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Total Synthesis of Pyridovericin: Studies toward the Biomimetic Synthesis of Pyridomacrolidin

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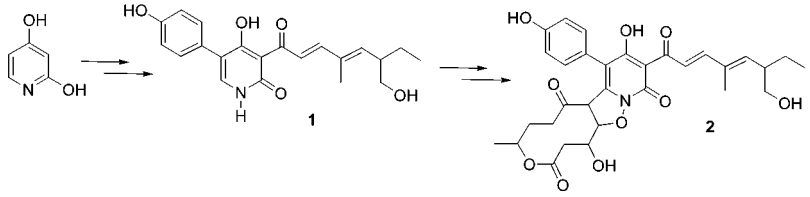
ABSTRACT



The total synthesis of the novel metabolite pyridovericin 1 is reported. The synthesis of this key intermediate in our proposed biomimetic synthesis of pyridomacrolidin 2 has been accomplished in good yield from readily available 2,4-dihydroxypyridine.

Pyridovericin **1** and pyridomacrolidin **2** are novel metabolites isolated in 1998 by Nakagawa and co-workers from the entomopathogenic fungus *Beauveria bassiana* (Figure 1).[1] Both pyridovericin **1** and pyridomacrolidin **2** contain the same *p*-hydroxyphenyl pyridone unit present in the related fungal metabolites tenellin **3**,[2] bassianin **4**,[3] and ilicicolin **5**.[4]

The biological activity of both pyridovericin **1** and pyridomacrolidin **2** has been shown to include the inhibition of protein tyrosine kinase (PTK) activity at concentrations of 100μg/mL.[1] PTK inhibitors are of potential use as therapeutic agents against a variety of proliferative and inflammatory diseases.[5] In common with several compounds found to inhibit PTKs, pyridovericin **1** and pyridomacrolidin **2** contain a *p*-hydroxy phenyl moiety, which presumably mimics tyrosine.

The combination of the structural novelty and complexity coupled with the promising biological activity prompted us to design a biomimetic synthesis of pyridomacrolidin **2**. The

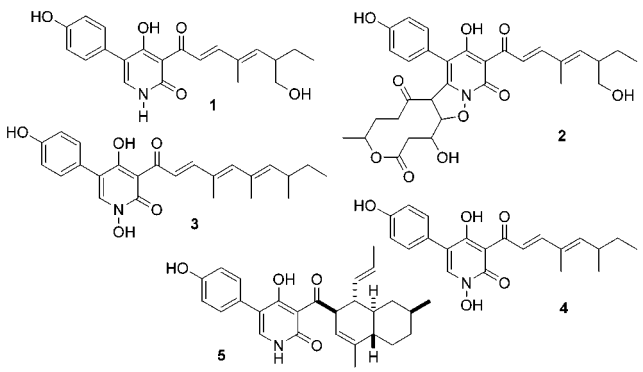


Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related metabolites.

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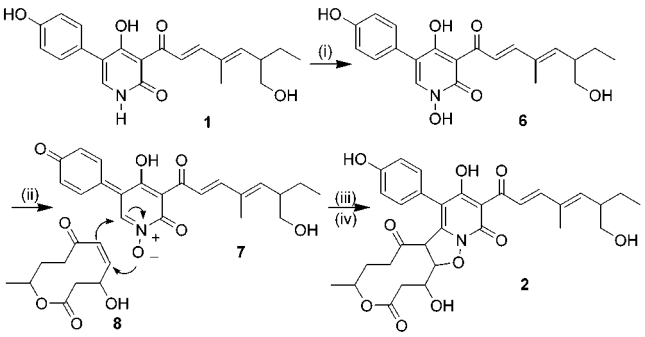
biosynthesis of tenellin **3**, bassianin **4**, and ilicicolin H **5** has been studied in some detail,[6−8] and it was shown that they are derived from a polyketide chain and an aromatic amino acid. While the biosynthesis of pyridovericin **1** presumably follows a similar pathway, the biosynthesis of pyridomacrolidin **2** has not yet been elucidated. However, it is possible to propose a biomimetic formation of pyridomacrolidin **2** from pyridovericin **1** (which was coisolated with **2** from the same fungus) via a number of steps (Scheme 1),

