OL Organic Letters

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Total Synthesis of Viridiofungins A and B

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Cite This: *Org. Lett.* 2021, 23, 3557−3560 Read Online

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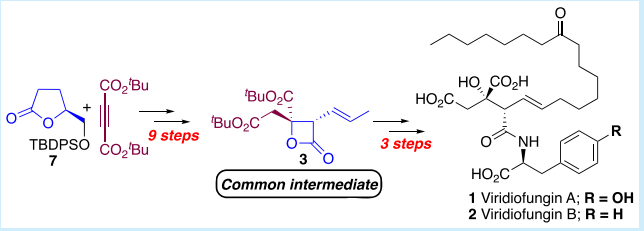
ABSTRACT: The total synthesis of viridiofungins A (**1**) and B (**2**) via *β*-lactone **3** in 13 steps is reported. Key steps included an HF-mediated rearrangement of cyclobutene diester **9** to form a bicyclic lactone **6**, an olefin cross metathesis between disubstituted alkene **3** and alkene **4** in which isomerization was suppressed, and a novel *β*-lactone ring opening to form the amide. Deprotection then gave either viridiofungin A (**1**) or B (**2**) in high yield.



The viridiofungins are a family of alkyl citrate natural products[1] that are nanomolar inhibitors of serine palmitoyl transferase, the enzyme involved in the first step of sphingolipid biosynthesis.[2] Viridiofungins A (**1**) and B (**2**) (Figure 1) were first isolated[3] from the fungus *Trichoderma*

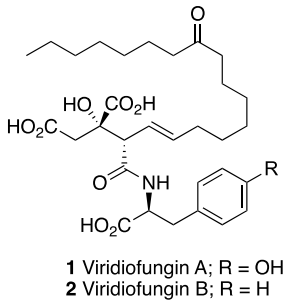


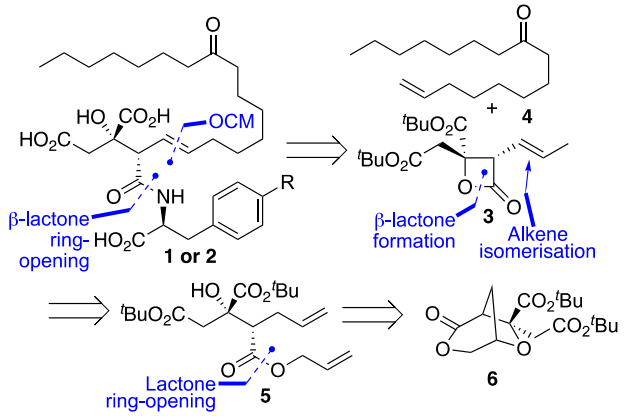
Figure 1. Viridiofungins A (**1**) and B (**2**).

viride, and several congeners were later found which differ in the alkyl chain or lack an *α*-amino acid moiety.[2b,d] In addition, some synthetic analogues with modified amino acid residues show promise for the treatment of the hepatitis C virus (HCV).[4]

The first total synthesis[5] of viridiofungin A was reported by Hatakayama[6] (23 step longest linear sequence [LLS]), and this was followed by two other syntheses by Shibasaki[7] (16 step LLS) and Ghosh[8] (16 step LLS). In addition, a number of routes to various ester derivatives have been described.[9] Our proposed route to the viridiofungins is shown in Scheme 1 and is based on our recent stereoselective and nonintuitive approach to alkyl citrate type natural products from cyclobutenediesters.[10]

As shown in Scheme 1, compounds **1** and **2** could be accessed by an olefin cross metathesis (OCM)[11] between the common intermediate *β*-lactone **3** and the known alkene **4**[6] followed by *β*-lactone ring opening with the appropriate amino acid. It was envisaged that the minimal steric demand in *β*-lactone **3** should allow the hindered alkene to participate in the challenging OCM reaction[12] as well as serve as an efficient means of both protection and subsequent amide formation. OCM has been utilized in previous approaches to viridiofungins, but the citrate partners were terminal alkenes.[6,9a] *β*-Lactone **3** could be sourced from orthogonally protected triester **5** which can be formed by ring opening of the known lactone **6** utilized in our recent total synthesis of citrafungin A.[10b] This approach would not involve any oxidative transformations but also allow for the synthesis of the entire family of natural products from a common intermediate.

