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SYNTHESIS OF OPTICALLY ACTIVE VERRUCARINIC ACID DERIVATIVES

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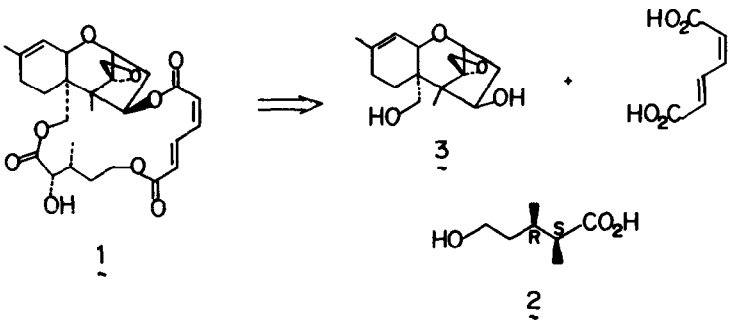
SUMMARY: Two syntheses of verrucarinic acid highlighting an oxidative cleavage of hydroxysulfides and use of mandelate esters for chromatographic resolution are reported.

Verrucarin A (1) is a member of the biologically active macrocyclic tricothecanes.[1] This class of mycotoxins exhibits outstanding *in vitro* cytotoxicity[2a] and has been shown to be potent inhibitors of protein synthesis.[2b] Because of our interest in the total synthesis of **1** from verrucarol (3)[3], verrucarinic acid (**2**), and an *E,Z*-muconic acid, recent reports on the synthesis of verrucarinic acid (**2**) and its derivatives[4,5] prompt us to report our work in this area at this time.

