

An Unusual Oxidative Cyclization: Studies towards the Biomimetic Synthesis of Pyridomacrolidin

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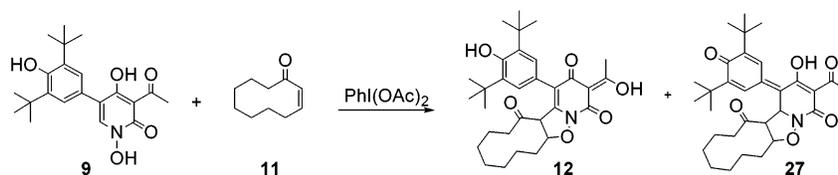
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ABSTRACT



An unusual oxidative cyclization of a *N*-hydroxy pyridone **9** with *Z*-2-cyclodecenone **11** has been achieved, thus demonstrating a possible biomimetic route to pyridomacrolidin **2**.

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 a common *p*-hydroxyphenyl pyridone unit that is also present in the related fungal metabolites tenellin **3**,² bassianin **4**,³ and ilicicolin **5**.⁴ Chemically, this class of compounds has elicited a significant amount of interest as demonstrated by synthetic work already published.^{5,6}

The biological activity of both pyridovericin **1** and pyridomacrolidin **2** has been shown to include the inhibition

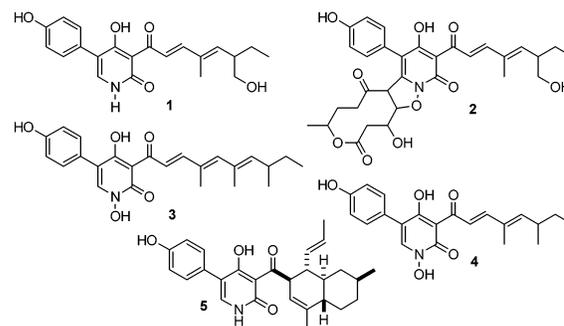


Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related metabolites.

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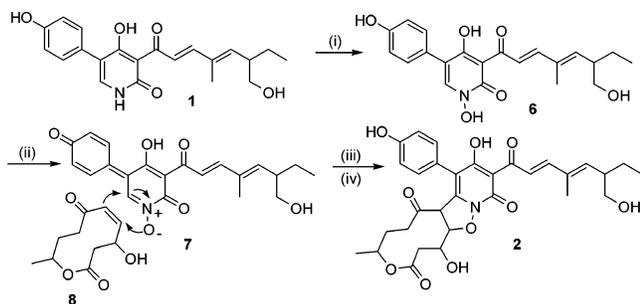
(1) (a) Takahashi, S.; Kakinuma, N.; Uchida, K.; Hashimoto, R.; Yanagishima, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 596. (b) Takahashi, S.; Kakinuma, N.; Uchida, K.; Hashimoto, R.; Yanagishima, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 1051.

(2) ElBayouni, S. H.; Brewer, D.; Vining, L. C. *Can. J. Bot.* **1968**, *46*, 441.

(3) Wat, C.-K.; McInnes, A. G.; Smith, D. G.; Wright, J. C. L.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4090.

(4) Matsumoto, M.; Minato, H. *Tetrahedron Lett.* **1976**, *17*, 3827.

Scheme 1. Proposed Biosynthesis of Pyridomacrolidin 2



of protein tyrosine kinase (PTK) activity at concentrations of 100 $\mu\text{g/mL}$.¹ PTK inhibitors are of potential use as therapeutic agents against a variety of proliferative and inflammatory diseases.⁷ In common with several compounds found to inhibit PTK's, pyridovericin **1** and pyridomacrolidin **2** contain a *p*-hydroxy phenyl moiety, which presumably mimics tyrosine.

