Published in final edited form as:
Angew Chem Int Ed Engl. 2011 February 1; 50(5): 1131–1134. doi:10.1002/anie.201006438.

Total Synthesis of Pederin and Analogs**

Dr. Fanghui Wu, **Dr. Michael E. Green**†, and **Prof. Dr. Paul E. Floreancig**
Department of Chemistry University of Pittsburgh Pittsburgh, Pennsylvania 15260, USA, Fax: (+1) 412-624-8611

Paul E. Floreancig: florean@pitt.edu

The search for the causitive agent for *Paederis* dermatitis, an inflammatory condition that results from contact with beetles of the *Paederis* family, resulted in the isolation of pederin (**1**).[1] Pederin subsequently inspired a substantial wave of investigation that led to the determination of its correct structure,[2] the observation of its potent cytotoxicity,[3] the postulation of protein synthesis inhibition as its likely mode of biological activity,[4] the identification of the 60S subunit of the ribosome as its potential biological target,[5] and the establishment of bacterial symbionts as its true biogenetic source.[6] Pederin's interesting biological activity and challenging structural features have spawned significant synthetic efforts, resulting in several total, formal, and analog syntheses.[7] A noteworthy advance in pederin accessibility was recently disclosed by Rawal,[7f] who reported that pederin could be prepared through a 12 step (longest linear sequence) route. In accord with our interest in the pederin family of molecules,[8] we report our total synthesis of **1**. In addition to the brief linear sequence, this approach highlights the utility of a late stage multicomponent construction of the *N*-acylaminal structure that allows for the efficient construction of analogs with structural variation in each of three distinct subunits.

We envisioned pederin to arise (Scheme 1) from the union of a pederic acid derivative (**2**), a tetrahydropyranyl nitrile (**3**), and MeOH through our recently reported[9] multicomponent amide synthesis. This late stage construction of the *N*-acyl aminal unit is well-suited for analog synthesis through variations on the pederic acid unit, the nitrile, and the alcohol. The nitrile can be prepared from lactol **4**, which can be accessed from keto alcohol **5**, a known compound[8c] that can be prepared in multigram quantities and with high enantiomeric purity in three steps from isobutyraldehyde.

Silylation of **5** proceeded through standard conditions to yield ether **6**. We postulated that the remaining carbons of the right-hand fragment could be introduced through an aldol reaction between an enolate of **6** and methoxyacetaldehyde. High levels of 1,5-*anti*-diastereocontrol have been reported for aldol reactions between aldehydes and dialkylboron enolates of β-alkoxy ketones, but β-silyloxy enolates show poor levels of control.[10] Thus we employed Paterson's pinene-derived boron enolate aldol strategy[11] to effect the conversion of **6** to **7** in 88% yield as a 15:1 mixture of diastereomers upon oxidative cleavage of the borinate intermediate. This degree of stereocontrol was gratifying in consideration of the modest levels of selectivity that are normally observed for aldol reactions with $(Ipc)_2B$ enolates of methyl ketones. Stereoselective reduction of **7** with Et_2BOMe and $NaBH_4$ yielded **8** efficiently. While the yields and stereocontrol for the aldol

**We thank the National Science Foundation for generous support of this work through grant CHE-0848299 and the the NIH for the 700 MHz NMR at the University of Pittsburgh (S10RR023404).

Correspondence to: Paul E. Floreancig, florean@pitt.edu.
†Current address: Pfizer Global Research and Development, Groton, CT 06430, USA

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

and reduction reactions were satisfactory, diol **8** could be accessed directly as a single stereoisomer in 80% yield by treating the borinate intermediate from the aldol reaction with $LiBH_4$[12] prior to oxidative cleavage. This one pot sequence also facilitated product separation from the pinene-derived by-products. Ozonlytic cleavage of the terminal alkene led to the formation of lactol **9**.

