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Sharpless Asymmetric Dihydroxylation of 5-Aryl-2-vinylfurans: Application to the Synthesis of the Spiroketal Moiety of Papulacandin D

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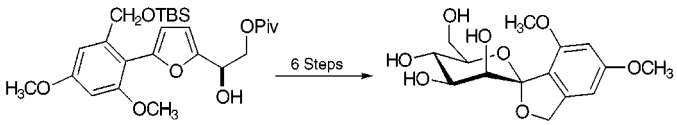
ABSTRACT



Using the Sharpless catalytic asymmetric dihydroxylation reaction on 5-aryl-2-vinylfurans, diols are produced in high enantioexcess. The resulting diols can be efficiently transformed into the spiroketal ring precursor of the antifungal compound papulacandin D. Stereoselective reduction of this precursor followed by a diastereoselective dihydroxylation completes the synthesis of a mannopyranoside isomer of a papulacandin derivative.

The papulacandins are a group of naturally occurring glycolipid-antifungal agents isolated from the fermentation broths of *Papularia spherosperma*[1] and *Dictyochaeta simplex*.[2] The papulacandins inhibit 1,3-β-glucan synthase which is essential for cell wall construction in fungal cells but not human cells.[3] Members of the papulacandin family exhibit potent in vitro activity against *Candida albicans* and related microorganisms. They are also found to be effective against *P. carinii pneumonia*, a most prevalent opportunistic infection that is a frequent cause of death in AIDS patients.[4] The high degree of selective toxicity and the fascinating molecular structure 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 succumbed to total synthesis, that being by the efforts of the Barrett group.[7]

In the context of a research program aimed at the synthesis of the papulacandins and analogues, we have been looking for an easy entry into the spiroketal moiety of compound **1**.

(1) Traxler, P.; Gruner, J.; Auden, J. A. L. *J. Antibiot*. **1977**, *30*, 289.

(2) (a) Van Middlesworth, F.; Omstead, M. N.; Schmatz, D.; Bartizal, K.; Fromtling, R.; Bills, G.; Nollstadt, K.; Honeycutt, S.; Zweerink, M.; Garrity, G.; Wilson, K. *J. Antibiot*, **1991**, *44*, 45. (b) Jabri, E. D. R.; Quigley, M.; Alders, M.; Hrmova, M.; Taft, C. S.; Phelps, P.; Selitrennikoff, C. P. *Curr. Microbiol*. **1989**, *19*, 153. (c) Bartizal, K.; Abruzzo, G.; Trainor, C.; Krupa, D.; Nollstadt, K.; Schmatz, D.; Schwartz, R.; Hammond, M.; Balkovec, J.; Van Middlesworth, F. L. *Antimicrob. Agent Chemother*. **1992**, *36*, 1648.

(3) (a) Baguley, B. C.; Rommele, G.; Gruner, J.; Wehrli, W. *Eur. J. Biochem*. **1979**, *97*, 345. (b) Perez, P.; Varona, R.; Garcia-Acha, I.; Duran, A. *FEBS Lett*. **1981**, *129*, 249. (c) Varona, R.; Perez, P.; Duran, A. *FEMS Microbiol. Lett*. **1983**, *20*, 243. (d) Rommele, G.; Traxler, P.; Wehrli, W. *J. Antibiot*. **1983**, *36*, 1539.

(4) (a) Schmatz, D. M.; Romancheck, M. A.; Pittarelli, L. A.; Schwartz, R. E.; Fromtling, R. A.; Nollstadt, K. H.; Van Middlesworth, F. L.; Wilson, K. E.; Turner, M. J. *Proc. Natl. Acad. Sci. U.S.A*. **1990**, *87*, 5950. (b) Kovacs, J.; Masur, H. *J. Infect. Dis*. **1988**, *158*, 254.

(5) (a) Kaneto, R.; Chiba. H.; Agematu, H.; Shibamoto, N.; Yoshioka, T.; Nishida, H.; Okamoto, R. *J. Antibiot*. **1993**, *46*, 247. (b) Chiba, H.; Kaneto, R.; Agematu, H.; Shibamoto, N.; Yoshioka, T.; Nishida, H.; Okamoto, R. *J. Antibiot*. **1993**, *46*, 356−358. (c) Aoki, M.; Andoh, T.; Ueki, T.; Masuyoshi, S.; Sugawara, K.; Oki, T. *J. Antibiot*. **1993**, *46*, 952. (d) Okada, H.; Nagashima, M.; Suzuki, H.; Nakajima, S.; Kojiri, K.; Suda, H. *J. Antibiot*. **1996**, *49*, 103. (e) Traxler, P.; Fritz, H.; Fuhrer, H.; Richter, W. J. *J. Antibiot*. **1980**, *33*, 967.