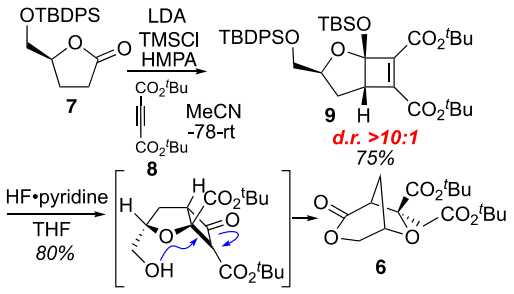
Scheme 1. Retrosynthesis of the Viridiofungins



Received: March 21, 2021
Published: April 22, 2021

The synthesis of the bicyclic lactone **6** is summarized in Scheme 2 and begins with lactone **7**, obtained by protection of

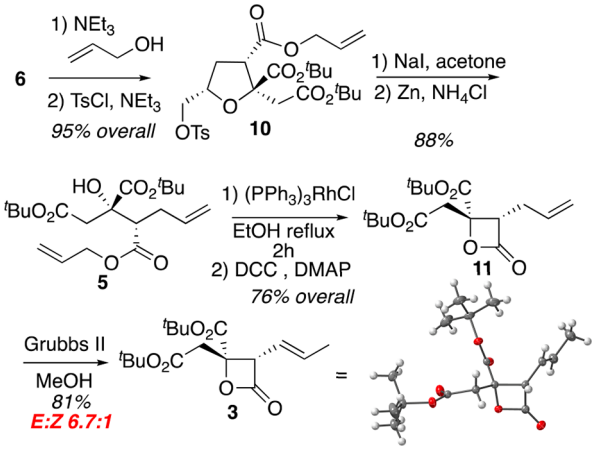
Scheme 2. Synthesis of Bicyclic Lactone 6[10b]



(*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone.[10a] A formal [2 + 2]-cycloaddition[10a,13] between the silylketene acetal derived from **7** and di-*t*-butylacetylene dicarboxylate (**8**) gave the cyclobutene diester **9**[10b] in good yield and high stereoselectivity. HF•pyridine-induced deprotection, concomitant *oxa*-Michael reaction, and intramolecular cyclobutanone ring opening[10b,c] gives the bicyclic lactone **6**.

Ring opening of the lactone **6** with allyl alcohol followed by tosylation of the labile alcohol product gave stable tosylate **10** (Scheme 3). Iodine displacement and immediate Zn-mediated

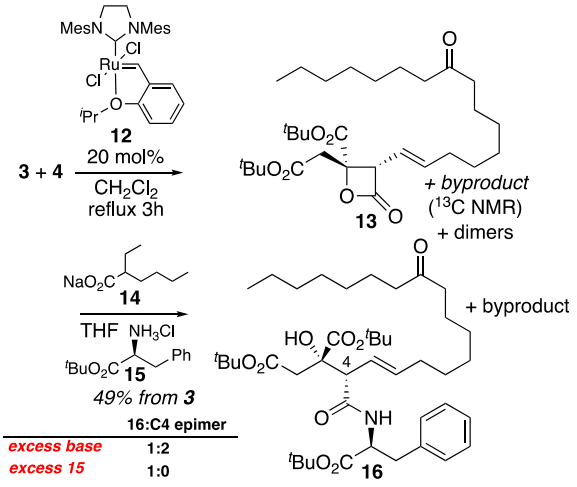
Scheme 3. Synthesis of Common Intermediate β-Lactone 3



elimination[10a] gave the orthogonally protected triester **5**. Removal of the allyl ester and treatment of the resultant hydroxyacid with DCC and DMAP afforded β-lactone **11** in good overall yield. Alkene isomerization was achieved by treatment with Grubbs II catalyst[14] in methanol to give crystalline **3** (*E*:*Z* = 6.7:1), and the structure was confirmed by a single-crystal X-ray analysis.

After testing a number of catalysts, OCM between alkene **3** and the side chain alkene **4** was best achieved using Grubbs–Hoveyda catalyst[15] (**12**) to afford the desired labile product **13**, but this was contaminated by a very similar inseparable byproduct which could only be detected by the presence of some doubled signals in the ^{13}C NMR spectrum along with the OCM homodimer derived from **4** (Scheme 4). Similar results were obtained using the dimer[9a] derived from alkene **4** as the OCM partner. In any case, we next examined the ring opening of the lactone with L-phenylalanine *t*-butyl ester hydrochloride (**15**) using sodium 2-ethylhexanoate (**14**) as base.[16] This mild

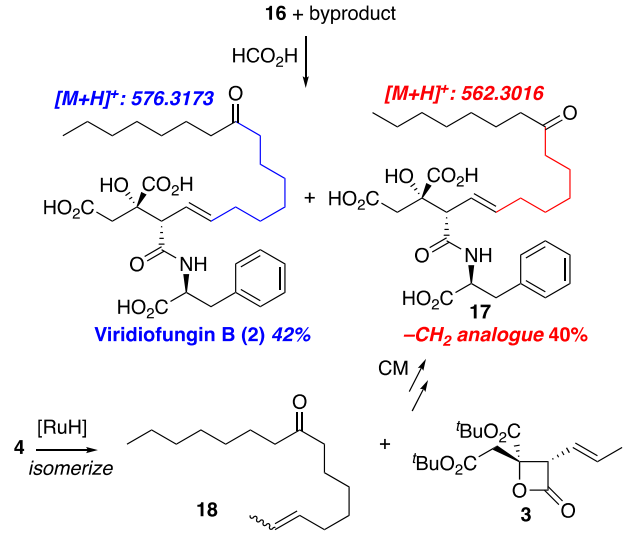
Scheme 4. Initial Olefin Cross Metathesis of β-Lactone 3