We proposed that the lactol could be ionized by $BiBr_3$ selectively in the presence of the unprotected secondary alcohol and the resulting oxocarbenium ion would react with TMSCN[13] to afford the desired nitrile by analogy to a similar transformation in our synthesis of leucascandrolide A.[14] This strategy would allow for the introduction of the cyano group into the structure while avoiding steps to incorporate leaving or protecting groups. Exposing **9** to TMSCN and $BiBr_3$ followed by an acidic work-up provided **10**, though in only a 35% isolated yield. Further examination revealed that lactol silylation was competitive with ionization, and that the lactol silyl ether was unreactive toward ionization by $BiBr_3$. This problem was solved by adding BF_3•OEt_2 to the mixture following the initial reaction with $BiBr_3$ and TMSCN. The stronger Lewis acid promoted ionization of the lactol silyl ether to yield **10** in 63% isolated yield as a single stereoisomer. Minimal product formation was observed when BF_3•OEt_2 was used in the absence of $BiBr_3$. Methylation of **10** was achieved with MeOTf and 2,6-di-*tert*-butylpyridine to provide **11**, the nitrile component for the multicomponent acyl aminal formation, in 86% yield.

The key fragment coupling reaction (Scheme 3) proceeded through the hydrozirconation of **11** followed by the addition of acid chloride **12**, prepared through our variant[8d] of Nakata's route,[15] to provide acylimine intermediate **13**. The acylation needed to be conducted at low temperature because, in contrast to studies on simpler systems, tautomerization of **13** was observed at room temperature. Analogs of **12** that employed a silyl ether to protect the C7 hydroxyl group were unreactive acylating agents as a result of steric hindrance around the carboxyl group. The addition of MeOH and $Mg(ClO_4)_2$ to **13** led to the formation of acyl aminal **14** as a single stereoisomer in 43% yield. We attribute the high stereocontrol[16] to a reactive conformation in which $Mg(ClO_4)_2$ coordinates the tetrahydropyranyl oxygen and the acylimine nitrogen, forcing the MeOH to approach from the less congested face. The total synthesis of pederin was completed through an efficient one pot cleavage of both protecting groups (Bu_4NF/THF, followed by LiOH/MeOH/H_2O).[7f] All spectral data for the final compound matched reported[7] values. The Supporting Information contains tabulated comparisons of ^1H NMR, ^{13}C NMR, and optical rotation data.