Scheme 1. Proposed Biosynthesis of Pyridomacrolidin **2**



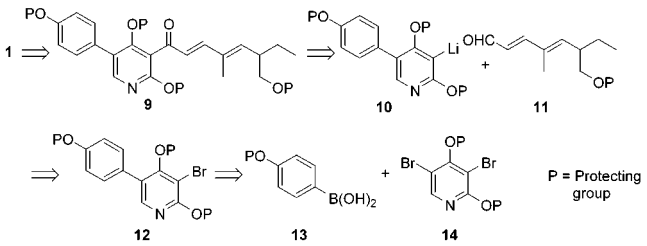
namely, (i) oxidation of pyridovericin **1** to hydroxamic acid **6**, (ii) further oxidation to the novel acyl nitrone intermediate **7**, (iii) 1,3-dipolar cycloaddition[9] with cephalosporolide B **8**, and (iv) re-aromatization to form pyridomacrolidin **2**. Cephalosporolide B **8** is itself a natural product, isolated independently from the fungus *Cephalosporium aphidicola*,[10] although it has not yet been isolated from *B. bassiana*.

Chemically, this class of compounds has elicited a significant amount of interest as demonstrated by the significant synthetic work already published.[11−15]

Herein, we describe our progress toward the biomimetic synthesis of pyridomacrolidin **2** by reporting a convergent and efficient synthesis of pyridovericin **1** from cheap and readily available starting materials.

We envisaged that the core structure of pyridovericin **1** could be constructed via addition of lithiated pyridine **10** to aldehyde **11**, giving precursor **9** after oxidation (Scheme 2). The organolithium **10** would be generated via metal−halogen exchange from the corresponding bromide **12**, which in turn

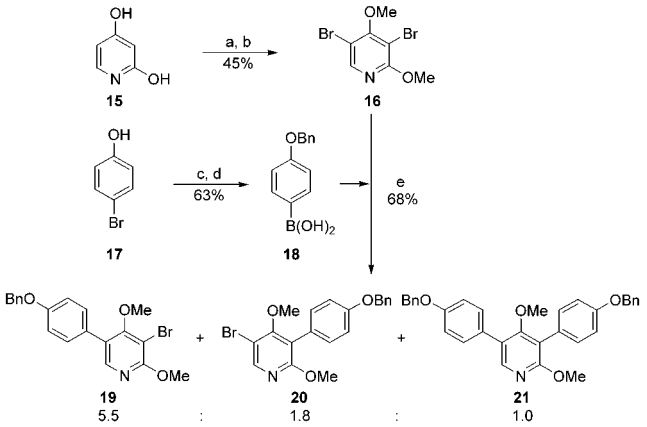
Scheme 2. Retrosynthetic Analysis of Pyridovericin **1**



would be synthesized via selective palladium-catalyzed monocoupling between boronic acid **13** and dibromide **14**.

The convergent synthesis began with commercially available 2,4-dihydroxypyridine **15**, which was selectively dibrominated at the C_3 and C_5 positions[16] and then bis-*O*-methylated[17] to give pyridine **16** in good yield (Scheme 3).

Scheme 3[a]



[a] (a) Br_2, 47% HBr; (b) MeI, Ag_2CO_3, DCM; (c) BnBr, TBAI, NaH, THF; (d) (i) *n*BuLi, $B(OiPr)_3$, THF; (ii) sat. NH_4Cl; (e) $Pd(PPh_3)_4$, Na_2CO_3, 4:1 toluene:ethanol.

Synthesis of the required boronic acid coupling partner began with 4-bromophenol **17**, which was readily protected under standard conditions[18] to generate the corresponding benzyl ether in good yield. Metal−halogen exchange followed by treatment with boron triisopropoxide[19] proceeded cleanly to afford, after hydrolysis, the desired boronic acid **18**.

Next, it was found that reaction of **16** and **18** under Suzuki-type conditions[20] afforded a separable mixture of mono- and bis-coupled adducts **19**−**21**, in which the major product was

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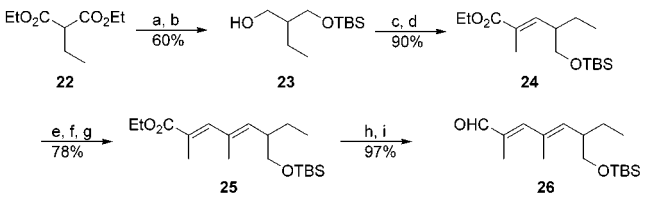
the desired biaryl **19**.[21] The selectivity observed in this reaction is consistent with the faster coupling being at the less hindered C_5 position.

