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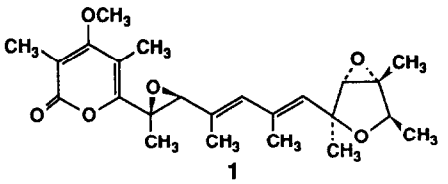
SYNTHETIC STUDIES TOWARD VERRUCOSIDIN: DETERMINATION OF THE ABSOLUTE CONFIGURATION[1]

Jin K. Cha* and R. J. Cooke
Department of Chemistry
Vanderbilt University
Nashville, TN 37235

Abstract: *The tetrahydrofuran portion 3 of verrucosidin 1, a potent neurotoxin, is synthesized in an enantiomerically pure form via the stereoselective osmylation of the chiral hydroxy diene ester 5 as a key step.*

The stereoselective synthesis of structurally complex tetrahydrofuran units has currently received extensive attention.[2] Development of a new methodology for the stereocontrolled construction of highly functionalized tetrahydrofurans poses a considerable synthetic challenge.

From the fungus *Penicillium verrucosum* var. *cyclopium*, verrucosidin, a potent neurotoxin, was isolated, the structure of which was established to be **1** by chemical, spectroscopic and x-ray crystallographic studies.[3,4] Very recently Yamamura and coworkers synthesized its degradation product **2** starting from D-glucose, establishing the absolute configuration of verrucosidin.[5] Thus, verrucosidin bears a close structural relationship to a group of biologically active polyene mycotoxins *viz.* citreoviridin, aurovertins and asteltoxin, which are known to act as potent inhibitors of oxidative phosphorylation.[6] Herein we report an enantio- and stereoselective synthesis of tetrahydrofuran **3**, which confirms the absolute configuration of verrucosidin.[7]



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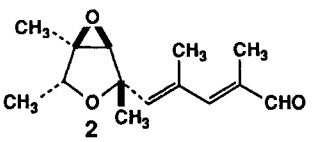

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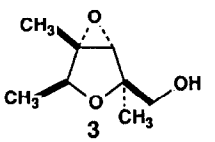
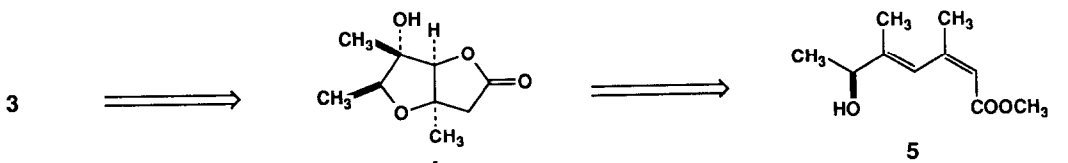


3

Shown below is our retrosynthetic plan for construction of the substituted tetrahydrofuran unit **3**, wherein bicyclic lactone **4** contains all oxygen functions in the required relative configurations. A salient feature of this approach involves the highly regio- and stereoselective osmylation of chiral diene ester **5**.