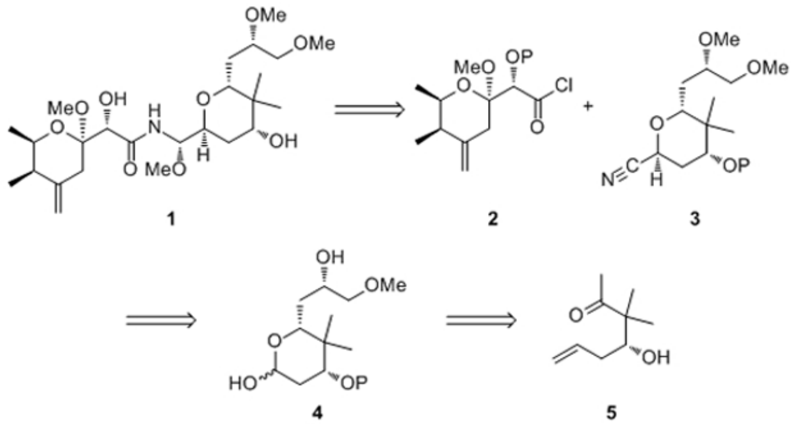
The brevity of the sequence and the opportunities that the late stage multicomponent reaction presents for diversification led us to explore the preparation of a number of pederin analogs. The syntheses of these compounds are shown in Scheme 4.[17] Analogs **15**-**18** were designed to study the importance of the alkoxy component at the C10 position on biological activity. The alkoxy groups of **15** and **16** are sterically similar, but the trifluoroethoxy group can ionize more readily, as evidenced by the isolation of enamide **19** as a significant byproduct in the preparation of **16**. The alkene geometry in compound **19** was assigned based on a NOESY cross peak between the vinyl hydrogen of the enamide and a C12 hydrogen in the tetrahydropyran ring. This lability could be useful if biological activity requires that the *N*-acylaminal group serve as a latent acyliminium ion. This mechanism has been suggested as a possible source of activity for the mycalamide family of molecules.[18] Benzylic ethers **17** and **18** were designed to test the steric tolerance at this site while also being able to serve as precursors to *N*-acyl hemiaminal analogs. The C13 methyl ether analog was prepared by subjecting **20**[19] to the multicomponent reaction and deprotection sequence to form **21**. The corresponding hydroxyl site is methylated in the structurally related and highly cytotoxic mycalamide family of natural products,[20] and incorporation of the methyl ether could remove one step from the sequence. The exocyclic alkene at the C4 site is a source of chemical instability but was shown[21] to be unnecessary for biological activity in mycalamide analogs. Therefore we synthesized acid chloride **22**[19] and employed it in the multicomponent reaction and deprotection sequence to yield **23**. This structural alteration also shortened the synthesis of the left fragment by two steps. Hydrogenolytic benzyl ether cleavage and concomitant alkene reduction of **17** provided a product that was unstable toward chromatographic purification but the formation of *N*-acyl hemiaminal **24** was consistent with ^{1}H NMR analysis, and the presence of $[M+Na]^{+}$ and $[M-H]^{-}$ ions from LCMS experiments using cation and anion detection, respectively. Attempts to cleave the dimethoxybenzyl ether of **20** with DDQ[22] resulted in decomposition. The ability to prepare *N*-acyl hemiaminal analogs provides support for their potential role as biogenetic precursors of pederin that could be converted to the natural product through a methylase enzyme.[23] Amide **25**, a minor by-product in the multicomponent reactions that arises from the reaction of acylimine **13** with excess Schwartz reagent, was converted to **26**. While indirect evidence has suggested that the C10 methoxy group is important for the biological activity of these molecules,[24] this hypothesis has never been tested. Moreover this structure can be used to determine whether it could serve as a biogenetic precursor to pederin through amide oxidation.[25]

We have reported a ten step (longest linear sequence) synthesis of pederin. This route is the shortest sequence to pederin that has been reported, and features a late stage multicomponent reaction to unite the subunits and form the challenging acylaminal group. Application of the method to analog synthesis yielded compounds that will be used to test hypotheses regarding the biological activity and biosynthesis of this intriguing natural product. While the multicomponent reactions did not proceed in excellent yields, the use of this process as a strategy level step provided useful amounts of products, a significant increase in molecular complexity, and unprecedented access to analogs. The results from biological assays will be reported in a full account of this work.

