerging from these studies was a class of spiroketal mono- or disaccharide natural products, the papulacandins.[3]

The papulacandins are a group of naturally occurring glycolipid antifungal agents isolated from the fermentation broths of *Papularia spherosperma*[3] and *Dictyochaeta simplex*.[4] There are various members in this family, which differ in acyl side chain substitution at C-3 and C-6′. The papulacandins A−D[5,6] (Figure 1) and the more recently isolated new members Mer-WF3010,[7] L-687−781,[8] Bu-4794F,[9] and BE-29602[10] all share a common spiroketal residue. The simplest member, papulacandin D, lacks the C-4 galactose with the C-6′ acyl group. All the isolated papulacandins have shown antifungal activity.

The papulacandin's high degree of selective toxicity and

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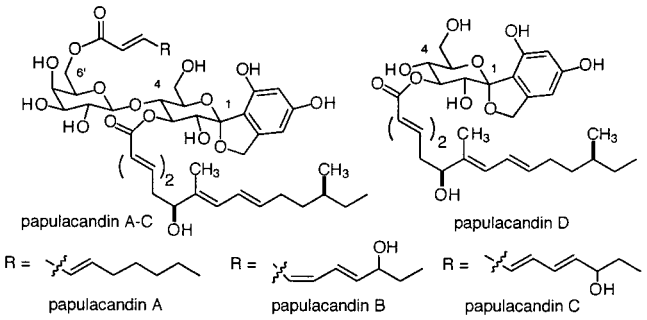

Figure 1.

the fascinating molecular structure have stimulated a significant amount of both biological[5,7,9,11] and synthetic investigations by a number of research groups.[12] So far, only one member of the papulacandins has succumbed to total synthesis, that being papulacandin D by the Barrett group.[13] Hitchcock and his group at Eli Lilly have completed a semisynthesis of papulacandin D by attaching the more readily available papulacandin A side chain to the papulacandin D ring system.[14] These two routes both correlated and assigned the C-3 acyl side chain absolute stereochemistry of papulacandins A and D.

With the exception of the work from the Danishefsky group[12a] and our own,[15] all other routes to the papulacandins derive 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.[12a] Our group has developed an approach to the mannose stereoisomers of the papulacandin ring system via an asymmetric dihydroxylation of 5-aryl-2-vinylfurans (vide infra).[15,16] In addition to potentially improved routes to the papulacandins, a synthetic route from achiral starting materials will allow for the preparation of analogues (i.e., D- and L-sugars as well as *manno*- and *allo*-isomers). Because of the difficulties Barrett encountered in introducing the acyl side chain on the C-3 hydroxyl group,[13] we decided to synthesize a mannopyranoside isomer of papulacandin D, which may allow for simple acylation of C-3 and then inversion at C-2.

In the context of a research program aimed at the synthesis and study of the mechanism of action of the papulacandins, we targeted three [4.5]spirocyclic ketal containing papulacandin stereoisomers **1**, **2**, and **3** for synthesis and study as glycosidase inhibitors (Figure 2). A key aspect to our study

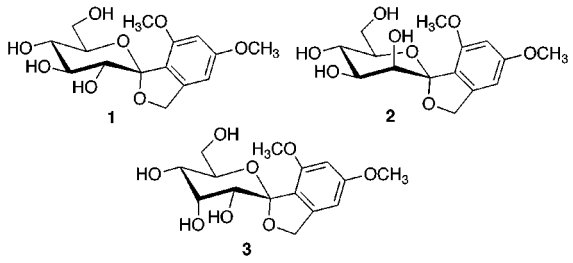

Figure 2.

is to test the hypothesis that an iminosugar will nicely mimic the spiroketal ring system of the papulacandins.[17] Crucial for testing this hypothesis is the development of a synthetic sequence to diastereomers of the papulacandin ring system that will allow for testing against their corresponding glycosidase enzymes and comparison with their analogous iminosugar analogues. Herein we would like to report our achievement of the enantioselective synthesis of three papulacandin spiroketal diastereoisomers, glucose **1**, mannose **2**, and allose **3**.

