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A Stereoselective Synthesis of (−)-Viridiofungin A Utilizing a $TiCl_4$-Promoted Asymmetric Multicomponent Reaction

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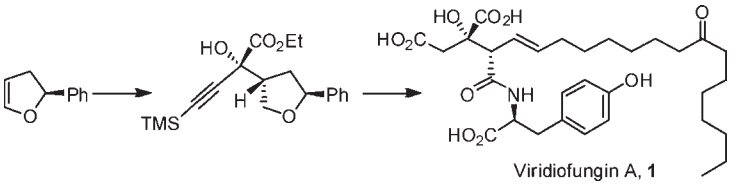
ABSTRACT



A stereoselective synthesis of (−)-viridiofungin A is described. The convergent synthesis utilized a unique highly diastereoselective multicomponent reaction between optically active phenyldihydrofuran and an α-ketoester to provide two chiral centers including a quarternary carbon center in a single step. Other key steps include an acyloxycarbonium ion-mediated tetrahydrofuran ring-opening reaction and a Julia−Kocienski olefination.

Viridiofungins were first isolated by Harris and co-workers in 1993 from the fungus, *Trichoderma viride*.[1] This family of alkyl citrates exhibited a broad spectrum of antifungal properties with minimum fungicidal concentrations in the range of 1−20 μg/mL against a number of species. Furthermore, viridiofungins inhibited rat and yeast squalene synthesis with IC_{50} values of 0.4−15 μM.[2] This antifungal activity is unrelated to the inhibition of ergosterol biosynthesis. Instead, viridiofungins showed very potent nanomolar inhibitory activity against serine palmitoyltransferase, the first enzyme in the sphingolipid biosynthesis which is responsible for viridiofungin's antifungal properties.[3] Sphingolipids are abundant membrane lipids important for cell recognition and signal transduction. Due to the ability of sphingolipids to form so-called lipid rafts, inhibition of serine palmitoyltransferase has been recognized as a possible target for the treatment of hepatitis C.[4] There are some indications that viridiofungin analogs could inhibit farnesyltransferase, which might lead to viridiofungin-based compounds with anticancer activity.[5]

The initial structural assignment of the viridiofungins was carried out by chemical degradation and spectroscopic studies.[1] The relative and absolute stereochemistry of viridiofungin A (**1**) was assigned by Hatakeyama and co-workers through their first total synthesis in 27 steps.[6] Several other synthetic studies led to the synthesis of ester derivatives of viridiofungins. Hiersemann and co-workers[7] and Barrett and co-workers[8] have reported the synthesis of viridiofungin ester derivatives. Hatakeyama and co-workers have reported a second generation synthesis of viridiofungin

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A in 22 steps.[9] Herein we report an asymmetric synthesis of viridiofungin A which can be utilized for analog preparation.

Our synthetic strategy to viridiofungin A is shown in Figure 1. Strategic bond disconnections provided funtio-

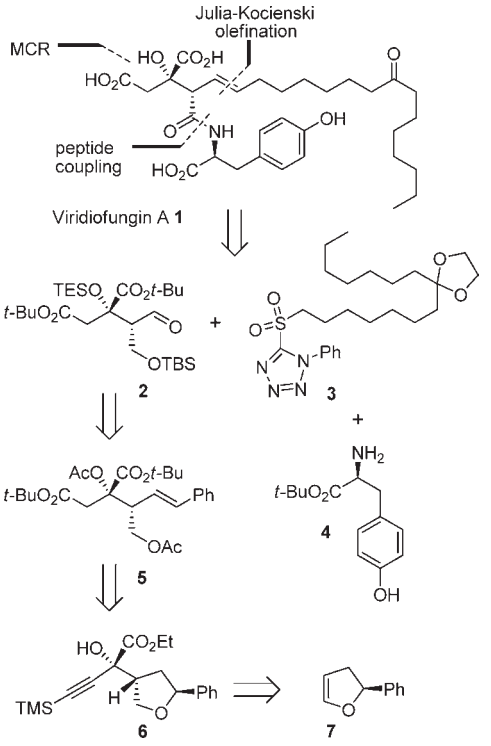
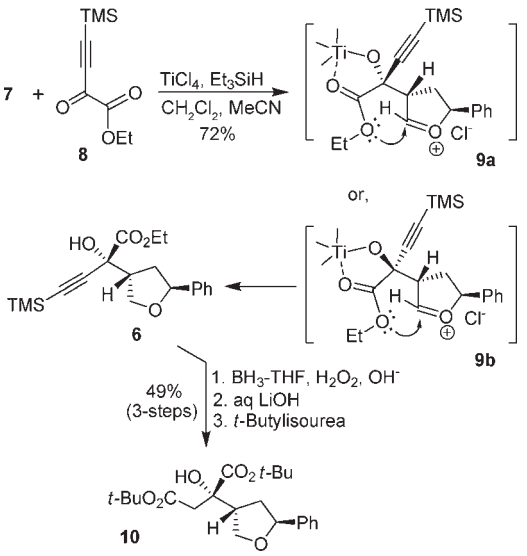