(6) For other approaches to the papulacandin ring system, see: (a) Danishefsky, S.; Philips, G.; Ciufolini, M. *Carbohydr. Res*. **1987**, *171*, 317. (b) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163. (c) Friesen, R. W. Sturino, C. F. *J. Org. Chem*. **1990**, *55*, 5808. (d) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem*. **1994**, *72*, 1262. (e) Friesen, R. W.; Daljeet, A. K. *Tetrahedron Lett*. **1990**, *31*, 6133. (f) Dubois, E.; Beau, J.-M. *Tetrahedron Lett*. **1990**, *31*, 5165. (g) Dubois, E.; Beau, J.-M. *Carbohydr. Res*. **1992**, *223*, 157. (h) Rosenblum, S.; Bihovsky, M. *J. Am. Chem. Soc*. **1990**, *112*, 2746. (i) Czernecki, S.; Perlat, M. C. *J. Org. Chem*. **1991**, *56*, 6289. (j) Barrett, A. G. M.; Dhanak, D.; Lebold, S. A.; Pena, M.; Pilipauskas, D. *Pest. Sci*, **1991**, *31*, 581. (k) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc*. **1995**, *117*, 6605.

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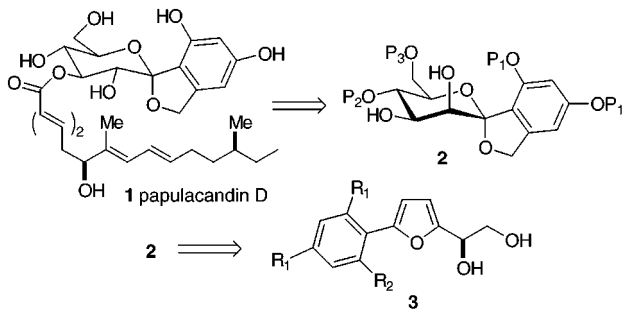
Because of the difficulties Barrett had in introducing the acyl side chain on the C-3 hydroxyl group, we decided to synthesize a mannopyranoside isomer of papulacandin D which may allow for simple acylation of C-3 and then inversion at C-2. Accordingly, we targeted [4.5]spirocyclic ketal **2** as a potentially versatile entry point for the synthesis of various papulacandins as well as analogues. Herein we describe our novel strategy for constructing the key intermediate **2** via a catalytic enantioselective oxidation of an achiral 5-aryl-2-vinylfuran.[8,9]

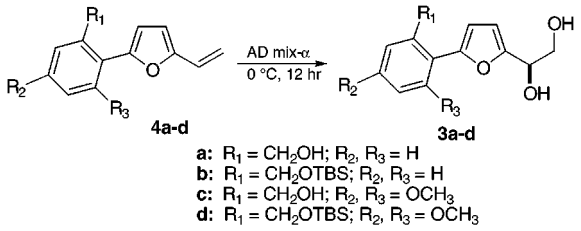
Sharpless asymmetric dihydroxylation of 5-substituted vinylfurans[10] should yield **3**, which upon Achmatowicz oxidative ring expansion, spiro-cyclization, Luche reduction, and dihydroxylation should afford spiroketal **2**. This approach allows flexibility for the construction of L-sugar analogues because it derives its asymmetry from a catalytic asymmetric reaction on an achiral molecule. Recently, we have used this methodology to synthesize various D- or L-hexoses (Scheme 1).[11]

Scheme 1



Initially, we investigated the efficiency of the Sharpless asymmetric dihydroxylation of various 5-aryl-2-vinylfurans. We recently disclosed a three-step Stille coupling route to 5-aryl-2-vinylfurans **4a**−**d** from furfural and the appropriate aryl halide.[9] Vinylfurans **4a**−**d** were asymmetrically oxidized with commercial AD-mix-α reagent to form diols **3a**−**d** in good enantioexcesses and yields (Table 1). The only complication occurred for highly electron-rich aryl vinyl-

Scheme 2



a: $R_1 = CH_2OH$; R_2, $R_3 = H$
b: $R_1 = CH_2OTBS$; R_2, $R_3 = H$
c: $R_1 = CH_2OH$; R_2, $R_3 = OCH_3$
d: $R_1 = CH_2OTBS$; R_2, $R_3 = OCH_3$

furans with unprotected benzylic alcohols which were oxidized into the corresponding benzaldehydes. Mosher ester analysis of the monoprotected diols **3a**−**d** were undertaken to assign the degree and sign of enantioinduction by examining ^{1}H NMR and ^{19}F NMR.[12]

