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

Nageswara Rao Irlapati,[†] Jack E. Baldwin,*[,†] Robert M. Adlington,[†] and Gareth J. Pritchard[‡]

Dyson Perrins Laboratory, Department of Chemistry, Oxford University, South Parks Road, Oxford OX1 3QY, United Kingdom, and Department of Chemistry, Loughborough University, Loughborough, Leicester LE11 3TU, United Kingdom

Andrew Cowley

Chemical Crystallography, Oxford University, South Parks Road, Oxford OX1 3QR, United Kingdom

jack.baldwin@chem.ox.ac.uk

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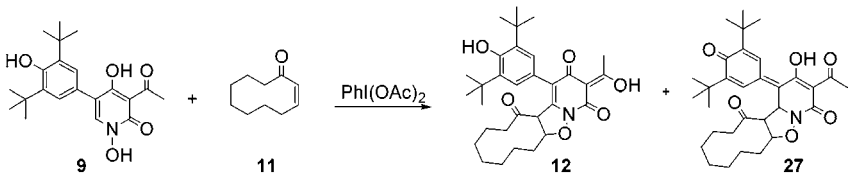
ABSTRACT



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

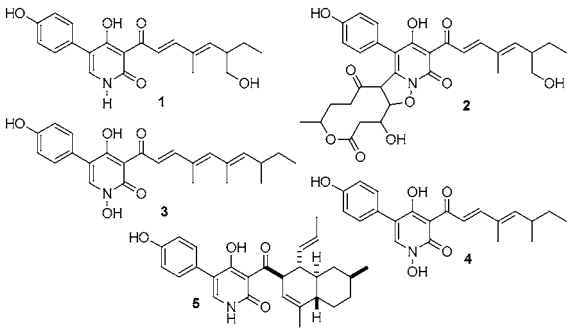


Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related metabolites.

[†] Oxford University.
[‡] Loughborough University.

(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.

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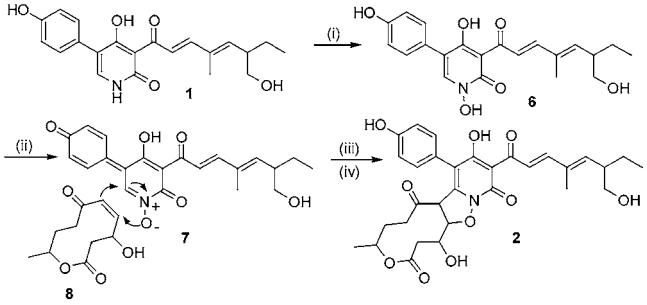
Scheme 1. Proposed Biosynthesis of Pyridomacrolidin **2**

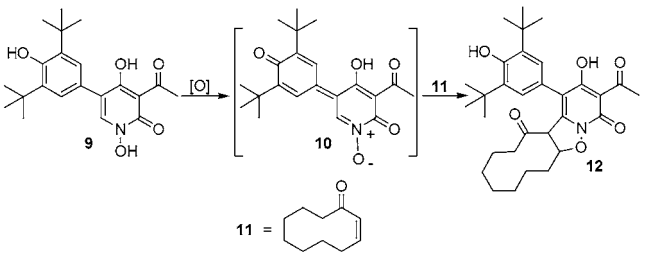


of protein tyrosine kinase (PTK) activity at concentrations of 100 μg/mL.[1] PTK inhibitors are of potential use as therapeutic agents against a variety of proliferative and inflammatory diseases.[7] In common with several compounds found to inhibit PTK's, pyridovericin **1** and pyridomacrolidin **2** 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 nitrone intermediate **7**, (iii) 1,3-dipolar cycloaddition[11] with cephalosporolide B **8**, and (iv) re-aromatization to form pyridomacrolidin **2** (Scheme 1). Cephalosporlide B is itself a natural product, isolated independently from the fungus *Cephalosporium aphidicola*,[12] although it has not yet been isolated from *B. bassiana*.

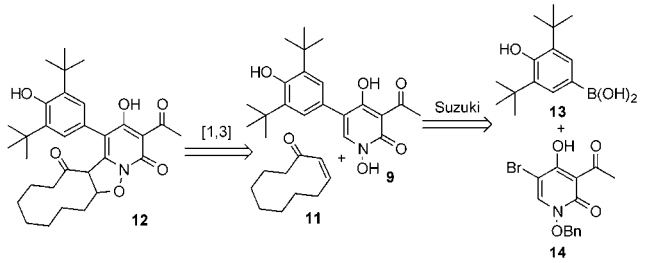
Although the 1,3-dipolar cycloadditions of nitrones with enones is well documented,[13] to the best of our knowledge, such reactions have not been demonstrated from a nitrone (such as **7**) derived from the oxidation of a 5-(4-hydroxyphenyl)-*N*-hydroxy-2-pyridone (such as **6**). Since, as expected, 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

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

(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.

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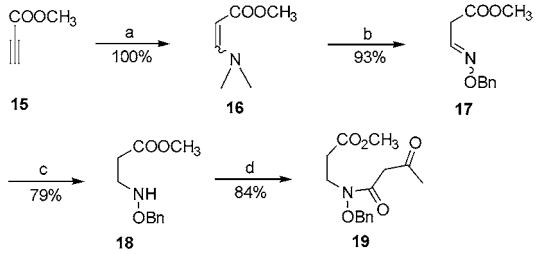
(15) Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem*. **1965**, *30*, 3141.

