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SYNTHESIS OF TRICHOVERROL B

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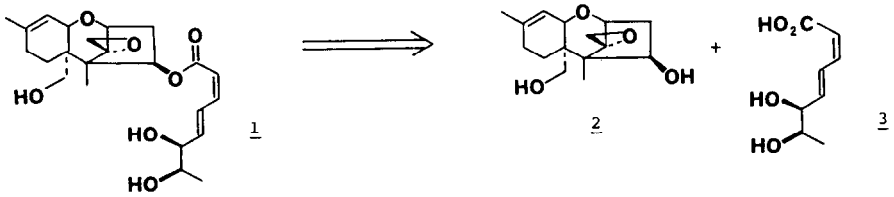
Summary: A highly diastereoselective synthesis of trichoverrol B (1) is described. Critical to the success of this work is the development of a method for esterification of (Z,E)-dienoic acid derivatives without olefin isomerization.

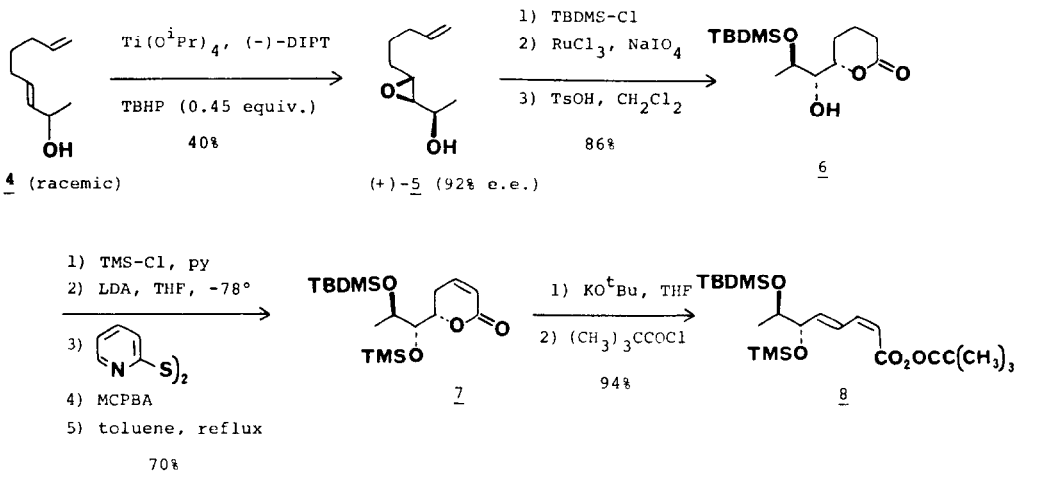
The trichoverroids, roridins, and verrucarins are important classes of trichothecenes produced by various Myrothecium species.[2] Whereas considerable effort has been expended on the synthesis of the verrucarins,[3] relatively few studies on the synthesis of the roridins or trichoverrins have appeared.[3b,4] Work in this area must address the problem of esterification of the requisite diene acid fragments to the trichothecene nucleus without olefin isomerization, a problem which has plagued all previous efforts in this area.[3] Accordingly, we report herein a synthesis of trichoverrol B (1) from verrucarol (2)[5] and a protected form of diene acid 3 (e.g., 8) which illustrates one solution to this problem.



1 2 3

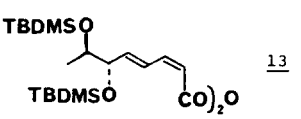
Diene acid derivative 8 was synthesized as outlined in Scheme I.[6] Subjection of racemic allylic alcohol 4 to the Sharpless kinetic resolution-enantioselective epoxidation procedure[7] (0.4 equiv. $Ti(O\text{-}i\text{-}Pr)_4$, 0.45 equiv. TBHP, 0.45 equiv. (-)-DIPT, CH_2Cl_2, -20°C, 24h) afforded the known[4a] epoxide (+)-5 ($[\alpha]_D^{23}$ + 8.6°, c=2, CH_2Cl_2; 92% e.e.) in 40% yield. Protection of 5 as a t-butyldimethylsilyl ether (TBDMS-Cl, imidazole, DMF) followed by oxidative cleavage of the vinyl group (cat. $RuCl_3$, $NaIO_4$ (4.5 equiv.), $CH_3CN\text{-}CCl_4\text{-}H_2O$)[7] afforded an epoxyacid [6a] which when treated with catalytic p-TsOH in CH_2Cl_2 smoothly cyclized to lactone 6[6a,b] ($[\alpha]_D^{23}$ - 5.0°, c=2.4, CH_2Cl_2) in 86% overall yield. Treatment of 6 with trimethylsilyl chloride in pyridine containing TMS_2NH proceeded smoothly to give the C.6-OTMS derivative[6a,b] in high yield.[8] This intermediate