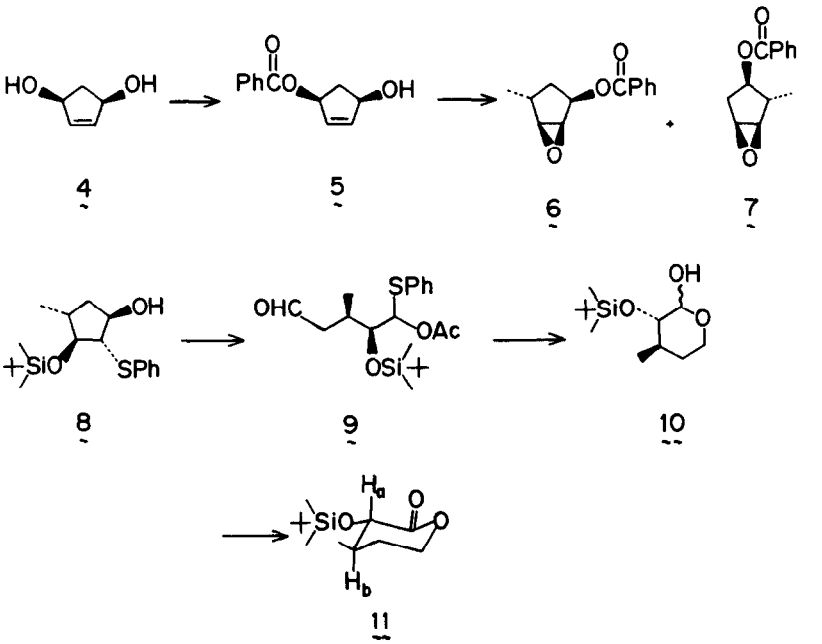


1 **3** **2**

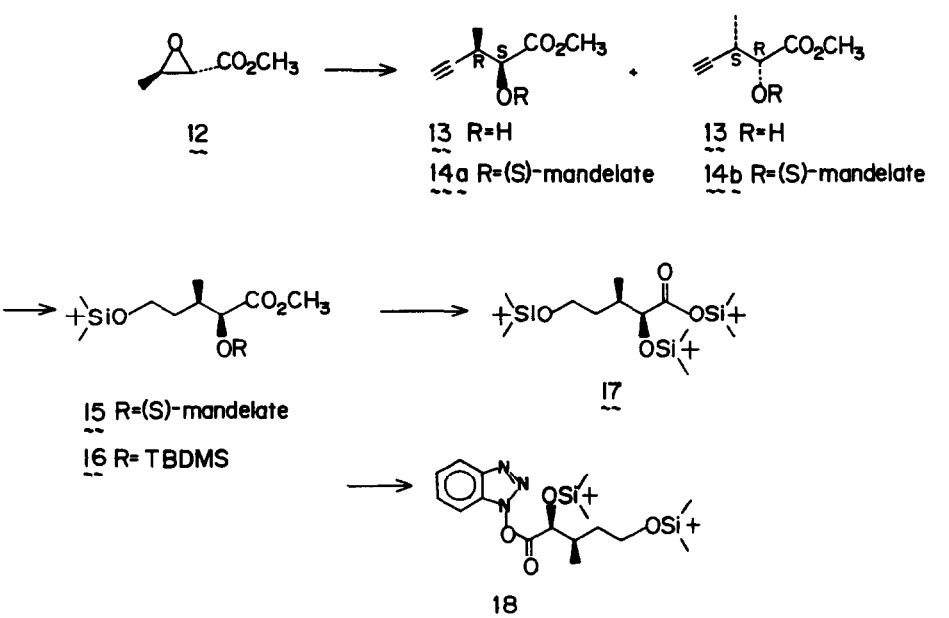
The first approach highlights the utility of the lead tetraacetate (LTA) cleavage of cyclic hydroxysulfides which generate a chemodifferentiated dialdehyde.[6] Applying such a reaction for the cleavage of **8** generates a flexible intermediate for the elaboration of a number of verrucarinic acid derivatives. Scheme I outlines this approach starting from the well-described *cis*-diol **4**.[7] The corresponding monobenzoate **5**, mp 54.5-6°, [PhCOCl (1.0x), pyridine (1.1x), DME, 0°, 64%] was reacted with lithium dimethylcuprate (4x, ether, -20°). After standard workup the crude residue was first treated with MCPBA (CH_2Cl_2, 0°) and then with benzoyl chloride (NaH, ether) to yield after chromatography the epoxide **6** (53%) along with its isomer **7** (26%, both yields from **5**).[8] Opening of the epoxide occurred completely regioselectively with lithium thiophenoxide[9] to give, after a protection-deprotection sequence [(1)1x t-$C_4H_9(CH_3)_2SiCl$(TBDMS-Cl), imidazole, DMF (2) Dibal·H, ether, -78°, 4h], the desired hydroxysulfide **8** (68% from **6**). Cleavage of **8** under our improved conditions[6b] [LTA (2x), HOAc (3x), pyr (4x), benzene, 80°C, 10 min] proceeded smoothly to yield the aldehyde **9** in 83%.

In order to confirm our regio- and stereochemical assignments, the cleavage product was converted to t-butyldimethylsilyl verrucarinolactone **11**. This was achieved by first treating **9** with Dibal·H (2.2x, toluene, -70°, 14h) which both reduced the aldehyde and unmasked the acetoxysulfide[10] to yield the lactol **10** (73%) as a mixture of anomers. Simple oxidation (CrO_3·2pyr, CH_2Cl_2) gave the desired lactone (91%) whose ^1H NMR was almost identical to that

SCHEME I. Hydroxysulfide Approach to Verrucarinolactone

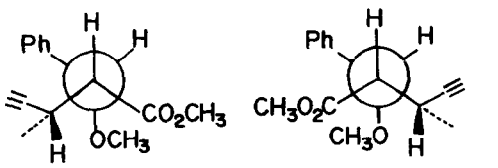


SCHEME II. Asymmetric Synthesis of Verrucarinic Acid



reported for verrucarinolactone,[5] except for the presence of the silyl group. Most importantly a coupling of 9.5 Hz between H_a and H_b was recorded indicative of a diaxial orientation for the two protons. Although the resolution of various derivatives of the diol **4** was known[11], another route was developed for the synthesis of optically active **2**.