The combination of structural novelty and complexity coupled with promising biological activity prompted us to design a biomimetic synthesis of pyridomacrolidin **2**. The biosynthesis of tenellin **3**, bassianin **4**, and ilicicolin **5** has been studied in some detail,^{8–10} 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 co-isolated with pyridomacrolidin from the same fungus) via a number of steps, namely (i) oxidation of pyridovericin **1** to hydroxamic acid **6**, (ii) further oxidation to the novel acyl nitron intermediate **7**, (iii) 1,3-dipolar cycloaddition¹¹ with cephalosporide B **8**, and (iv) re-aromatization to form pyridomacrolidin **2** (Scheme 1). Cephalosporide B is itself a natural product, isolated independently from the fungus *Cephalosporium aphidicola*,¹² although it has not yet been isolated from *B. bassiana*.

Although the 1,3-dipolar cycloadditions of nitrones with enones is well documented,¹³ to the best of our knowledge,

(5) (a) Williams, D. R.; Lowder, P. D.; Gu, Y. G. *Tetrahedron Lett.* **1977**, 38, 327. (b) Buck, J.; Madeley, J. P.; Adeley, J. P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 67. (c) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, 54, 5853. (d) Williams, D. R.; Sit, S. Y. *J. Org. Chem.* **1982**, 47, 2846. (e) Zhang, Q. S.; Curran, D. P. *Abstracts of Papers*, 222nd National Meeting of the American Chemical Society, Chicago, IL, Aug. 26–30, 2001; American Chemical Society: Washington, DC, 2001; ORGN-519.

(6) Baldwin, J. E.; Adlington, R. M.; Aurelia, C.; Nageswara Rao, I.; Marquez, R.; Pritchard, G. *J. Org. Lett.* **2002**, 4, 2125.

(7) Levitzki, A.; Gazit, A. *Science* **1995**, 267, 1782

(8) McInnes, A. G.; Smith, D. G.; Wat, C.-K.; Vining, L. C.; Wright, J. L. *J. Chem. Commun.* **1974**, 281.

(9) Tanable, M.; Urano, S. *Tetrahedron* **1983**, 39, 3569.

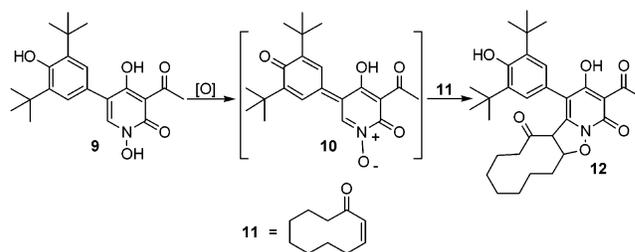
(10) Leete, E.; Kowanko, N.; Newmark, R. A.; Vining, L. C.; McInnes, A. G.; Wright, J. L. *Tetrahedron Lett.* **1975**, 16, 4103.

(11) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984.

(12) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. R.; Ratcliff, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843.

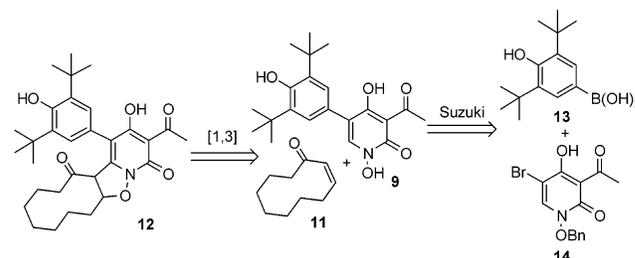
such reactions have not been demonstrated from a nitron (such as **7**) derived from the oxidation of a 5-(4-hydroxyphenyl)-*N*-hydroxy-2-pyridone (such as **6**). Since, as expected, our attempts to oxidatively generate and trap unsubstituted quinonoid species similar to **7** were unsuccessful, probably due to competing additions to this highly electron deficient system as well as solubility problems, we chose to block the phenolic ortho-positions by sterically hindering groups. Thus we prepared **9** and studied its oxidative cycloaddition with *Z*-2-cyclodecenone **11**¹⁴ (Scheme 2).

