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METHODOLOGY FOR THE SYNTHESIS OF THE ACYCLIC PORTIONS OF VERRUCARINS A AND J

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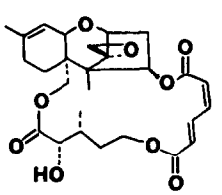
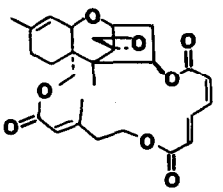
Summary: Syntheses of the acyclic chains of verrucarin A and J are described; the revised stereochemistry of verrucarin J is confirmed.

The macrocyclic epoxytrichothecene di- and trilactones (the roridins and verrucarins, respectively) possess a range of remarkable biological properties including antitumor activity.[1] Two well-known members of the trilactone group are verrucarin A (1)[2] and verrucarin J (2).[3]



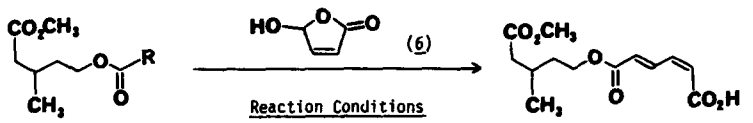
Verrucarin A (1)



Verrucarin J (2)

Whereas considerable effort has been devoted towards the synthesis of the trichothecene nucleus, verrucarol,[4] the macrocyclic portions of the roridins and verrucarins have received relatively little attention.[5,6] We describe herein methodology suitable for the synthesis of the acyclic portions of 1 and 2.

A major chemical problem associated with the synthesis of the verrucarin side chains concerns the unambiguous elaboration of the (Z,E)-muconic acid unit. Two solutions to this problem appeared feasible. Either a differentiated muconic acid derivative could be synthesized and then be coupled to the appropriate left-hand portion (e.g., 17 for verrucarin A), or, alternatively, the coupling step could be incorporated into the differentiation sequence. The latter strategy was examined in a preliminary model study involving phosphorane 3 and phosphonate 4, which were prepared by standard procedures from bromoacetate 5.[7,8a,b] Treatment of 3[8a]



3 R = $CHP(C_6H_5)_3$
4 R = $CH_2PO(OMe)_2$
5 R = CH_2Br

(6)

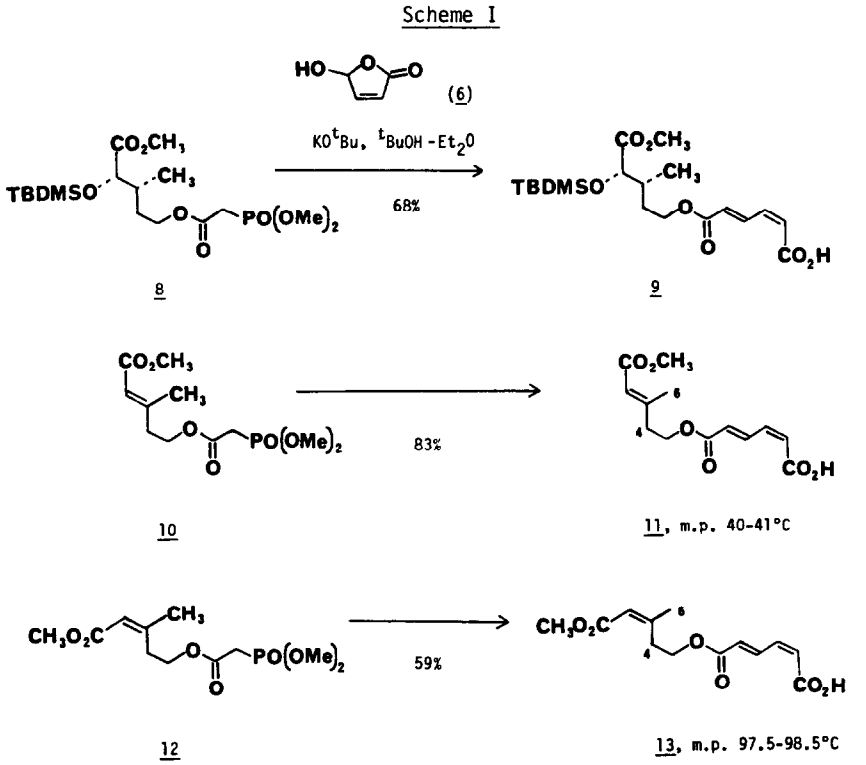
Reaction Conditions
CH_2Cl_2, 23°C, 30%
KO^tBu, ^tBuOH-Et_2O, 23°C, 73%

7

with malealdehydic acid, 6,[9] in CH_2Cl_2 afforded acid 7[8a] in only 30% yield. The yield of 7 was substantially improved when phosphonate 4[8a] was employed in the coupling procedure.[10] Thus, treatment of 4 with 1.05 equiv. of 6 and 2.05 equiv. of KO^tBu in a Et_2O-^tBuOH (1 : 1) solvent mixture (23°C, 1 h) afforded 7 in 73% yield along with 7% of the (Z,Z)-diene isomer.