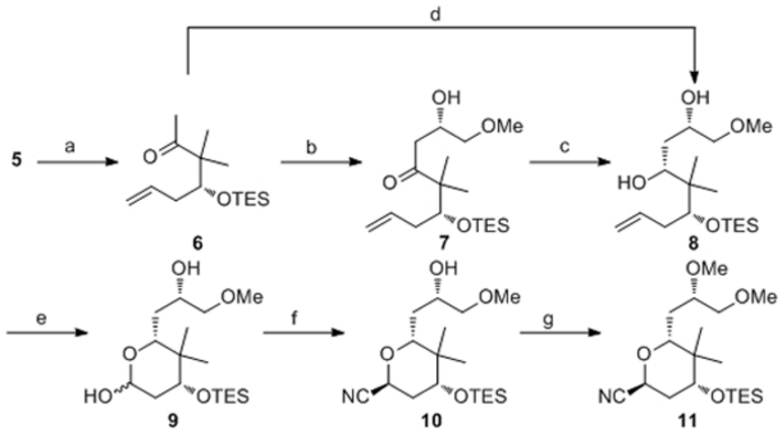
References

1. Pavan M, Bo G. Phys Comp Oec. 1953; 3:307.
2. a) Cardani C, Ghiringhelli D, Mondelli R, Quilico A. Tetrahedron Lett. 1965; 8:2537.b) Furusaki A, Watanabé T, Matsumoto T, Yanagiya M. Tetrahedron Lett. 1968; 9:6301.
3. a) Soldati M. Experimentia. 1966; 22:176.b) Richter A, Kocienski P, Raubo P, Davies DE. Anticancer Drug Des. 1997; 12:217. [PubMed: 9154112]
4. Carrasco L, Fernandez-Puentes C, Vasquez D. Mol Cell Biochem. 1976; 10:97. [PubMed: 768741]
5. Nishimura S, Matsunaga S, Yoshida M, Hirota H, Yokoyama S, Fusetani N. Bioorg Med Chem Lett. 2005; 13:449.
6. a) Piel J. Proc Natl Acad Sci USA. 2002; 99:14002. [PubMed: 12381784] b) Piel J, Butzke D, Fusetani N, Hui DQ, Platzer M, Wen GP, Matsunaga S. J Nat Prod. 2005; 68:472. [PubMed: 15787465]
7. a) Matsuda F, Tomiyoshi N, Yanagiya M, Matsumoto T. Tetrahedron. 1988; 44:7063.b) Hoffmann RW, Schlapbach A. Tetrahedron. 1992; 48:1959.Kocienski P, Narquizian R, Raubo P, Smith C, Farrugia LJ, Muir K, Boyle FT. J Chem Soc-Perkin Trans. 2000; 1:2357.d) Takemura T, Nishii Y, Takahashi S, Kobayashi J, Nakata T. Tetrahedron. 2002; 58:6359.e) Jiang X, Williams N, De Brabander JK. Org Lett. 2007; 9:227. [PubMed: 17217271] f) Jewett JC, Rawal VH. Angew Chem. 2007; 119:6622.Angew Chem Int Ed. 2007; 46:6502.g) Liu D, Xue J, Xie Z, Wei L, Zhang X, Li Y. Synlett. 2008:1526.
8. a) Rech JC, Floreancig PE. Org Lett. 2003; 5:1495. [PubMed: 12713307] b) Green ME, Rech JC, Floreancig PE. Org Lett. 2005; 7:4117. [PubMed: 16146366] c) Rech JC, Floreancig PE. Org Lett. 2005; 7:5175. [PubMed: 16268531] d) Green ME, Rech JC, Floreancig PE. Angew Chem. 2008; 120:7427.Angew Chem Int Ed. 2008; 47:7317.