Scheme 2



A retrosynthetic analysis reduced the target compound **9** to a Suzuki cross-coupling between boronic acid **13** and bromide **14** followed by deprotection (Scheme 3). The

Scheme 3. Retrosynthetic Scheme



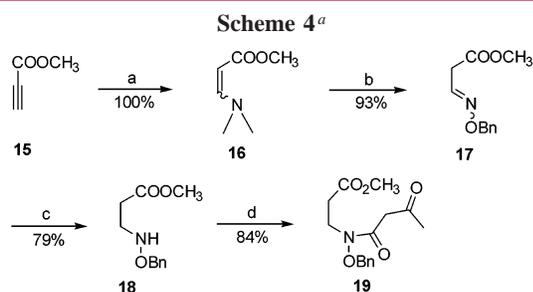
bromide **14** itself should be available following modification of methodology developed by Williams *et al.*^{5d}

Thus, a requisite hydroxamic acid derivative **19** was initially prepared in excellent overall yield as illustrated in Scheme 4. First, the enamine **16**¹⁵ was prepared by passing dimethylamine gas into an ice-cooled solution of methyl propiolate **15** in diethyl ether, which on subsequent reflux

(13) See for example: (a) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, 42, 6715. (b) Fourets, O.; Cauliez, P.; Simonet, J. *Tetrahedron Lett.* **1998**, 39, 565. (c) Gothelf, K. V.; Jorgensen, K. A. *J. Org. Chem.* **1994**, 59, 5687. (d) Joucla, M.; Tonnard, F.; Gree, D.; Hamelin, J. *J. Chem. Res. (S)* **1978**, 240. (e) Joucla, M.; Hamelin, J.; Carrie, R. *Bull. Chem. Soc. Fr.* **1973**, 11, 3116. (f) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984, Chapters 1, 9, and 12.

(14) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, 124, 2245.

(15) Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, 30, 3141.



^a Reagents and conditions: (a) $(\text{CH}_3)_2\text{NH}$, Et_2O , rt, 1 h; (b) H_2NOBn , xylene, reflux, 24 h; (c) NaCNBH_3 , $\text{EtOH}\cdot\text{HCl}$, rt, 12 h; (d) diketene, DMAP, Et_3N , THF 0 °C, 30 min.

in xylene with *O*-benzylhydroxylamine containing a catalytic amount of camphor sulfonic acid gave **17**¹⁶ in excellent yield. Oxime **17** was then reduced with sodium cyanoborohydride in ethanolic aqueous HCl. Acylation of the resulting amine **18** with diketene, conducted in anhydrous THF containing triethylamine and a catalytic amount of 4-(dimethylamino)-pyridine, afforded the amide **19** (Scheme 4).

Ester hydrolysis of the amide **19** in a 1:1 mixture of THF and water was achieved with lithium hydroxide in quantitative yield. The resultant crude carboxylic acid, **20**, was treated with 1,1'-carbonyldiimidazole in THF, which after intramolecular cyclization following addition of sodium hydride yielded the 5,6-dihydro pyridone **21** in very good yield. Unlike the Williams chemistry precedent^{5d} attempted oxidation of pyridone **21** with several oxidants (MnO_2 , DDQ, *p*-chloranil, Pd/C, H_2SO_4 , PhSeCl/LDA then H_2O_2) met with failure. After considerable experimentation oxidation was achieved with lead tetraacetate¹⁷ in 25% yield to provide pyridone **22**, which on bromination¹⁸ afforded the crucial Suzuki coupling partner **14** in good yield.

The phenyl boronic acid **13** required for the Suzuki coupling was prepared by the transmetalation of the commercially available 4-bromo-2,6-di-*tert*-butyl phenol **23** with *tert*-butyllithium and quenching of the organo lithium species with triisopropyl borate, followed by acid hydrolysis. Coupling of the bromide **14** and boronic acid **13** was carried out under standard Suzuki conditions¹⁹ to yield the *N*-protected pyridone **24**. Deprotection of the benzyl group with 10% palladium on carbon/hydrogen furnished the *N*-hydroxy pyridone **9** in excellent yield (Scheme 5).

