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Synthesis of aryl spiroketals related to the papulacandins via allylation of phthalides

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Abstract

The synthesis of a range of aryl spiroacetals related to the papulacandins is reported. Key steps involve treatment of a phthalide acetate with an allylstannane followed by a hydroboration/oxidative cyclization sequence.

Keywords: allyl stannanes; aryl spiroacetals; papulacandins; oxidative cyclization; phthalides.

Many metabolites produced by a wide variety of microbes, insects, plants, fungi and microorganisms incorporate spiroacetal units.[1] The *C*-arylglycosyl spiroacetal antifungal agents papulacandins A **1**, B **2**, C **3**, D **4** and E were isolated from *Papularia spherosperma*[2] and were found to exhibit potent in vitro activity against *Candida albicans* and related microorganisms.[3,4] More recent members of the papulacandin family, Mer-WF3010 **5** and L-687,781 **6**[5] were found to overcome *Pneumoocystis carinii* pneumonia, the common opportunistic infection in AIDS patients. The simplest member of this family of antibiotics, papulacandin D **4** exhibits significant antifungal activity, hence the synthesis of simpler analogues of papulacandin D **4** may lead to improved biological activity.

The tricyclic *C*-arylglycosyl spiroacetal nucleus has been assembled via a Diels–Alder reaction,[6] a palladium(0) catalyzed coupling of an aryl halide with a stannyl glucal[7–9] and the reaction of a 2-bromobenzyl ether with an appropriately protected gluconolactone.[10–12] Recently, the [4.5]spiroacetal moiety of the papulacandins was assembled by condensation of a D-arabino-1,4-lactone with an α-lithiated carbanion of a β-phenylsulfonyldihydrofuran.[13]

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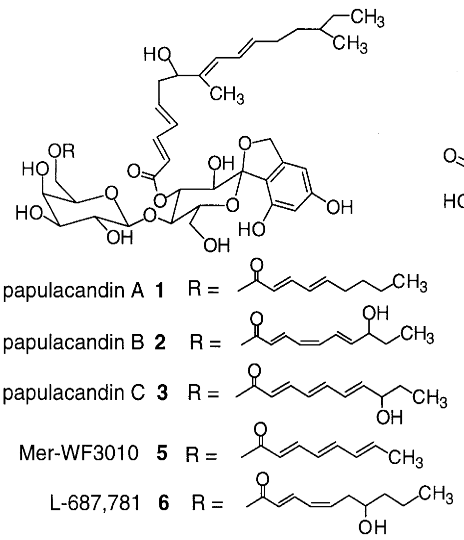


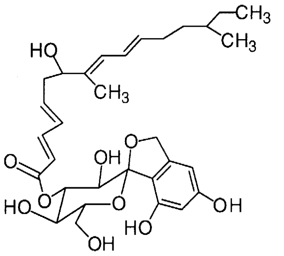
papulacandin A **1** R =

papulacandin B **2** R =

papulacandin C **3** R =

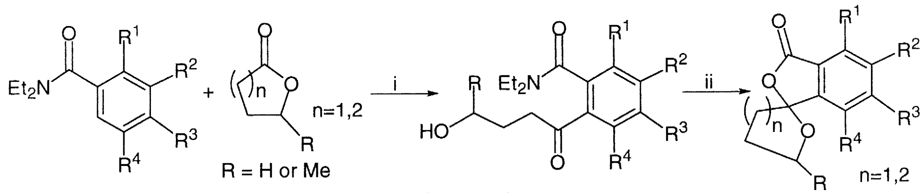
Mer-WF3010 **5** R =

L-687,781 **6** R =



papulacandin D **4**

We have reported an efficient two-step synthesis of a range of aryl spiroacetals related to the papulacandins, via the addition of *ortho*-lithiated tertiary benzamides **7** to lactones followed by acid-catalyzed cyclization of the resultant keto alcohols (Scheme 1).[14] This approach was unsuitable for the preparation of the arylspiroacetals with a similar oxygenation pattern to that present in the papulacandins in that this required the addition of the bulky lactone electrophile to the *ortho* position of amides **8** and **9** which suffered from steric hindrance by the neighbouring methoxy group.