Previously, we have reported the Sharpless asymmetric dihydroxylation reaction on vinylfurans and have applied this methodology to synthesize various D- or L-hexoses.[18,19] More recently, we have described an asymmetric dihydroxylation of 5-substituted vinylfuran for the synthesis of enantioenriched furyl alcohols such as **4**,[15] which were converted via an Achmatowicz[20] oxidation/Luche[21] reduction sequence

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(13) For a synthesis of a papulacandin D and for relevant references, see: Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.

(14) Hitchcock, S. A.; Gregory, G. S.; Kraynack, E. A.; Mayhugh, D. R. Presented at the 218th National Meeting of the American Chemical Society, New Orleans, Aug 22−26, 1999.

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(17) It has been proposed that the spiroketal ring system inhibits the enzyme $\beta(1-3)$glucan synthases as a transition state inhibitor analogously with iminosugars; in fact, Urbina has found some simple arylamines inhibit fungal cell wall synthesis. See: Urbina, J. M.; Cortes, J. C. G.; Palma, A. *Bioorg. Med. Chem.* **2000**, *8*(4), 691.

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(21) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *110*, 2226.

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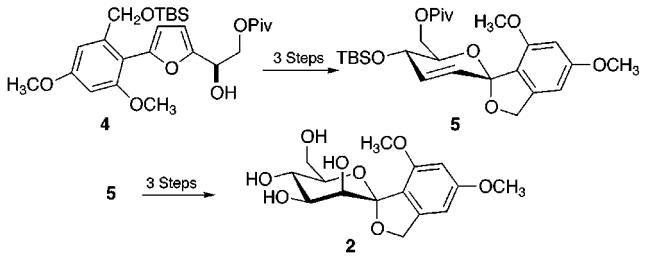
into spiroketals such as **5** (Scheme 1).[22] Finally the spiroketal **5** was converted into the *manno*-papulacandin **2** via a

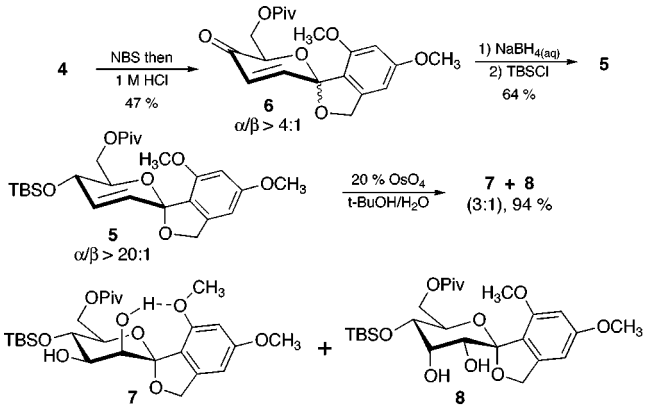
Scheme 1



dihydroxylation/deprotection sequence. Herein we would like to disclose the synthesis of the allose and glucose diastereoisomers **1** and **3** from the spiroketal **5**.

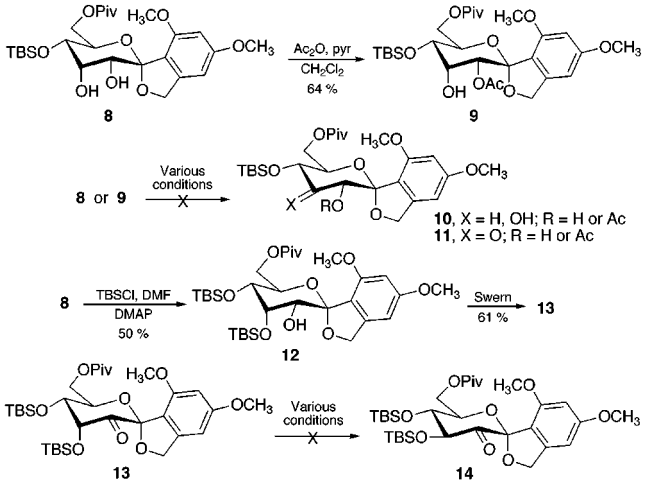
Exposure of **4** to aqueous NBS conditions oxidatively rearranges the furyl alcohol into a 4:1 mixture of spiroketals **6** (47% yield) after treatment with aqueous acid (Scheme 2). Both anomers of the enone **6** were stereoselectively