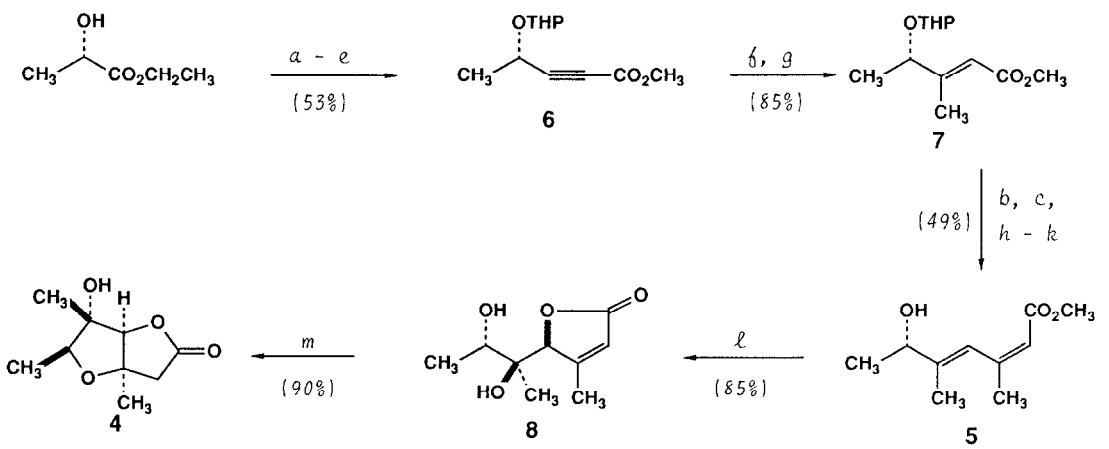


4 **5**

The requisite E,Z-diene ester **5** was prepared in good yield starting from readily available (S)-ethyl lactate as outlined in Scheme I. The yne ester **6**, obtained *via* a modified Wittig dichloroolefination and subsequent elimination, was then converted to the trisubstituted E ester **7** by the procedure of Mukaiyama.[8,9] An iterative homologation followed by the dimethylcuprate addition[10] and deprotection, proceeded cleanly to afford the desired E,Z-diene ester **5**, $[\alpha]_D^{25} = +13.7°$ (c 0.8, $CHCl_3$).[9]

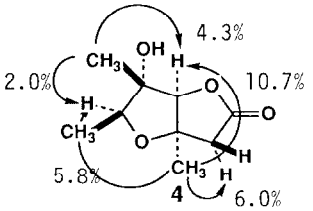
Next it was gratifying to find that the OsO_4-catalyzed hydroxylation (0.02 equiv. OsO_4, 1.2 equiv. NMO,[11] 1:1 THF-H_2O, 0°C) of this compound provided an 85% yield of a **single** lactone **8**![9] None of the other possible regio- and stereoisomers were found.[12,13] Upon treatment with $NaHCO_3$ in methanol, it was then smoothly converted into bicyclic lactone **4** (90%), $[\alpha]_D^{25} = +5.6°$ (c 1.0, $CHCl_3$).[9] The stereochemical assignment was unambiguously made by the difference NOE spectroscopy, and confirmed by its further chemical transformations to the authentic degradation product **3** (*vide infra*).[14] An excellent diastereoselectivity (≥10:1) was also observed for osmylation of the trisubstituted ester **7**, and a single lactone was obtained from the corresponding free hydroxy ester.[15] The "sense" and "extent" of asymmetric induction in these stereoselective OsO_4 reactions are in good agreement with those previously reported by Kishi[16a] and Stork.[16b]

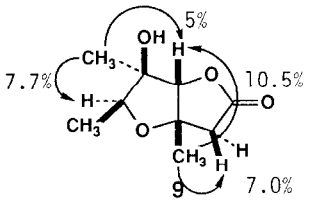
Scheme I



a. dihydropyran, PPTS; *b*. LAH, ether; *c*. Swern oxid.; *d*. $BrCCl_3$, HMPT, -23°C; *e*. 2 equiv. ^nBuLi / $ClCO_2Me$, -78°C; *f*. PhSNa, MeOH; *g*. MeMgBr, CuI, THF, -78°C; *h*. $Ph_3P{=}CHCl$, THF, -78°C; *i*. MeLi / $ClCO_2Me$, -78°C; *j*. Me_2CuLi, THF, -78°C; *k*. PPTS, MeOH; *l*. OsO_4(0.02 equiv), NMO(1.2 equiv), THF-H_2O, 0°C; *m*. $NaHCO_3$, MeOH.

With **4** (possessing all four contiguous chiral centers of verrucosidin) in hand, we required a one-carbon degradation of the lactone moiety, which turned out not to be a trivial problem. Although a silyl ketene acetal formation followed by oxidative cleavage was envisioned for this purpose, numerous attempts to generate a ketene acetal failed.[17] Other unsuccessful attempts included a modified Barbier-Wieland degradation, the ketene