The asymmetric synthesis, shown in Scheme II, is based on the resolution of the propargylic alcohol **13** via its (S)-O-methylmandelate ester **14**.[12,13] The requisite alcohol was prepared (63%) from the crotyl epoxide **12** by treatment with diethylaluminum trimethylsilylacetylide[14] (1.5x, toluene rt, 2h) followed by removal of the TMS group with sodium methoxide (1.2x, MeOH, rt, 1.5h). When the alcohol was acylated with (S)-O-methylmandelic acid ($[\alpha]_D^{23}$ = 148° (c=1.17, EtOH)) in THF containing DCC (1.5x) along with one equivalent of N-hydroxybenzotriazole (HBT) and pyridine the esters **14a** and **14b** were formed in 93% without any detectable epimerization of the mandelate piece.[15] Separation of the esters was easily achieved by HPLC[17] and the absolute configuration assigned by both ^{1}H NMR[13a,18] and chemical correlation.[19] Using the model we presented earlier,[13a] inspection of the extended Newman projections A and B allows assignment of the less polar isomer to the absolute configuration in A and the more polar one to that depicted in B.



The least polar ester ($[\alpha]_D^{23}$ = +5.83 (c=1.47, acetone)) was partially hydrogenated to an olefin [H_2 (1.02X), Lindlar cat., 96%], hydroborated with disiamylborane in THF (7h, RT, oxidatively worked up with MCPBA[20] at 0° to rt, 1h) and silylated (TBDMS-Cl, CH_2Cl_2, DMAP) to yield **15** in 89%. The mandelate was then exchanged for a silyl protecting group by hydrolysis with sodium methoxide (1.0x, MeOH, rt, 3h) and silylation [TBDMS-Cl, DMF, imidazole (2x), 37°] to give **16** (85%, $[\alpha]_D^{23}$ = -13.09° (c=1.10, acetone)). The final step needed was to convert **16** to an active acylating agent necessary for its inclusion into verrucarin A. Demethylation of the ester with excess $LiSCH_3$[21] (HMPA, rt, 48h) also effected desilylation at the secondary position, so that the crude mixture was resilylated [TBDMS-Cl (7x), DMF, imidazole (14x)] to yield the trisilyl derivative **17** (88%). Attempts to convert **17** to an acid chloride[22] failed; however, an equally attractive acylating agent **18** could be synthesized by treating **17** with DCC (1.5x), HBT (2.0x), and pyridine (1.0x). Standard aqueous workup (hexane as co-solvent) followed by chromatography (silica gel) gave the acyl hydroxybenzotriazole **18** (54%) as a colorless oil. Similar species[23] have been utilized as acylating agents and in our hands **18** has esterified various alcohols, with the aid of DMAP.

In conclusion, two routes[24] have been developed for the synthesis of the verrucarinate moiety of verrucarin A in racemic and optically active form. We are presently utilizing

compounds synthesized by this latter route for the reconstruction of verrucarin A from verrucarol.

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REFERENCES.