Scheme 4[a]



[a] Reagents and conditions: (a) $(CH_3)_2NH$, Et_2O, rt, 1 h; (b) H_2NOBn, xylene, reflux, 24 h; (c) $NaCNBH_3$,EtOH·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 tetraacetate[17] in 25% yield to provide pyridone **22**, which on bromination[18] 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 conditions[19] 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.
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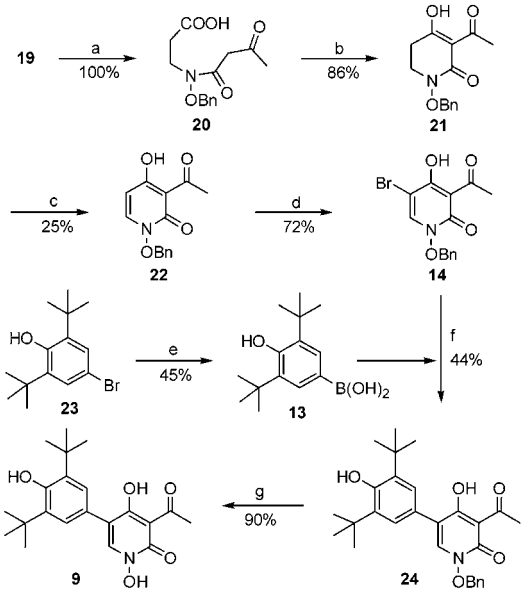
Scheme 5[a]



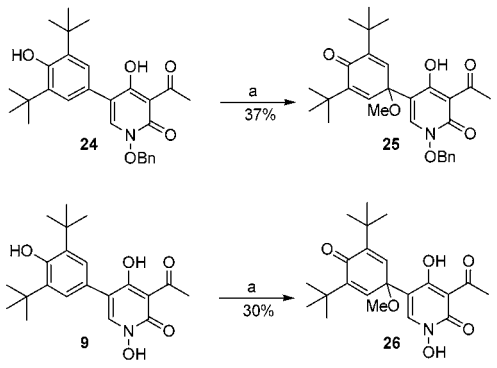
[a] Reagents and conditions: (a) LiOH, THF + H_2O, rt, 2 h; (b) CDI, THF, NaH, rt, 12 h; (c) $Pb(OAc)_4$, benzene, 70 °C, 24 h; (d) Br_2, DCM, reflux, 12 h; (e) *t*-BuLi, $B(OCH(CH_3)_2)_3$, THF, rt, 12 h; (f) $Pd(Ph_3)_4$, Na_2CO_3, 4:1 toluene:ethanol, reflux, 12 h; (g) 10% Pd/C, dioxane, H_2, rt, 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 nitrone 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.

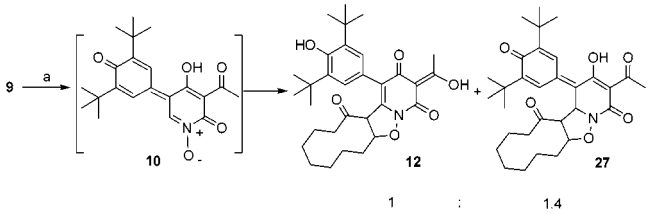
Various attempts to equilibrate the two cyclized products in the presence of trifluoroacetic acid or Hunig's base in

Scheme 6[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 40 °C, 20 h.

Scheme 7 [a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, 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 nitrone **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

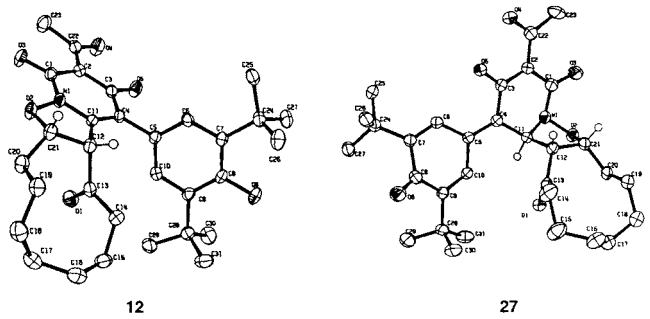
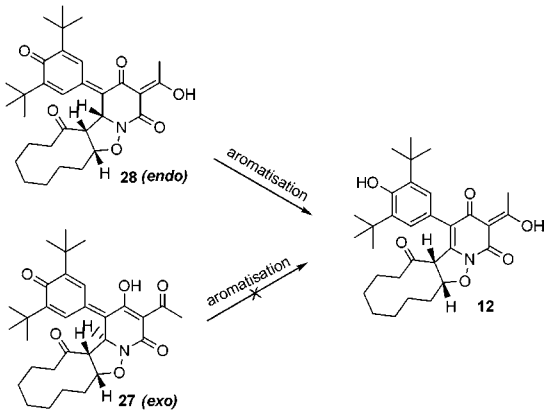


Figure 2. Crystal structures of phenol **12** and quinone **27**.

Scheme 8



(Scheme 8). Whether *endo* **28** was formed with the same tautomeric structure as phenol **12**, thus permitting fascile 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**.

Acknowledgment. N.R.I. is indebted to Dr. Reddy's Research Foundation (DRF), Hyderabad, India for their support and financial assistance.

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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