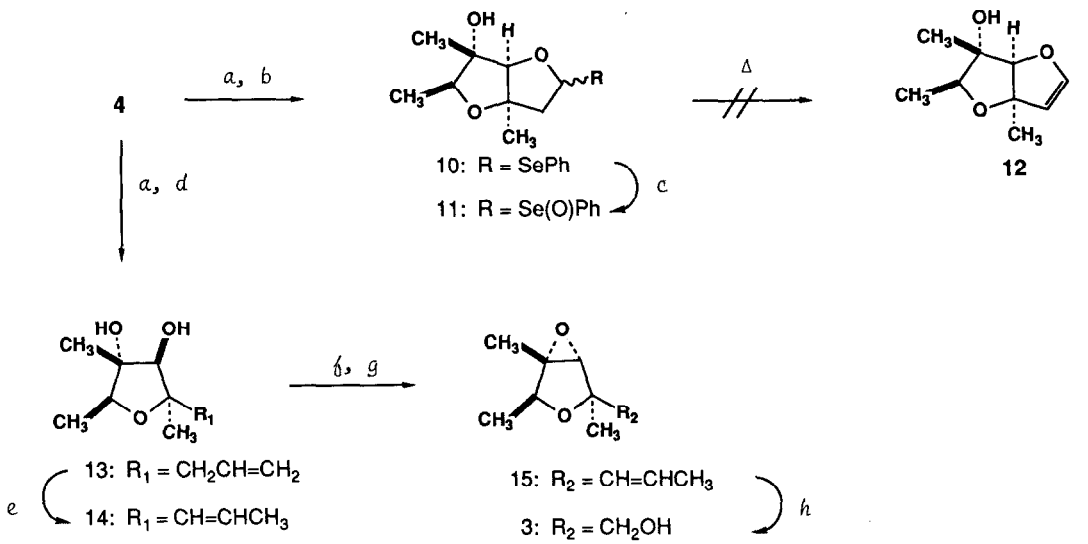




thioacetal formation with bis(dimethylaluminum)ethanedithiolate,[18] and an α-hydroxy lactone route through the action of iodobenzene diacetate, Gold's reagent or MoOPH.

Formation of a dihydrofuran would provide an entry to the desired product **3** via an oxidative cleavage. The DIBAL-H reduction of **4** followed by treatment with benzeneselenol in the presence of $BF_3 \cdot Et_2O$ gave cleanly phenylselenide **10** in 60~70% yield.[19] **10** was then smoothly oxidized to yield selenoxide **11**. However, the phenylselenoxide **11** could not be converted into enol ether **12** through the thermal elimination process. Under forcing conditions only the starting lactone **4** was isolated.

Scheme II



a. DIBAL-H, CH_2Cl_2, -78°C; *b*. PhSeH, $BF_3 \cdot Et_2O$, -78°C; *c*. O_3, -78°C;
d. $Ph_3P=CH_2$, THF; *e*. $PdCl_2(PhCN)_2$, PhH, ↑↓; *f*. MsCl, pyr, CH_2Cl_2, RT;
g. NaOMe, MeOH; *h*. O_3, CH_2Cl_2-MeOH, -78°C / $NaBH_4$.

Finally, the desired transformation to tetrahydrofuran **3** was achieved by a simple series of transformations featuring olefin isomerization through the aegis of Pd(II) as shown in Scheme II.[20] The Wittig reaction ($Ph_3P=CH_2$, THF, -78°C) of the lactol obtained before gave allyltetrahydrofuran **13**, $[\alpha]_D^{25}$ = +0.17° (c 1.0, $CHCl_3$), in 70% overall yield.[9] Olefin **13** was then isomerized [$PdCl_2(PhCN)_2$, benzene, 80°C, 90%] to provide **14** (≥8:1),[21] which was further converted into epoxide **15** in a straightforward manner [1. MsCl, pyr, CH_2Cl_2, RT; 2. NaOMe, MeOH, RT]. Subsequent ozonolysis followed by reductive workup with $NaBH_4$ gave the desired alcohol **3**. Alcohol **3** thus obtained was spectroscopically and chromatographically identical with the degradation product from verrucosidin. As the authentic alcohol could not be obtained pure, the Mosher esters[22] were prepared; 400-MHz ^1H spectra showed that synthetic **3** was >95% optically pure, but **enantiomeric** to the natural material.