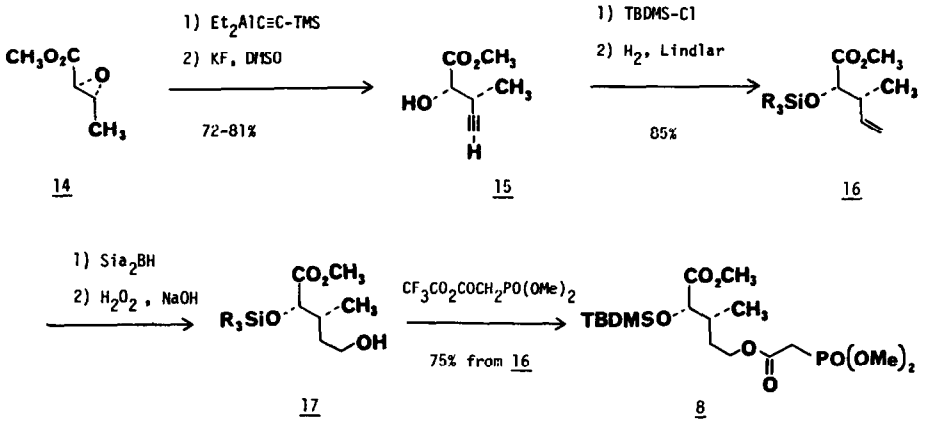
We have applied the phosphonate procedure to the synthesis of the monomethyl esters of the verrucarin A (9[8a,b]), verrucarin J (11[8a,b]), and "iso" verrucarin J (13[8a,b]) side chains (Scheme I). Phosphonates 10[8a,b] and 12[8a] were prepared from the corresponding hydroxyesters[11] by bromoacetylation ($BrCH_2COBr$, pyridine, CH_2Cl_2) followed by treatment with trimethylphosphite

Scheme I

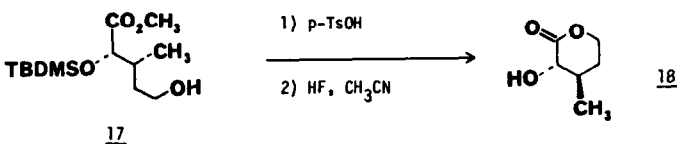


in toluene (100°C; 70-92% overall yield). Phosphonate 8 was prepared as outlined in Scheme II. Thus, treatment of trans epoxyester 14 with 2.05 equiv. of $Et_2AlC{\equiv}CSiMe_3$ (prepared in the usual manner from $LiC{\equiv}CSiMe_3$ and Et_2AlCl)[12] in toluene at 5-10°C for 2 h followed by removal of the trimethylsilyl protecting group with KF in wet DMSO afforded acetylene 15[8a,b] in 72-81% yield. Protection of the free hydroxyl group as a t-butyldimethylsilyl ether (TBDMS-Cl, imidazole, DMF) and partial reduction of the triple bond (Lindlar catalyst, H_2, CH_2Cl_2) afforded 16[8a,b] in high yield (85%). Attempts to simplify the preparation of 16 by using sequences involving reactions of 14 with diethylethynylaluminum[13] or diethylvinylaluminum have been unsuccessful. Hydroboration of 16 with Sia_2BH in THF (H_2O_2-NaOH workup) afforded 17 which was immediately

Scheme II



esterified with 1.2 equiv. of the mixed anhydride prepared from trifluoroacetic anhydride and dimethylphosphonoacetic acid[14] (CH_2Cl_2, pyridine) to give 8[8a,b] in 75% overall yield. The stereochemistry of these intermediates was confirmed by lactonization (p-TsOH, CH_2Cl_2) and deprotection (HF, CH_3CN, H_2O) of 17 to give racemic verrucarinolactone 18 (m.p. 71-72°C; lit.[15] m.p. 71-72.5°C) in 41% overall yield from 16.



Each of the olefination reactions reported in Scheme I afforded a 9 : 1 mixture of (Z,E)- and (Z,Z)-muconic acids. The desired (Z,E)-isomers 9, 11, and 13 were readily purified by silica gel chromatography (yields of pure (Z,E)-diene are given in the scheme). No epimerization of the stereocenter at C.2 of 9 was detected and no isomerization of the C.2-double bonds of 11 or 13 was observed.

The results summarized in Scheme I permit us to confirm the stereochemistry of the verrucarin J side-chain. Tamm originally assigned a $\Delta^{2,3}$ cis configuration (as in 13) to the natural product on the basis of chemical evidence,[3] but recently reversed this assignment.[5b] Indeed, the NMR data for the side-chain segment of the natural product are more consistent with the stereochemistry depicted for 11 than for 13 (selected ^1H NMR data (δ): for verrucarin J,[3] 2.50 (t, J = 6 Hz, C.4'-H), 2.28 (d, J = 1.5 Hz, C.6'-H); for 11, 2.50 (t, J = 6.3 Hz, C.4'-H), 2.19 (d, J = 1.7 Hz, C.6'-H); for 13, 2.99 (t, J = 6.8 Hz, C.4'-H), 1.96 (d, J = 1.5 Hz, C.6'-H). The olefin stereochemistry in the roridin series has also been reversed.[16]

Future reports from this laboratory will describe a synthesis of the optically active verrucarin A side chain and partial syntheses of verrucarins A and J.

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7. Bromoacetate 5 was synthesized starting from methyl 3-methylpent-4-enoate by hydroboration (BH_3-THF; H_2O_2-NaOH workup) and esterification with $BrCH_2COBr$ and pyridine in CH_2Cl_2.

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

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