Scheme 2



reduced with aqueous $NaBH_4$ and protected with TBSCl to give a single stereoisomer of **5** (64% yield). Treating a *t*-BuOH/H_2O solution of **5** with OsO_4/NMO at 80 °C resulted in a 3:1 ratio of diols **7** and **8** in a 94% combined yield. The relative stereochemistry of the *manno*-diol **7** was assigned by examination of coupling constants and confirmed by single crystal X-ray analysis. The allose stereochemistry for diol **8** was assigned by examination of analogous coupling constants. With a rapid and convenient route to the mannose and allose isomers **7** and **8**, we turned our attention toward the conversion of the less desirable allose isomer **8** into the glucose isomer **10** (Scheme 3). The diol **8** was easily differentiated to form the C-2 acetate **9** and C-3 TBS-ether **12** by selective protections with Ac_2O and TBSCl, respectively. Unfortunately, we were unsuccessful in uncovering conditions for the inversion of the C-3 axial alcohol of **8** or **9** into the glucose isomer **10** or **11**. These efforts included Mitsunobu conditions, mesylate and triflate formation, and various oxidation conditions (e.g., Swern and Dess−Martin).

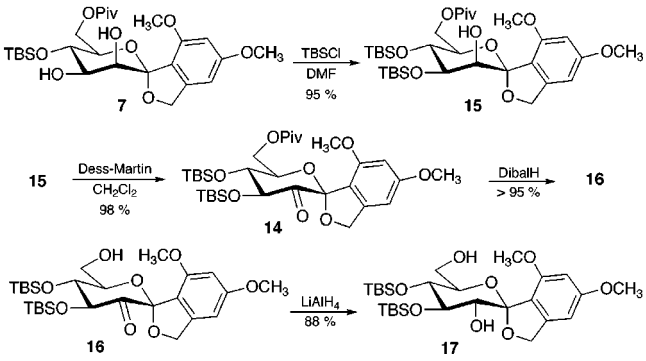
Scheme 3



In contrast to the axial alcohol of **9**, the equatorial C-2 alcohol of **12** was easily oxidized to the C-2 ketosugar **13**; however no C-3 epimer was found under various acid or basic epimerization conditions (e.g., TsOH/MeOH, DABCO/THF, Et_3N/MeOH).

Although we were unsuccessful at converting the allose isomers **8** into the glucose stereochemistry, success was achieved at converting the mannose isomer **7** into the *gluco*-isomer **17** (Scheme 4). By taking advantage of the hydrogen