The synthesis of the C_7-C_{15} side-chain aldehyde began with diethyl 2-ethylmalonate **22**, which was reduced to the corresponding diol and then monoprotected[22] to afford the desired silyl ether **23** in good yield (Scheme 4). Swern

Scheme 4[a]

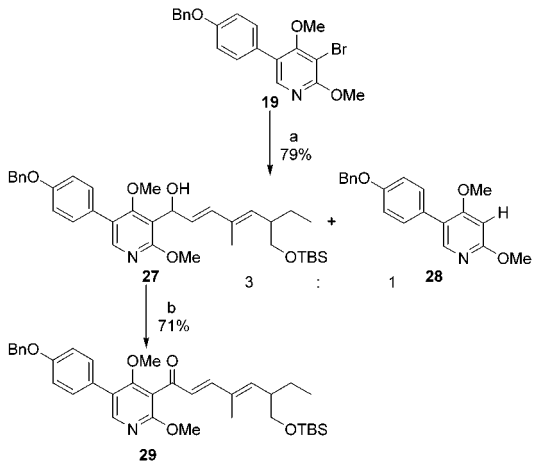


[a] (a) LAH, THF; (b) TBSCl, NaH, THF; (c) Swern; (d) PPh_3CHCO_2Et, Benzene; (e) Dibal-H, THF; (f) Swern; (g) PPh_3-$CHCO_2Et$, Tol.; (h) Dibal-H, THF; (i) Swern.

oxidation and then Wittig olefination gave ester **24**; then, ester reduction followed by another Swern oxidation/Wittig olefination sequence gave diene **25** in excellent overall yield. Finally, reduction of the ester to the corresponding alcohol followed by oxidation gave the desired aldehyde intermediate **26**, which was ready to be coupled to the pyridine unit.

Metal−halogen exchange of bromo-pyridine **19** followed by treatment with aldehyde **26** gave the desired alcohol **27**, together with the dehalogenated product **28** (Scheme 5). The

Scheme 5[a]

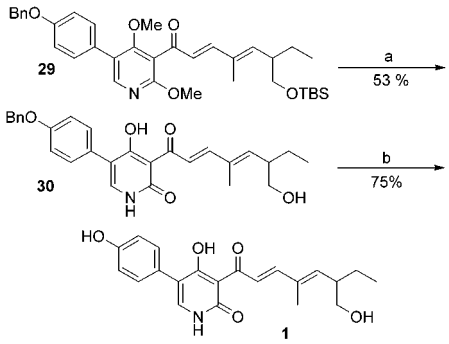


[a] (a) *t*-BuLi, **26**, THF; (b) MnO_2, DCM.

formation of compound **28** can be explained as the product of the deprotonation of the aldehyde's ϵ-position or from the *tert*-butyl bromide by the lithiated pyridine. Subsequent oxidation of alcohol **27** afforded the fully protected pyridovericin **29** in good yield and with no observable side products.

The deprotection of compound **29** at this point proved to be challenging, as most of the methods attempted for removal of the protecting groups either resulted in no reaction or caused complete decomposition of the starting material. It was only after considerable experimentation that it was found that in situ generated trimethylsilyl iodide[23] was successful in removing the methyl ethers to afford diol **30** (Scheme 6),

Scheme 6[a]



[a] (a) TMSCl, NaI, MeCN; (b) BBr_3, DCM.

though the benzyl group was left intact. Finally, removal of the obdurate benzyl protecting group was effected using boron tribromide[24] to generate racemic pyridovericin **1** in thirteen steps for the longest linear sequence. The spectral data (^1H and ^{13}C NMR, HRMS, TLC) for synthetic **1** exactly matched that reported for natural pyridovericin **1**.[1] Furthermore, doping experiments of synthetic and natural pyridovericin samples generated a single set of NMR signals.

In conclusion, we have completed the total synthesis of pyridovericin **1** starting from cheap and readily available starting materials. Our synthesis is convergent, fast, efficient, and easily modifiable for the synthesis of analogues. Further work on the investigation of the biomimetic synthesis of pyridomacrolidin **2** is in progress, and the results will be reported shortly.

Acknowledgment. We are very indebted to Professor Akira Nakagawa (Teikyo University) for generous amounts of authentic samples. We thank the EPSRC for funding to A.C. N.R.I thanks the Dr. Reddy's Research Foundation (DRF), Hyderabad, India, for support and encouragement.

Supporting Information Available: Experimental procedure for compound **1** and NMR data for compounds **29**, **30**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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