Figure 1. Retrosynthetic analysis.

nalized aldehyde **2**, sulfone **3**, and tyrosine derivative **4**. A Julia–Kocienski olefination of **2** with **3** is planned to provide the *trans*-olefin in **1**. This side chain attachment was previously explored by Hiersemann and co-workers.[7] The highly functionalized aldehyde could be derived from the oxidative cleavage of styrene derivative **5**, which in turn could be obtained from a ring-opening reaction of the corresponding functionalized tetrahydrofuran derivative of **6**. The key intermediate would be synthesized by an asymmetric multicomponent reaction of optically active phenyldihydrofuran **7** and an appropriately functionalized ketoester. Such asymmetric multicomponent reactions and acyloxycarbonium ion mediated opening of tetrahydrofuran rings were developed previously in our laboratory.[10,11]

The synthesis begins with the titanium tetrachloride mediated multicomponent reaction between optically

Scheme 1. Multicomponent Reaction



active phenyldihydrofuran **7**,[11] α-ketoester **8**,[12] and triethyl silane (Scheme 1). The reaction involved $TiCl_4$-promoted activation of the α-ketoester followed by attack of phenyldihydrofuran, presumably *anti* to the phenyl group forming an oxocarbenium ion. Subsequent reaction of this presumed oxocarbenium ion with a hydride from triethylsilane formed two adjacent chiral centers including a quarternary carbon center diastereoselectively. This reaction proceeded with good yield and an excellent diastereomeric ratio (*dr* > 20:1). The stereochemical outcome can be rationalized based upon product-like transition-state models **9a** and **9b**. Presumably, the model **9b** is preferred, as the developing nonbonded interactions are less for an *exo*-oriented bulky five-membered Ti-chelate compared to an *endo*-oriented Ti-chelate in **9a**. Similar transition-state models were proposed by us previously.[10d]

The acetylene functionality in **6** was converted to the corresponding carboxylic acid via hydroboration with borane–THF complex followed by oxidation with alkaline hydrogen peroxide.[13] The ethyl ester was subsequently hydrolyzed with aqueous lithium hydroxide to provide the corresponding diacid. This diacid was converted to the di-*tert*-butyl ester **10** by treatment with *N,N*-diisopropyl-*O*-2-*tert*-butylisourea in CH_2Cl_2. The *tert*-butyl ester is necessary due to base incompatibility at later stages of the synthesis.[7]

With the synthesis of requisite tetrahydrofuran **10**, we then explored the ring-opening reaction. Previously, we carried out similar ring-opening reactions using a catalytic amount of $ZnCl_2$ in the presence of acetic anhydride.[11] However, subjecting **10** to these conditions led to unwanted side reactions. After surveying a number of Lewis