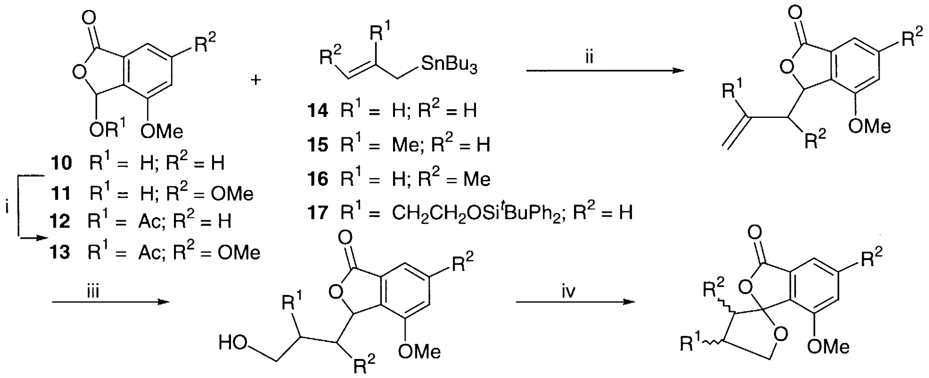
7 R^1,R^3 = H or OMe; R^2,R^4 = H; **8** R^1,R^2,R^3 = H; R^4 = OMe

9 R^1,R^3 = H; R^2,R^4 = OMe

Scheme 1. Reagents and conditions: (i) ^{t}BuLi, THF, TMEDA, −78°C, then lactone; (ii) *p*-TSA, THF, H_2O

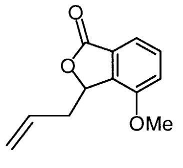
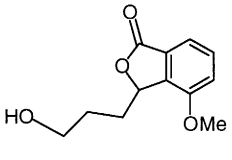
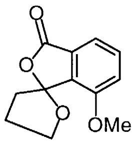
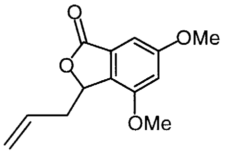
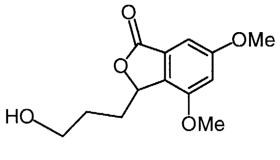
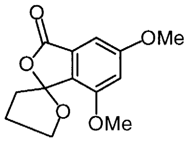
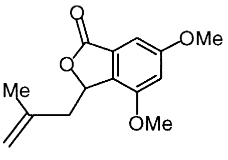
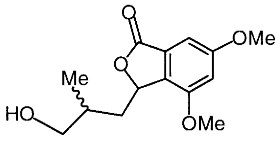
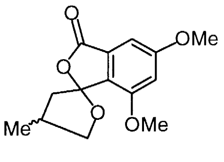
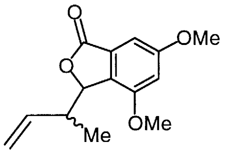
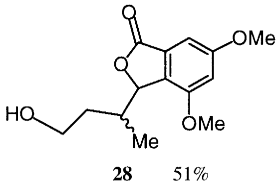
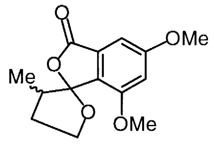
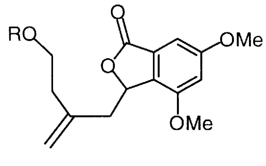
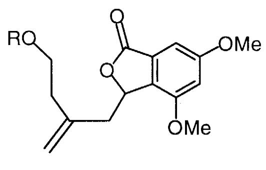
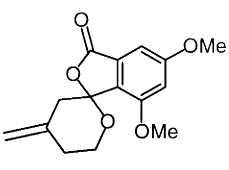
The focus of the present work was to prepare arylspiroacetals with the correct oxygenation pattern as that present in the papulacandins adopting an alternative strategy. We therefore herein report the synthesis of arylspiroacetals related to papulacandin D **4** starting from phthalide acetates **12** and **13** which are readily prepared via acetylation of the known hydroxyphthalides **10** and **11**[15] (Scheme 2). The key step involved Lewis acid mediated addition of an allylstannane to the phthalide acetates **12** and **13**, thereby capitalizing on the electron donating effect of the requisite methoxy groups(s) to stabilize the resultant oxocarbenium ion. The resultant alkene was converted to a primary alcohol by hydroboration thereby facilitating formation of a tricyclic arylspiroacetal via oxidative cyclization using iodobenzene diacetate and iodine under photolytic conditions (Table 1).[16]