method has been applied to the ring opening of a β-lactone with a simple amine but, to our knowledge, not with amino acid esters. When an excess of base was used, we observed low yields and considerable epimerization of the labile C4 stereocenter. Fortunately, this could be suppressed by the use of an excess of the amino acid HCl salt to deliver a single stereoisomer of the amide **16** which was also contaminated with a similar inseparable amide byproduct.

Deprotection of the mixture of **16** and the byproduct with formic acid and purification by RP-HPLC allowed for the separation of the two products (Scheme 5). One was identified

Scheme 5. Completion of the Initial Synthesis of 2



as viridiofungin B (**2**), while the other product possessed one less methylene unit as judged by mass spectrometry and ^{13}C NMR spectroscopy (one less methylene signal in the 29–30 ppm region). This compound was therefore assigned as the desmethylene analogue **17**. The formation of **17** can be attributed to production of isomerized alkene side chain **18** in the OCM reaction probably mediated by traces of a ruthenium hydride contaminant formed by decomposition of the catalyst as shown in Scheme 5.[17] In this case, the lower reactivity of the disubstituted alkene in the OCM reaction probably allows for isomerization to become a significant pathway, and OCM

https://doi.org/10.1021/acs.orglett.1c00971
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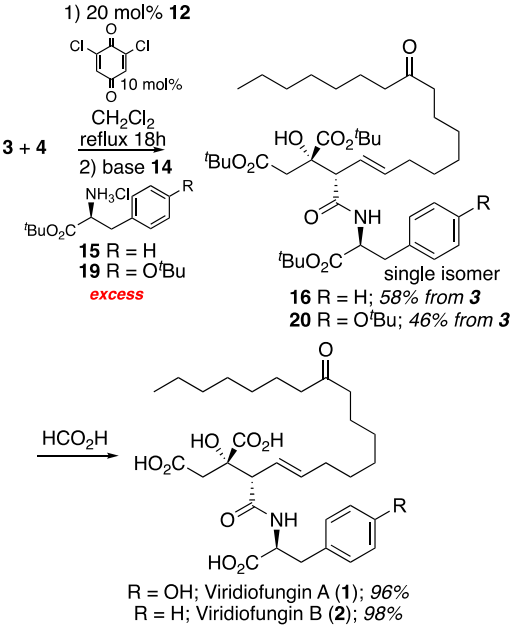
between the isomerized alkene **18** and alkene **3** forms the desmethylene adduct.

While this furnished the target compound viridiofungin B (**2**), a more selective route was required. Grubbs and co-workers have reported that unwanted alkene isomerization of OCM products by ruthenium hydride contaminants can be thwarted by the addition of electron-deficient benzoquinones which neutralize the hydrides without affecting catalyst reactivity.[17] We found that the OCM between the alkene **3** and side chain **4** could be best achieved with catalyst **12** in the presence of 10 mol % of 2,6-dichlorobenzoquinone without any formation of the undesired desmethylene compound. Rapid purification followed by subsequent amide formation using an excess of either amino acid HCl salt **15** or **19** in the presence of base **14** gave the amides **16** or **20** as single stereoisomers. Deprotection of each with formic acid then afforded viridiofungins A (**1**) and B (**2**) in excellent yields (Scheme 6). The data for the synthetic compounds matched those reported for the natural products.[3]

Scheme 6. Completion of the Synthesis of 1 and 2



In conclusion, we have developed a highly stereoselective route to the viridiofungins A (**1**) and B (**2**) in 13 steps from commercially available (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone. Key steps included the stereoselective synthesis of bicyclic lactone **6** by a formal [2 + 2]-cycloaddition and HF-mediated rearrangement sequence which allows for simple orthogonal protection to access triester **5**, a challenging olefin cross metathesis involving the disubstituted alkene **3** without isomerization and a novel β-lactone ring opening to form the amide. In addition, no oxidative manipulations were required. The stable crystalline β-lactone alkene **3** serves as a useful precursor the viridiofungins as well as analogues for further evaluation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00971.

Experimental procedures and copies of NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 2069178 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council Discovery Program (DP200100722) and the University of Melbourne Faculty of Science Research Grant Support Scheme for funding. We also thank Dr. Christian Gunawan and Tony Duncan (Circa Pty Ltd.) for the generous gift of (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone.

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