9. a) Wan S, Green ME, Park JH, Floreancig PE. Org Lett. 2007; 9:5385. [PubMed: 18020344] b) DeBenedetto MV, Green ME, Wan S, Park JH. Org Lett. 2009; 11:835. [PubMed: 19152262]
10. a) Paterson I, Gibson KR, Oballa RM. Tetrahedron Lett. 1996; 37:8585.b) Evans DA, Coleman PJ, Côte B. J Org Chem. 1997; 62:788.c) Evans DA, Côte B, Coleman PJ, Connell BT. J Am Chem Soc. 2003; 125:10893. [PubMed: 12952469]
11. Paterson I, Goodman JM, Lister MA, Schumann RC, McClure CK, Norcross RD. Tetrahedron. 1990; 46:4663.
12. Paterson I, Perkins MV. Tetrahedron Lett. 1992; 33:801.
13. Komatsu N, Uda M, Suzuki H, Takahashi T, Domae T, Wada M. Tetrahedron Lett. 1997; 38:7215.
14. Jung HH, Seiders JR II, Floreancig PE. Angew Chem. 2007; 119:8616.Angew Chem, Int Ed. 2007; 46:8464.
15. Trotter NS, Takahashi S, Nakata T. Org Lett. 1999; 1:957.
16. For a related, though less selective reaction, see: Huang X, Shao N, Palani A, Aslanian R, Buevich A. Org Lett. 2007; 9:2597. [PubMed: 17523653]
17. The stereochemical outcomes of the multicomponent reactions were assigned based on the highly predictable trends of the N–H and C10 hydrogens in the 1H NMR spectra of the desired and undesired stereoisomers. Please see the Supporting Information for tabulated data.
18. Hong CY, Kishi Y. J Org Chem. 1990; 55:4242.
19. Please see the Supporting Information for details on the syntheses of **18** and **20**.
20. Perry NB, Blunt JW, Munro MHG, Thomson AM. J Org Chem. 1990; 55:223.
21. Fukui H, Tsuchiya Y, Fujita K, Nakagawa T, Koshina H, Nakata T. Bioorg Med Chem Lett. 1997; 7:2081.
22. a) Smith AB III, Safonov IG, Corbett RM. J Am Chem Soc. 2002; 124:11102. [PubMed: 12224958] b) Rishel MJ, Hecht SM. Org Lett. 2001; 3:2867. [PubMed: 11529777]
23. Zimmermann K, Engeser M, Blunt JW, Munro MHG, Piel J. J Am Chem Soc. 2009; 131:2780. [PubMed: 19206228]
24. a) Matsunaga S, Fusetani N, Nakao Y. Tetrahedron. 1992; 48:8369.b) Simpson JS, Garson MJ, Blunt JW, Munro MHG, Hooper JNA. J Nat Prod. 2000; 63:704. [PubMed: 10843596]
25. Fisch KM, Gurgui C, Heycke N, van der Sar SA, Anderson SA, Webb VL, Taudien S, Platzer M, Rubio BK, Robinson SJ, Crews P, Piel J. Nature Chem Biol. 2009; 5:494. [PubMed: 19448639]

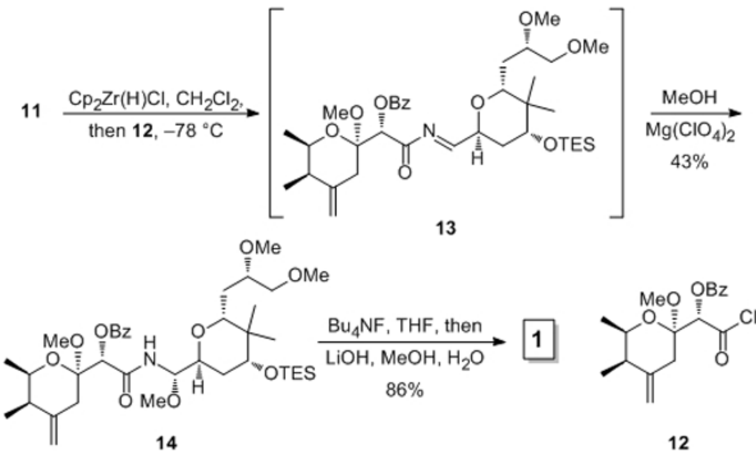


Scheme 1.
Retrosynthetic analysis of pederin.