In summary, we have developed an efficient route to **3** and also confirmed the absolute configuration of verrucosidin as shown in **1**.[23] Total synthesis of verrucosidin in the correct absolute configuration is currently in progress. Further synthetic applications of the strategy outlined above to other members of this group of polyene mycotoxins are underway as well.

Acknowledgment: Financial support from the National Institutes of Health (GM 35956 and ES 00267) is gratefully acknowledged. We thank Professor T. M. Harris for encouragement and a sample of verrucosidin.

References and Footnotes

1. Presented at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 1986: ORGN 296.
2. For a general review, see P. A. Bartlett, **Tetrahedron, 36**, 2 (1980).
3. (a) L. Burka, M. Ganguli, and B. J. Wilson, **J. Chem. Soc., Chem. Commun.**, 544 (1983); (b) M. Ganguli, L. T. Burka, and T. M. Harris, **J. Org. Chem., 49**, 3762 (1984).
4. Contrary to the original report,[3] verrucosidin does not appear to cause sustained tremoring in experimental animals; T. M. Harris and R. P. Hodge, private communication (1986).
5. S. Nishiyama, Y. Shizuri, H. Shigemori, and S. Yamamura, **Tetrahedron Lett., 27**, 723 (1986).
6. For the pertinent references, see H. Venkataraman and J. K. Cha, **Tetrahedron Lett., 28**, 2455 (1987), and references cited therein.
7. For other synthetic studies, see (a) verrucosidin: L. L. Klein, **Tetrahedron Lett., 27**, 4545 (1986); (b) citreoviridin: S. Nishiyama, Y. Shizuri, and S. Yamamura, **ibid., 26**, 231 (1985); C. S. Wilcox, G. W. Long, and H. Suh, **ibid., 25**, 395 (1984); Y. Shizuri, S. Nishiyama, H. Shigemori, and S. Yamamura, **J. Chem. Soc., Chem. Commun.**, 292 (1985); M. C. Bowden, P. Patel, and G. Pattenden, **Tetrahedron Lett., 26**, 4793 (1985); D. R. Williams and F. H. White, **ibid., 27**, 2195 (1986).
8. S. Kobayashi and T. Mukaiyama, **Chem. Lett.**, 705 (1974).
9. Satisfactory spectroscopic data were obtained for all new compounds. Listed below are some selected IR, ^1H and ^{13}C(in $CDCl_3$ noted otherwise), and mass spectroscopic data:

   3 $^1H(CDCl_3)$ 1.25(d,J=6.8Hz,3H), 1.27(s,3H), 1.46(s,3H), 3.43(s,1H), 3.49(s,2H), 4.19(q,J=6.8Hz,1H); $^1H(C_6D_6)$ 0.96(d,J=6.8Hz,3H), 1.12(s,3H), 1.40(s,3H), 3.11(s,1H), 3.27(d,J=11.0Hz,1H), 3.32(d,J=11.0Hz,1H), 4.19(q,J=6.8Hz,1H); ^{13}C 13.84, 18.54, 19.83, 67.80, 67.46, 67.88, 77.29, 81.80; exact mass calcd for M-CH_3($C_7H_{11}O_2$) 127.0759, Found 127.0760(100%).

   4 υ_{max} 3485, 1795 cm^{-1}; ^1H 1.16(d, J=6.7Hz, 3H), 1.34(s,3H), 1.59(s,3H), 2.60(d,J=18.5Hz,1H), 2.80(d,J=18.5Hz,1H), 4.12(q,J=6.7Hz,1H), 4.40(s,1H); ^{13}C 17.01, 19.08, 23.57, 43.35, 81.18, 83.64, 83.79, 94.60, 175.03; exact mass calcd for $C_9H_{14}O_4$ 186.0892, Found 186.0895.

   5 υ_{max} 3500, 1710 cm^{-1}; 1.30(d,J=6.4Hz,3H), 1.69(s,3H), 2.01(s,3H), 3.65(s,3H), 4.30(q,J=6.4Hz,1H), 5.72(br s,1H), 6.55(br s,1H).