Our initial approach to the spirocyclic ring system of Papulacandin D started with aldehyde **5a**, which was prepared by Stille coupling of the ethylene glycol acetal of 5-tributylstannylfurfural and *o*-bromobenzyl alcohol.[9] Wittig olefination followed by dihydroxylation afforded diol **3a** in a 46% overall yield and in only three steps from furfural (Scheme 2). Exposure of diol **3a** to Achmatowicz oxidative

Table 1. Results of Sharpless Dihydroxylation of **4a**−**d**

entry	product	yield (%)[a]	ee %[b]
1.	3a	71	87
2.	3b	93	87
3.	3c	62	85
4.	3d	77	85

a = After purification. *b* = Mosher ester analysis (both by ^{1}H & ^{19}F NMR).

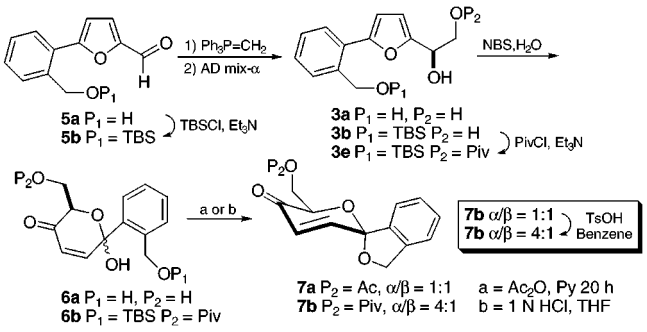
ring expansion conditions (NBS/THF/H_2O, 0 °C),[11,13,14] formed a mixture of hemiacetals **6a**, which were subjected to dehydration conditions (Ac_2O/pyridine) to form spiroketal **7a**. Unfortunately, under these conditions the spiroketal **7a** was formed in low yield (~20%) and as a 1:1 mixture of anomers.

Although the ideal approach would use the spiroketalization step to differentiate triol **6a**, a significantly improved procedure was found by incorporating some selective protection steps. Protection of **5a** using TBSCl affords aldehyde **5b**, which undergoes Wittig olefination in an improved yield (95%) to give vinylfuran **4b**. In addition, **4b** reacted under the dihydroxylation conditions to give **3b** with no concomitant oxidation to the aldehyde (93%). The primary alcohol of **3b** was selectively protected with pivaloyl chloride to give compound **3e** in a 65% yield. As before, furan alcohol **3e** oxidatively rearranged to hemiketal **6b** in 72% yield after filtration through silica gel. The acid, base, and light-sensitive hemiketal **6b** cyclized to form a 1:1 mixture of spiroketals

(7) Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.
(8) For other Achmatowicz oxidation approaches to spiroketals, see: (a) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901. (b) Perron, F. Albizati, K.; F. *J. Org. Chem.* **1989**, *54*, 2047. For a review on the synthesis of spiroketals, see: (c) Perron, F. Albizati, K.; F. *Chem. Rev.* **1989**, *89*, 1617. (d) Brimble, M. A.; Fares, F. A. *Tetrahedron* **1999**, *55*, 7661.
(9) For a general synthesis of vinylfurans such as **4**, see: Devan, B.; Quinn, L.; O'Doherty, G. A. *Tetrahedron Lett.* **1999**, *40*, 4769.
(10) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(11) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982.
(12) (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1975**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363. (c) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1991**, *56*, 4875.
(13) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.
(14) For the NBS conditions see: ref 10 and Georgiadis, M. P.; Couladouros, E. A. *J. Org. Chem.* **1986**, *51*, 2725.

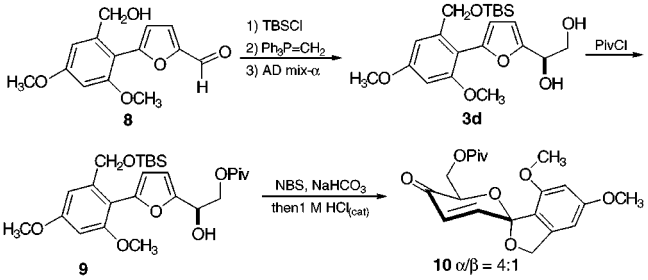
7b upon dilute aqueous acid deprotection of the TBS group on **6b** (49%). The reaction must be carefully monitored because the resulting pyranone **7b** slowly decomposes at longer reaction times. Under anhydrous acid conditions (TsOH/benzene), the anomeric ratio of **7b** can be enhanced to 4:1 with no loss of material (Scheme 3).