When oxidation of the benzyl-protected pyridone **24** was carried out with iodobenzene diacetate in methanol there was obtained the cyclohexadienone **25** in moderate yield.²⁰ Likewise oxidation of hydroxamic acid **9** in methanol gave a similar cyclohexadienone **26** in moderate yield (Scheme 6).

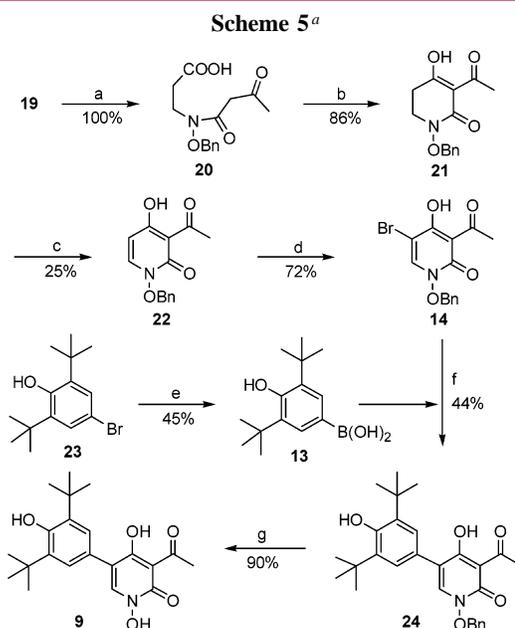
(16) Macchia, M.; Menchini, E.; Nencetti, S.; Orlandini, E.; Rossello, A.; Belfore, M. S. *II Farmaco* **1996**, *51*, 255.

(17) Daniel, L.; Jean-Charles, L.; Max, R. *Tetrahedron Lett.* **1985**, *26*, 1295.

(18) Japanese Patent 5-78324, 1993.

(19) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

(20) Pelter, A.; Elgandy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

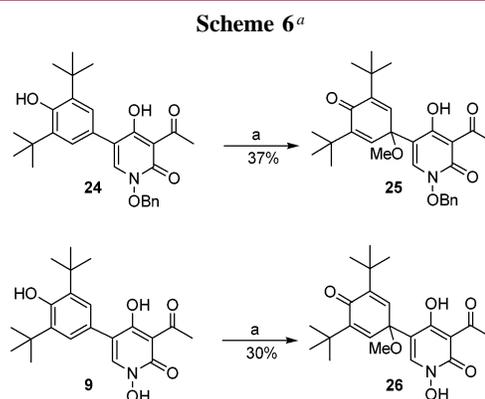


^a Reagents and conditions: (a) LiOH, THF + H_2O , rt, 2 h; (b) CDI, THF, NaH, rt, 12 h; (c) $\text{Pb}(\text{OAc})_4$, benzene, 70 °C, 24 h; (d) Br_2 , DCM, reflux, 12 h; (e) *t*-BuLi, $\text{B}(\text{OCH}(\text{CH}_3)_2)_3$, THF, rt, 12 h; (f) $\text{Pd}(\text{Ph}_3)_4$, Na_2CO_3 , 4:1 toluene:ethanol, reflux, 12 h; (g) 10% Pd/C, dioxane, H_2 , rt, 1 h.