   9 ^1H1.20(d, J=6.3Hz,3H), 1.29(s,3H), 1.57(s,3H), 2.64(d,J=19.1Hz,1H), 2.78(d,J=19.1Hz,1H), 3.77(q,J=6.3Hz,1H), 4.33(s,1H); ^{13}C 11.92, 18.45, 25.62, 41.83, 79.10, 79.36, 82.99, 93.20, 177.15.

   8 ^1H 1.34(s,3H), 1.38(d,J=6.8Hz,3H), 2.23(br s, 3H), 2.29(d,J=10.0Hz,1H), 3.03(s,1H), 3.71(m,1H), 4.96(d,J=0.8Hz,1H), 5.90(br s, 1H); ^{13}C 16.62, 17.80, 21.19, 74.62, 74.72, 88.46, 118.90, 167.39, 171.97.

   13 exact mass calcd for M-C_3H_5($C_7H_{13}O_3$) 145.0865, Found 145.0867(100%).
10. (a) E. J. Corey and J. A. Katzenellenbogen, **J. Amer. Chem. Soc., 91**, 1851 (1969); (b) J. B. Siddall, M. Biskup, and J. H. Fried, **ibid., 91**, 1853 (1969).
11. V. VanRheenen, R. C. Kelly, and D. Y. Cha, **Tetrahedron Lett.**, 1973 (1976).
12. The lower diastereoselectivity was observed in the OsO_4 oxidation of the corresponding THP-protected alkoxy diene esters: one THP diastereomer gave a 5:1 stereoselectivity, while a poor (2:1) selectivity was found for the other isomer.
13. Given similar steric effects, electron withdrawing substituents in the olefin appear to retard the OsO_4 oxidations whereas the permanganate oxidations are accelerated by the same substituents; H. O. House, "Modern Synthetic Reactions," p. 277, 2nd ed., W. A. Benjamin, Menlo Park, CA, 1972.
14. The authentic alcohol **3** was obtained by the ozonolysis (O_3, -78°C, MeOH-CH_2Cl_2) of verrucosidin, which was kindly provided by Professor T. M. Harris, followed by the reductive workup (Me_2S; $NaBH_4$).
15. The stereochemistry of the major OsO_4 product was unequivocally determined by an independent synthesis starting from diacetone-D-glucose: R. J. Cooke and J. K. Cha, unpublished results.
16. (a) J. K. Cha, W. J. Christ, and Y. Kishi, **Tetrahedron Lett., 24**, 3943, 3947 (1983); (b) G. Stork and M. Kahn, **ibid., 24**, 3951 (1983).
17. (a) H. Emde and G. Simchen, **Liebigs Ann. Chem.**, 816 (1983); (b) T. J. Barton and C. R. Tully, **J. Org. Chem., 43**, 3649 (1978); (c) C. S. Wilcox and R. E. Babston, **Tetrahedron Lett., 25**, 699 (1984).
18. E. J. Corey and D. J. Beams, **J. Amer. Chem. Soc., 95**, 5829 (1973).
19. D. J. Goldsmith, D. C. Liotta, M. Volmer, W. Hoekstra, and L. Waykole, **Tetrahedron, 41**, 4873 (1985). We thank Professor Michael P. Cava for bringing this paper to our attention.
20. Alternatively, the desired transformation was achieved by the following, albeit lengthy, steps: l. LAH, ether; 2. tBu(Ph)$_2$SiCl, imidazole, DMF; 3. MsCl, cat. DMAP, CH_2Cl_2; 4. NaOMe, MeOH; 5. nBu$_4$NF, THF; 6. nBu$_3$P, *o*-NO_2(C_6H_4)SeCN; H_2O_2; 7. O_3; $NaBH_4$.
21. This ratio does not necessarily reflect the equilibrium mixture.
22. J. A. Dale, D. L. Dull, and H. S. Mosher, **J. Org. Chem., 34**, 2543 (1969).
23. We have also synthesized the other portion of verrucosidin, 6-ketoepoxy-α-pyrones in both optically pure forms: H. Venkataraman and J. K. Cha, unpublished results.

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