Scheme 3



With the stereochemical issues at C-1 and C-5 having been addressed, we applied the ketalization procedures to a protected furan diol with an appropriately oxygenated arene, such as **9** (Scheme 4). Protection of the benzylic alcohol of

Scheme 4

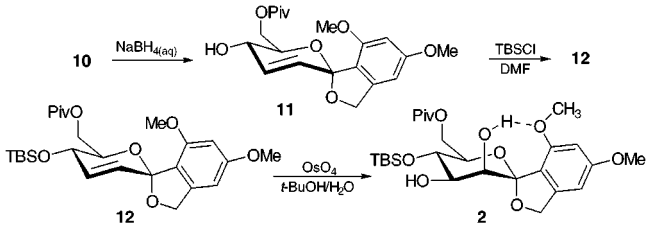


8 with TBSCl allows for a near quantitative yield of Wittig methylenation (**4d**). Similarly, the AD reaction of **4d** occurs without the complication of overoxidation and the selective pivaloylation of diol **3d** occurs in a 69% yield to give furyl alcohol **9**. Exposure of **9** to the Achmatowicz/spiroketalization conditions as above affords an good yield of enone **10** as a 4:1 mixture of anomers (47% yield).

Having demonstrated that we can obtain the required spiro framework of the papulacandins, we focused our attention on further functionalizing the ring system. In the course of these endeavors, we found that the spiroketal ring systems of **7a**, **7b**, and **10** were extremely acid sensitive. Only ring-opened products were observed upon treatment of **10** to the normal Luche reduction conditions ($NaBH_4/CeCl_3$ in MeOH). In fact, ring-opened products were also observed upon treatment of **10** with $CeCl_3$/MeOH and even $NaBH_4$/MeOH (Scheme 5).

However, resorting to aqueous $NaBH_4$ reduction of enone **10** afforded a single diastereomer of the spiroallylic alcohol

Scheme 5

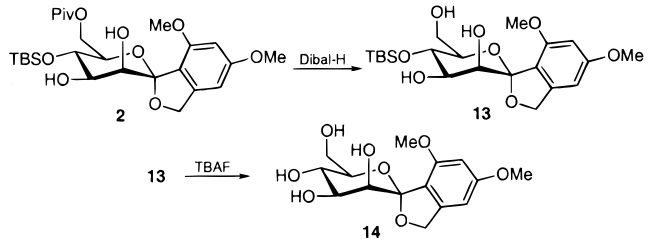


11 in an 88% yield after chromatographic purification (Scheme 5). We rationalized the elevated selectivity for the α-spiroketal anomer in **11** as a result of the increased preference of the chair form induced in the dihydropyran ring by the additional stereocenter at C-4 and hence increased anomeric effect. Our attempts to convert the spiroallylic alcohol **11** to the spiroketal *C*-aryl glucopyranoside nucleus were met with complications. The allylic alcohol **11** either oxidized to enone **10** or the spiroketal ring opened during attempts to oxidize the olefin (e.g., mCPBA; *t*-BuOOH, VO(acac)$_2$; etc.). In fact, long-term exposure of **11** to air resulted in autoxidation to enone **10** along with decomposition.

To overcome these problems, the allylic alcohol was protected as silyl ether **12** (64% yield). Surprisingly, TBS ether **12** was resistant to various dihydroxylation conditions (OsO_4, $KMnO_4$); however, dihydroxylation using more vigorous conditions (10% OsO_4, NMO in *t*-BuOH/H_2O, 75 °C, 20 h) afforded the spiroketal containing the tricyclic *C*-aryl mannopyranoside nucleus of papulacandin **2** as the major isomer in 69% yield. At this stage the relative and absolute stereochemistry of compound **2** was confirmed by both ^{1}H NMR and X-ray crystallographic analysis.

The unprotected manno-sugar **14** was prepared via a high-yielding two-step procedure (Scheme 6). Treatment of **2** with

Scheme 6



2 equiv of Dibal-H reduced the C-6 pivaloate protecting group to give **13** in a 93% yield. The synthesis of the mannopapulacandin ring system was then completed upon fluoride deprotection, affording **14** in 93% yield.

In summary, we have studied the Sharpless asymmetric dihydroxylation of various substituted aryl vinylfurans and utilized the resulting furan diols to diastereoselectively synthesize the key spiroketal ring system of mannopapulacandin derivative **14**. This sequence can conveniently produce for the first time the mannopapulacandin ring system

along with its enantiomer in only 12 steps from 3,5-dimethoxybenzyl alcohol and 7% overall yield. The strategy disclosed herein is now being applied toward an asymmetric total synthesis of papulacandin D and its analogues, and the results 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 and crystal structure information. This material is available free of charge via the Internet at http://pubs.acs.org.

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