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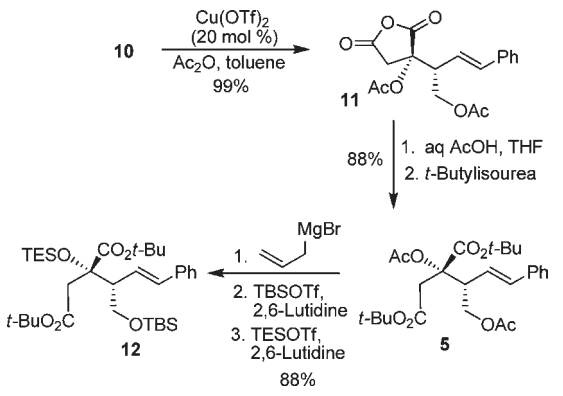
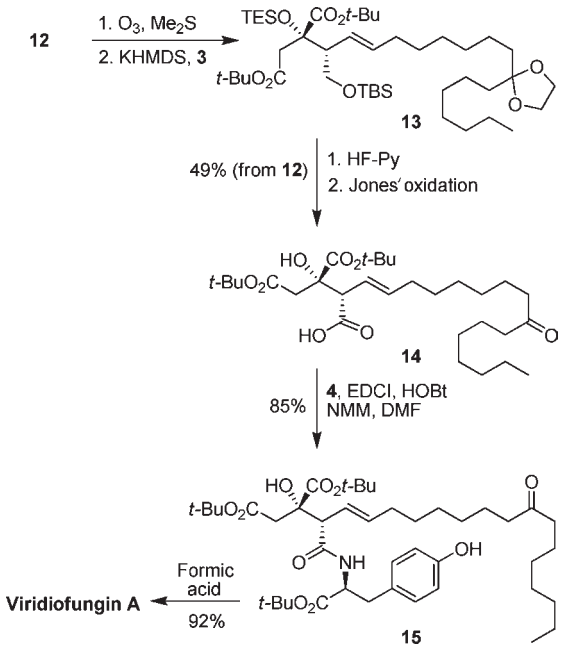
Scheme 2. Tetrahydrofuran Ring Opening



Scheme 3. Completion of Viridiofungin A



acids, we found that exposure of **10** to a catalytic amount of $Cu(OTf)_2$ (20 mol %) and acetic anhydride in refluxing toluene smoothly gave rise to a ring opened product through a presumed acyloxycarbonium ion intermediate followed by an unexpected collapse of the di-*tert*-butyl esters to provide anhydride **11** in near-quantitative yield (Scheme 2).

Basic hydrolysis conditions only provided the elimination product. However, treatment with aqueous acetic acid in THF resulted in anhydride opening to the corresponding diacid. The resultant diacid was esterified by treatment with *N,N*-diisopropyl-*O*-2-*tert*-butylisourea in CH_2Cl_2 to give di-*tert*-butyl ester **5**. For the subsequent Julia–Kocienski olefination,[14] protecting group manipulations were necessary. Standard conditions for acetate hydrolysis such as K_2CO_3 in methanol resulted in elimination rather than deprotection. To circumvent this problem, diacetate **5** was treated with allyl magnesium bromide at −78 °C to give the diol. The primary alcohol was protected as its *tert*-butyldimethylsilyl ether with TBSOTf and 2,6-lutidine at −78 °C. Subsequent protection of the tertiary alcohol as its triethylsilyl ether provided styrene derivative **12**.

Oxidative cleavage of styrene **12** with ozone followed by reductive workup afforded the corresponding aldehyde (Scheme 3). This aldehyde was subjected to Julia–Kocienski olefination with known sulfone **3**.[7] Thus, treatment of sulfone **3** with KHMDS in THF at −78 °C followed by addition of the aldehyde via cannula afforded the alkene **13** as a single *trans*-stereoisomer. Removal of the silyl protecting groups with HF-pyridine followed by oxidation of the primary alcohol using Jones' reagent afforded the acid **14** with concomitant deprotection of the dioxolane protecting group.

To complete the synthesis of viridiofungin A, coupling of acid **14** with tyrosine *tert*-butyl ester **4** was carried out by utilizing EDCI hydrochloride, *N*-methylmorpholine, and hydroxybenzotriazole in DMF to provide tri-*tert*-butyl ester **15**. While deprotection of tri-*tert*-butyl ester **15** is known from the second generation synthesis by Hatakeyama,[9] commercial grade (88%) formic acid gave incomplete conversion to (−)-viridiofungin A and instead gave a mixture of mono- and di-*tert*-butyl esters. However, when 96% formic acid was used, removal of all three *tert*-butyl esters was accomplished in 1 h. As such, deprotection of the *tert*-butyl esters by treatment with neat 96% formic acid at 23 °C for 1 h furnished synthetic (−)-viridiofungin A (**1**, $[\alpha]^{23}_D$ −11.0 (*c* 0.39, MeOH)). The spectral data (^{1}H and ^{13}C NMR) of synthetic (−)-viridiofungin A are identical with those reported for the natural (−)-viridiofungin A.[1]

In summary, we have achieved a stereoselective synthesis of (−)-viridiofungin A (**1**). The convergent synthesis features a highly diastereoselective multicomponent reaction to form two key stereocenters including a quaternary stereocenter in high yield. Both stereogenic centers are derived from (*S*)-2-phenyl-2,3-dihydrofuran. The synthesis will provide a convenient access to a variety of viridiofungin derivatives.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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