Scheme I



was then oxidized to unsaturated lactone 7[6a,b] ($[\alpha]_D^{20}$ - 85.9°, c=1.62, CH_2Cl_2) via the intermediate α-pyridylsulfoxide[9] ((i) LDA, THF, -78°C; (ii) dipyridyl disulfide, -78°C; (iii) MCPBA, CH_2Cl_2, 0°C; (iv) toluene, reflux, 30 min; 70% yield from 6). Finally, exposure of 7 to 1.1 equiv. of KO^{t}Bu in THF at 0°C (30 min) unmasked the (Z,E)-diene carboxylate salt which was treated *in situ* with 1.1 equiv. of pivaloyl chloride (0°C, 30 min) to afford mixed anhydride 8[6a] ($[\alpha]_D^{20}$ - 16.3°, c=0.44, CH_2Cl_2) in 94% yield.

The selection of conditions for coupling of 8 to the trichothecene nucleus was based on preliminary studies involving diene acid 11 ($[\alpha]_D^{20}$ - 22.3°, c=1.28, CH_2Cl_2; mp 76-78°C; lit. mp[3b] 77-79°C; see Scheme II).[10] Attempts to couple 11 to C.15-monoprotected trichothecene 9[11] or other hindered alcohols in the presence of a variety of dehydrating agents (BOP-Cl, Et_3N, menthol;[12] N-methyl-2-chloropyridinium iodide, CsF, 9;[13] DCC, 4-pyrrolidinopyridine, isopropanol; TFAA, 9; mesitylenesulfonyl chloride, pyridine, 9) led to no ester formation. Noteworthy, however, was the isolation of symmetrical anhydride (13)[6a] in 70-80% yield from the Mukaiyama salt and BOP-Cl experiments. This result showed



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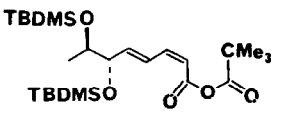

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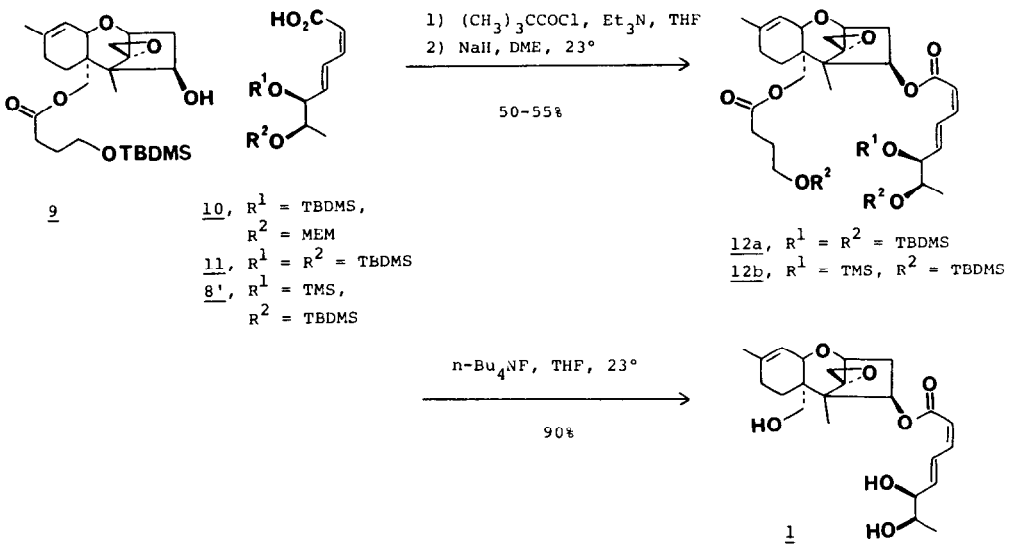
Scheme II