Allylstannanes **14**, **15** and **16** were prepared following the method reported by Naruta et al.[17] and allylstannane **17** was prepared following the procedure of Weigand and Bruckener.[18] The optimum procedure[19] for reaction of phthalide acetates **12** and **13** with allyltributylstannanes **14**–**17** involved the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid in dichloromethane at −78°C using 2 equivalents of the stannane. We believe this is the first report of the addition of an



Scheme 2. Reagents and conditions: (i) Ac_2O, Et_3N; (ii) Me_3SiOTf, CH_2Cl_2, −78°C; (iii) $BH_3 \cdot THF$, 0°C; (iv) $PhI(OAc)_2$, I_2, hν

Table 1

Entry	Starting Materials	Allylated product	Alcohol	Arylspiroacetal
1	**12**,**14**	 **18** 71%	 **19** 67%	 **20** 78%
2	**13**,**14**	 **21** 98%	 **22** 50%	 **23** 83%
3	**13**,**15**	 **24** 72%	 **25** 58%	 **26** 83%
4	**13**,**16**	 **27** 43%	 **28** 51%	 **29** 72%
5	**13**,**17**	 **30** 94%; R=SiᵗBuPh₂	 **31** 80%; R=H	 **32** 44%

allylstannane to an oxocarbenium ion generated from a phthalide acetate providing a facile preparation of functionalized 1(3*H*)-isobenzofuranones.

The presence of a substituent at C2 or C3 on the allylstannane (**15** and **16**, respectively) did not affect the outcome of the allylation reaction although a lower yield was obtained in the latter case with allyl phthalide **27** only being obtained in 43% yield. Use of methyl substituted allylstannanes **15** and **16** finally led to the formation of arylspiroacetals **26** and **29**, respectively, as a 1:1 mixture of diastereomers.

In the present work our goal was to convert the allylated 1(3*H*)-isobenzofuranones to aryl spiroacetals. Hydroboration of alkenes **18**, **21**, **24** and **27** with $BH_3 \cdot THF$ cleanly afforded the primary alcohols **19**, **22**, **25** and **28**, respectively. Conversion of these primary alcohols to aryl spiroacetals **20**, **23**, **26** and **29** was then effected by oxidative cyclization using iodobenzene diacetate and iodine under photolytic conditions. Similar oxidative cyclizations have been used by this research group as a method to prepare bis-spiroacetals.[20]

Whilst oxidative cyclization of alcohols **19**, **22**, **25** and **28** led to the formation of a spiro[1(3*H*)isobenzofuran, 2′-tetrahydrofuran] ring system, the homologous spiro[1(3*H*)isobenzofuran, 2′-tetrahydropyran] ring system that is present in the papulacandins was formed by oxidative cyclization of alcohol **31**. Alcohol **31** was obtained by desilylation of silyl ether **30** which in turn was prepared via treatment of phthalide acetate **13** with functionalized allylstannane **17**.

In conclusion, we have developed an efficient procedure for the synthesis of arylspiroacetals similar to those present in the potent antifungal agents, the papulacandins. The methodology combines the use of a novel allylation of phthalide acetates followed by an oxidative cyclization.

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