Scheme 4

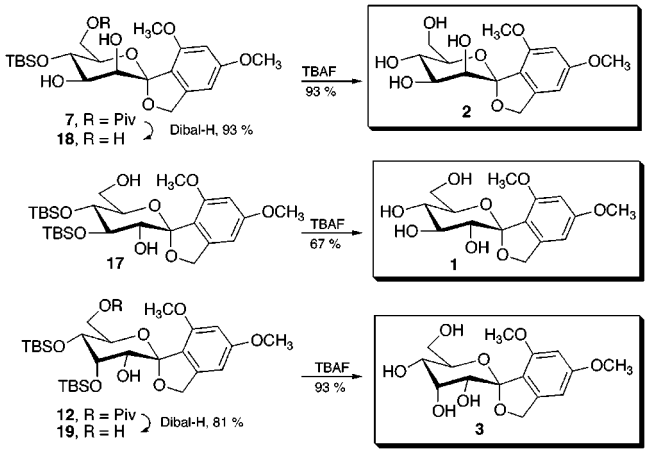


bond that exists between the C-2 axial alcohol and the C-12 methoxy group in **7**, the diols were easily differentiated with excess TBSCl, affording **15** in good yields (95%). The axial C-2 alcohol of **15** was cleanly oxidized to the 2-ketosugar **14** under Dess−Martin conditions (98% yields). All that remained was to find a suitable reducing agent that would reduce the ketone functionality of **14** to the desired equatorial alcohol. Various borohydride reagents were examined to no avail; no reaction occurred even with excess $NaBH_4$ in refluxing MeOH. Switching to $LiAlH_4$ at room temperature provided sufficient reactivity to reduce the C-2 ketone, providing a 1:1 mixture of the depivolated glucose isomer **17** in addition to its mannose isomer. Selective reduction

was achieved by switching to the more hindered reducing agent, Dibal-H. This greater selectivity was proven in that the C-6 pivolate group could be selectively deprotected upon the addition at −78 °C of 2 equiv of Dibal-H, affording the ketosugar **16** in >95% yield. The C-2 ketone of **16** was selectively reduced upon exposure at −78 °C of 2 equiv of $LiAlH_4$, providing **17** in an 88% yield as a single stereoisomer.

With access to protected forms of the allose, glucose, and mannose sugars, we decided to investigate the deprotection of **7**, **12**, and **17** to form the unprotected hexoses **1**, **2**, and **3**. Selection of the appropriate deprotected sequence was crucial, because purification of the crude reaction mixture proved to be quite difficult. After some experimentation, it was discovered that TBAF-mediated TBS removal followed by Florisil chromatography provides access to substantial amounts of pure materials.[23] The deprotected mannose isomer **2** was produced from **7** in a straightforward manner (Scheme 5). The C-6 pivolate of was removed upon the treatment of

Scheme 5



Dibal-H, affording the triols **18** in excellent yield (93%). The C-4 TBS ether of **18** were removed upon treatment with a THF solution of TBAF, providing the deprotected *manno*-papulacandin **2** in good yield (93%). The partially and fully deprotected glucose sugar **1** was produced from **17** in a similar manner (Scheme 5). Treatment of a THF solution of **17** with TBAF provided **1** in a 67% yield.

Finally, the deprotected allose sugar **3** was produced from **12** by a similar Dibal-H/TBAF deprotection sequence. The C-6 pivolate of **12** was removed with Dibal-H, affording the diol **19** in excellent yield (81%), and exposure of **19** to TBAF cleanly removed the C-2 and C-3 TBS groups, producing the allose spiroketals **3** (93%).[24]

In summary, we have synthesized the three stereoisomeric papulacandin derivatives **1**, **2**, and **3** from the furyl alcohol **4**. This sequence can conveniently produce for the first time both the papulacandin ring system and its enantiomer and diastereomers in only 10−14 steps from 3,5-dimethoxybenzyl alcohol and 5−8% overall yield. The strategy disclosed herein allows access to significant quantities (∼50−100 mg from several runs) of these diastereomeric papulacandin analogues for evaluation as glycosidase and glycosyl transferase inhibitors as well as further biological analysis. Currently, we are applying the same sequence on the 3,5-dibenzyloxybenzyl alcohol to produce the free resorcinol forms of **1**, **2**, and **3**. The results of such investigations will be reported in due course.

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

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(23) The significance of this procedure is evident in that previous synthetic routes to the glucose paplulacandin isomer **1** only provided impure materials, which were characterized as their tetraacetates: see ref 12i.

(24) The allose papulacandin **3** was also prepared from **8** by this sequence; however, the intermediate triol was difficult to characterize because of TBS group migration.