9

10, R^1 = TBDMS, R^2 = MEM
11, R^1 = R^2 = TBDMS
8', R^1 = TMS, R^2 = TBDMS

12a, R^1 = R^2 = TBDMS
12b, R^1 = TMS, R^2 = TBDMS

1

that 11 could be activated without olefin isomerization. Treatment of a CH_2Cl_2 solution of 9 and 13 with 4-DMAP[14] effected esterification, but a 2:1 mixture of the (Z,E)- and (E,E)-isomers of 12a was obtained (25% yield). More extensive olefin isomerization occurred with other mixed anhydrides (e.g., 14) using acylation catalysts to promote the esterification reaction.

We suspected that the olefin isomerization was caused by reversible Michael addition of the acylation catalyst (DMAP) to the active acylating agent and reasoned, therefore, that this problem could be avoided if such nucleophilic species were omitted.[15] Indeed, sequential treatment of 9 with NaH in DME (23°C, 30 min) followed by 1.5 equiv. of mixed anhydride 14[6a] (prepared from 11, Et_3N, and pivaloyl chloride in THF) for 1 h at 23°C afforded ester 12a[6a] in 50% yield. None of the (E,E)-isomer was detected (Scheme II). Acylation of 9 with mixed anhydride 8 (1.5-2 equiv.) under analogous conditions afforded isomerically pure 12b[6a] in 52-55% yield. Deprotection of 12a or 12b by using n-Bu_4NF (5 equiv.) in THF (23°C, 10 min) smoothly afforded trichoverrol B ($[\alpha]_D^{20}$ - 8.7°, c=0.25, $CHCl_3$) in 90% yield. The synthetic trichothecene so obtained was identical in all respects with an authentic sample provided by Professor B.B. Jarvis.[16]

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5. (a) Verrucarol was prepared from natural anguidine according to the literature method (ref. 3b); (b) Three syntheses of racemic verrucarol have been recorded: Schlessinger, R.H.; Nugent, R.A. J. Am. Chem. Soc. 1982, 104, 1116; Trost, B.M.; McDougal, P.G. Ibid. 1982, 104, 6110; (c) Roush, W.R.; D'Ambra, T.E. Ibid. 1983, 105, 1058.

6. (a) The spectroscopic properties (NMR, IR, mass spectrum) of all new compounds were fully consistent with the assigned structures. (b) A satisfactory combustion analysis (± 0.3% for C and H) was obtained for this compound.

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8. It was not possible to prepare the bis-TBDMS ether of 6 owing to steric congestion around C.6-OH. Interestingly, silylation of 6 with TBDMS-OTf/lutidine occurred on the lactone carbonyl leading to a bicyclic orthoester derivative.

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10. Acid 11 was prepared from 10[4a] in 40% overall yield as follows: (i) DOWEX-H^+, MeOH, Δ; (ii) TBDMS-Cl (excess), imidazole, DMF; (iii) LiOH, DME, H_2O.

11. Prepared by treatment of 2 with $HO_2C(CH_2)_3OTBDMS$, DCC, and 4-DMAP in CH_2Cl_2 (70% yield).

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14. Hölfe, G.; Steglich, W.; Vorbruggen, H. Angew. Chem., Int. Ed. Engl. 1978, 17, 569.

15. Isomerization observed in the Fraser-Reid/Jarvis synthesis of trichoverrin B is likely promoted by sodium imidazolide, the leaving group employed in their coupling sequence (reference 3b).

16. The isomerically pure natural product had $[\alpha]_D^{20}$ - 9.3°, C=0.27, $CHCl_3$. The literature value for trichoverrol B, however, is $[\alpha]_D$ - 3.3° (ref. 2a).

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