1. Reviews: Tamm, Ch. Fortsch. Chem. Org. Naturst. **1974**, 31, 63. Bamberg, J.R.; Strong, F.M. in "Microbial Toxins"; Kadis, S.; Ed. ; Academic Press: New York, 1973, Vol. 3, pp 207-292. Doyle, T.W.; Bradner, W.T. in "Anticancer Agents Based on Natural Product Models"; Cassidy, G.M.; Duros, J.; Eds.; Academic Press: New York, 1980, Chapter 2.
2. a) Harri, C.; Loeffler, W.; Sigg, H.P.; Stahelin, Ch.; Tamm, Ch.; Wresinger, D. Helv. Chim. Acta, **1962**, 45, 839. b) Ueno, Y. Pure Appl. Chem. **1977**, 49, 1737.
3. For our recent synthesis of verrucarol see: a) Trost, B.M.; McDougal, P.G. J. Am. Chem. Soc. in press. b) McDougal, P.G.; Ph.D. Thesis, University of Wisconsin, Madison, 1982.
4. a) Still, W.C.; Ohmizu, H. J. Org. Chem. **1981**, 46, 5242. b) Roush, W.R.; Blizzard, T.A.; Basha, F.Z. Tetrahedron Lett. 1982, 23, 2331. c) Also see: ref 13a. d) Tomioka, k.; Sato, F.; Koga, K. Heterocycles, **1982**, 17, 311.
5. Gutzwiller, J.; Tamm, Ch. Helv. Chim. Acta, **1965**, 48, 157. Mohr, P.; Tori, M.; Grossen, P.; Herold, P.; Tamm, Ch. ibid., **1982**, 65, 1412.
6. a) Trost, B.M.; Hiroi, K. J. Am. Chem. Soc. **1975**, 97, 6911. b) Trost, B.M.; Ochiai, M.; McDougal, P.G. J. Am. Chem. Soc. **1978**, 100, 7103.
7. We chose to synthesize the diol via the photooxygenation of cyclopentadiene. See: Schenck, G.O.; Dunlap, D.E. Angew. Chem. **1956**, 63, 248.
8. The mixture arises at the cuprate step where a 2:1 ratio of S_N2 vs S_N2' attack was observed. When the free hydroxyl group was silylated even greater amounts of S_N2' were obtained.
9. Interestingly the lithium salt is an absolute necessity to achieve a clean reaction.
10. This presumably occurs by reduction of the acetate to the aluminum acetal, which falls apart to an aldehyde upon workup.
11. a) Terashima, S.; Yamada, S.; Nara, M. Tetrahedron Lett. **1977**, 1001. b) Miura, S.; Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Matsubara, S. Tetrahedron, **1976**, 32, 1893.
12. For a leading reference on the resolution of enantiomers via chromatography, see Pirkle, W.H.; Adams, P.E. J. Org. Chem. **1980**, 45, 4111.
13. For examples of the use of mandelate derivatives see: a) Trost, B.M.; in "Asymmetric Reactions and Processes in Chemistry", Eliel, E.L.; Otsuka, S.; Eds.; Advances in Chemistry Series 168; American Chemical Society: Washington, DC 1982, pp 3-20. b) Trost, B.M.; Curran, D.P. Tetrahedron Lett. **1981**, 22, 4929. c) Corey, E.J.; Hopkins, P.B.; Kim, S.; Yoo, S.E.; Nambiar, K.P.; Fack, J.R. J. Am. Chem. Soc. **1979**, 101, 7131.
14. Chavdarian, C.G.; Wood, S.L.; Clark, R.D.; Heathcock, C.H. Tetrahedron Lett. **1976**, 1769.
15. Esterification with DCC and DMAP (ref 16) proceeded with substantial (~30%) epimerization of the mandelate as demonstrated by a chiral shift study.
16. Hassner, A.; Alexanian, V. Tetrahedron Lett. **1978**, 4475.
17. 6.5 g of the mixture could be separated by HPLC (Waters Prep 500) in two injections onto two columns (one recycle).
18. Dale, J.A.; Mosher, H.S. J. Am. Chem. Soc. **1973**, 95, 512.
19. The undesired antipode **14b** was converted to the benzhydrylamide of verrucarinic acid and found to rotate light in the opposite sense than that from the natural isomer (ref. 5).
20. For oxidation of alkylboranes with peracid, see Johnson, J.R.; Van Campen, M.G. Jr. J. Am. Chem. Soc. **1938**, 60, 121. Normal basic H_2O_2 oxidation gave substantial amounts of lactone.
21. Kelly, T.R.; Dali, H.M.; Tsang, W.G. Tetrahedron Lett. **1977**, 3859.
22. Wissner, A.; Grudzinskas, C.V. J. Org. Chem. **1978**, 43, 3972.
23. Itoh, M.; Hagiwara, D.; Notani, J. Synthesis, **1975**, 456.
24. All new compounds have been fully characterized (IR, NMR, MS). Also, satisfactory elemental analysis was obtained by either high resolution MS or combustion analysis.

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