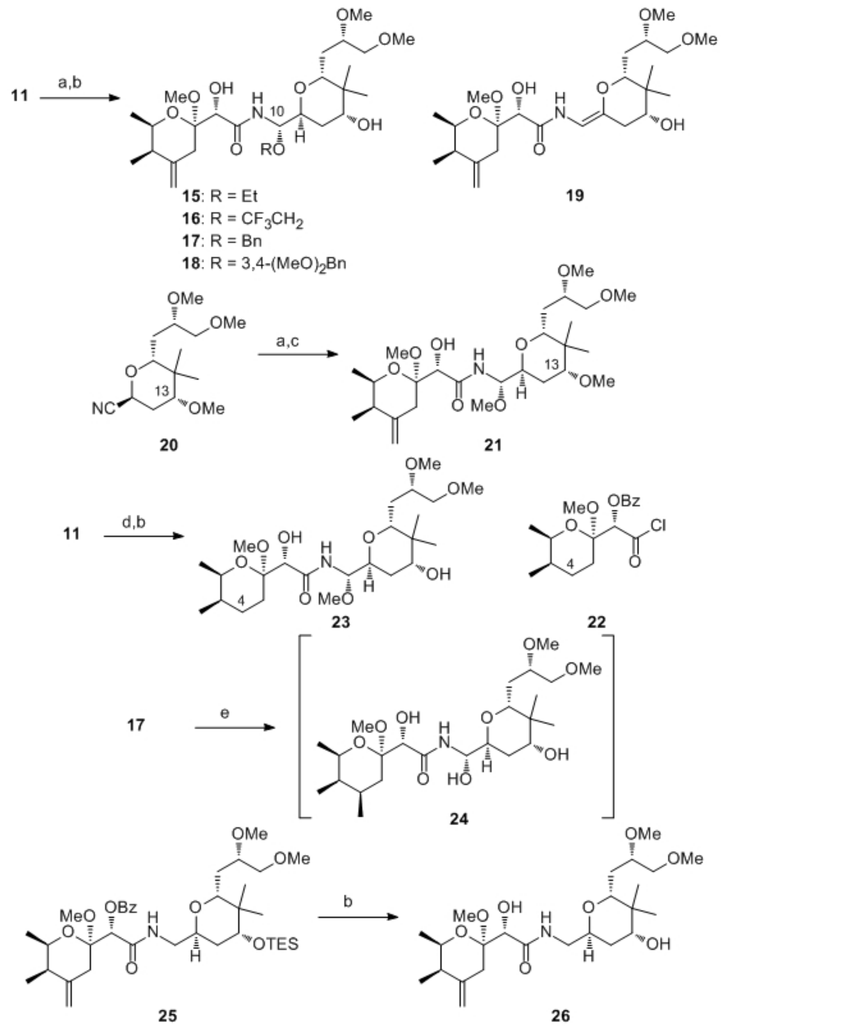


Scheme 2.

Synthesis of the nitrile component. Reagents and conditions: a) TESCl, imidazole, CH_2Cl_2, 100%; b) (+)-DIP-Cl, Et_3N, $MeOCH_2CHO$, Et_2O, −78 °C, 88%, dr = 15:1; c) $NaBH_4$, Et_2BOMe, MeOH, THF, −40 °C, 95%; d) (+)-DIP-Cl, Et_3N, Et_2O, −78 °C, then $LiBH_4$, −40 °C, 80%; e) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 95%; f) TMSCN, $BiBr_3$, CH_3CN, 0 °C, then BF_3•OEt_2, −40 °C, 63%; g) MeOTf, 2,6-^{t}Bu_2Py, CH_2Cl_2, 86%. DIP-Cl = B-chlorodiisopinocam-phenylborane, TMSCN = trimethylsilyl cyanide, MeOTf = methyl trifluoromethanesulfonate, 2,6-^{t}Bu_2Py = 2,6-di-*tert*-butylpyridine.



Scheme 3.
Completion of the total synthesis.



Scheme 4.

Analog synthesis. Reagents and conditions: a) $Cp_2Zr(H)Cl$, CH_2Cl_2, then **12**, −78 °C, then $Mg(ClO_4)_2$, ROH, −78 °C to −40 °C, 40% for EtOH (dr = 15:1), 21% for CF_3CH_2OH, 29% for DMBOH (dr = 4:1), 30% from **20**; b) Bu_4NF, THF, 0 °C, then LiOH, MeOH, H_2O, 78% for **15**, 64% for **16** (+ 29% **19**), 21% for **17** (two steps), 75% for **18**, 82% for **23**, 80% for **26**; c) LiOH, MeOH, 80%; d) $Cp_2Zr(H)Cl$, CH_2Cl_2, then **22**, −78 °C, then $Mg(ClO_4)_2$, then MeOH, 35%; e) H_2, Pd/C, EtOH. DMBOH = 3,4-dimethoxybenzyl alcohol.