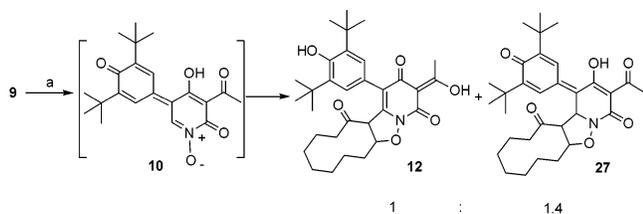
Next, oxidation of the hydroxamic acid **9** in the presence of *Z*-2-cyclodecenone **11** with iodobenzene diacetate in dichloromethane at reflux temperature was attempted. Encouragingly, the unstable nitron formed by the oxidation of hydroxamic acid **9** underwent [3+2] cycloaddition with enone **11** smoothly to give the cyclized products phenol **12** and quinone methide **27** in 60% combined yield (Scheme 7).

The structures of the cyclized products **12** and **27** were established by extensive NMR studies and confirmed by single-crystal crystallography. It is clear from the crystal structures (Figure 2) that the nitrogen in quinone methide **27** is pyramidal whereas in phenol **12** it is planar.

Various attempts to equilibrate the two cyclized products in the presence of trifluoroacetic acid or Hunig's base in



^a Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, MeOH, 40 °C, 20 h.

Scheme 7^a

^a Reagents and conditions: (a) $\text{PhI}(\text{OAc})_2$, 2-cyclodecenone **11**, DCM, reflux, 24 h, 60%.

tert-butyl alcohol were unsuccessful; quinone methide **27** was found to be stable under these conditions.

The formation of these compounds can be rationalized by the addition of nitron **10** to the alkene **11** via [3+2] cycloaddition to obtain a mixture of *endo* (**28**) and *exo* (**27**) quinone methide adducts. Under the reaction conditions the *endo* product **28** selectively underwent further aromatization to provide phenol **12**. It is noticeable that the X-ray structures of **12** and *exo* **27** indicate that these molecules exist in different tautomeric structures in the pyridone-like core

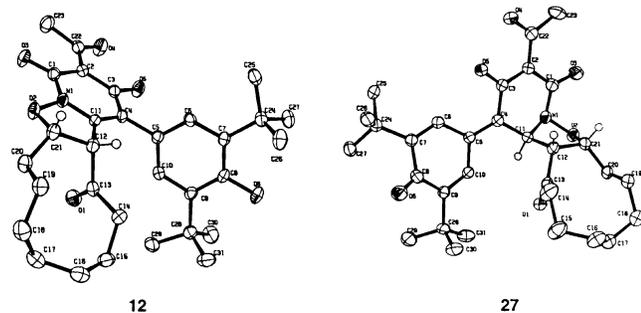
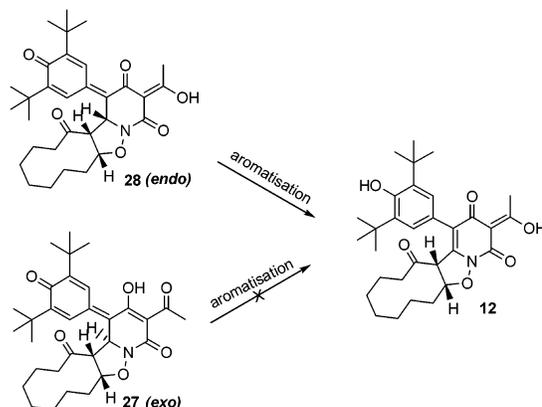


Figure 2. Crystal structures of phenol **12** and quinone **27**.

Scheme 8



(Scheme 8). Whether *endo* **28** was formed with the same tautomeric structure as phenol **12**, thus permitting facile aromatization, or that these differences result from crystal packing is unknown at this time.

In conclusion an unusual oxidative cyclization of *N*-hydroxy pyridone **9** with *Z*-2-cyclodecenone **11** has been achieved, thus demonstrating a possible biomimetic route to pyridomacrolidin **2**. The beneficial effect of the *tert*-butyl groups in this process is notable. It may well be that in an enzyme-mediated oxidation that the enzyme structure provides a similar protective effect on the proposed key intermediate **7**.

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Supporting Information Available: Experimental procedure and spectral data for compounds **12** and **27**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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