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SYNTHESIS OF 13-NORTRICHOTHEC-9(10)-ENE.
A MODEL REACTION TOWARD THE TOTAL SYNTHESIS OF TRICHODERMIN

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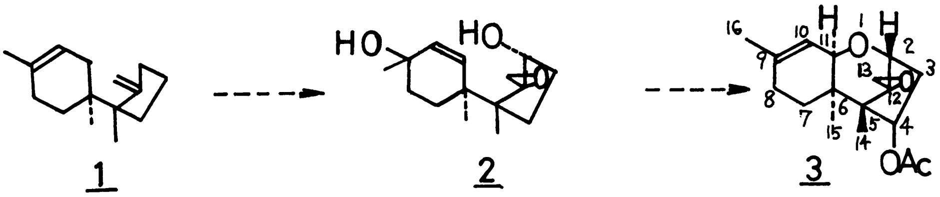
The synthesis of the title compound 20 modelled on the proposed biogenetic scheme is described. The key intermediate 11 has been synthesised by photocycloaddition followed by acid cleavage.

The biosynthesis of trichodermin 3 is most commonly considered to proceed *via* an intermediate 2, which can be subsequently cyclised by an intramolecular S_N2' mechanism.[1]



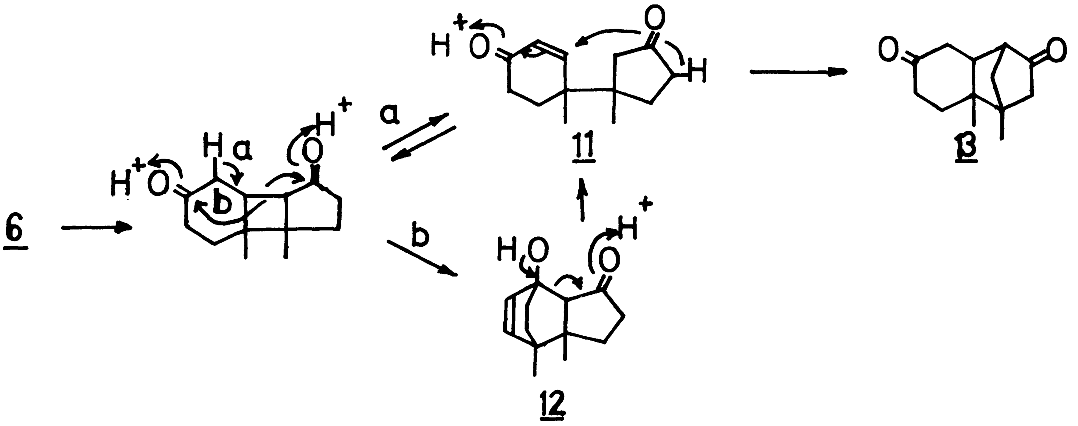
1 2 3

Although a number of elegant syntheses of trichodermin have appeared in recent years,[2] in this paper, we wish to report a construction of trichothecane skeleton modelled on this biogenetic scheme. Very recently Yamakawa et al.[3] reported the photocycloaddition reaction between 3-methylcyclohexenone and 2-hydroxy-3-methylcyclopentenone for the synthesis of trichodiene 1. As the key reaction for construction of the intermediate 11 we chose a photocycloaddition reaction.

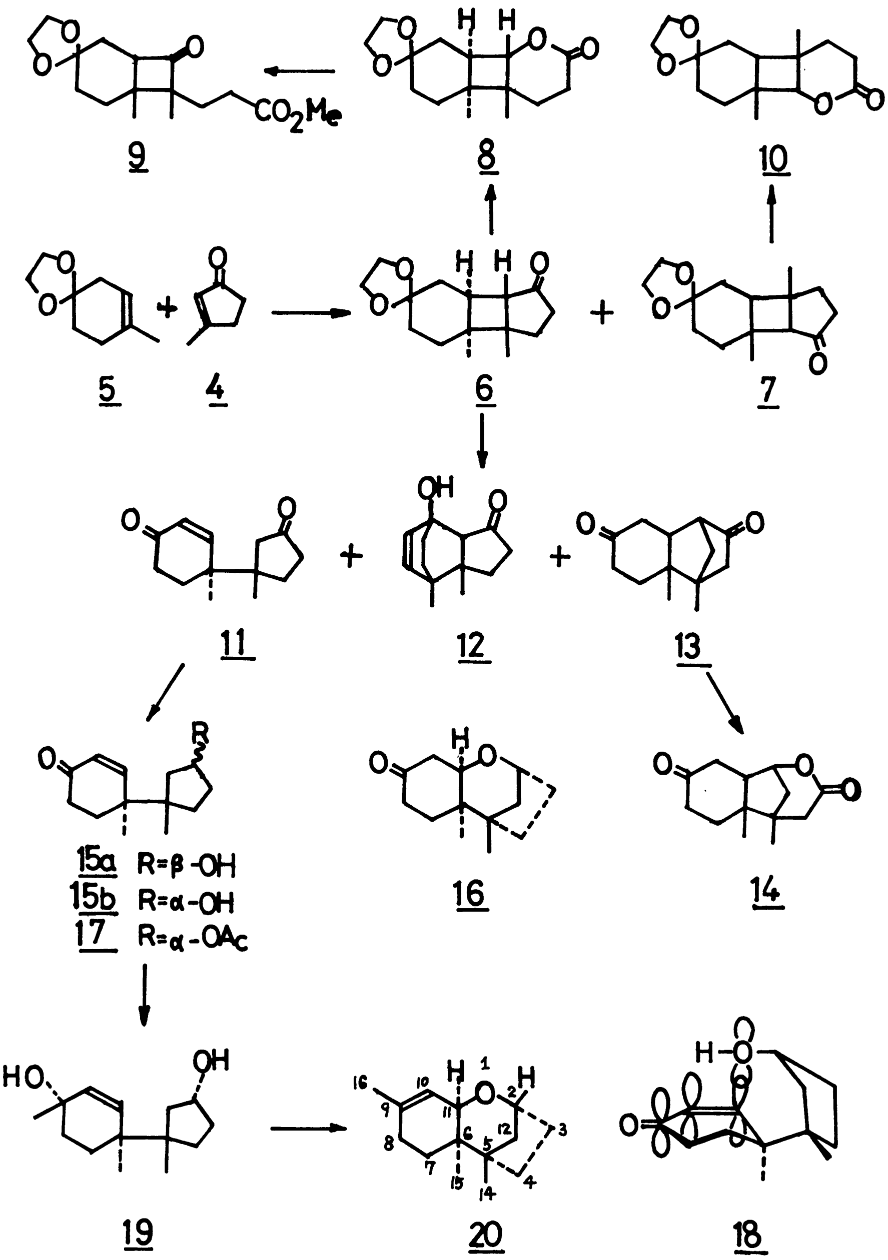
Irradiation of ether solution[4] of 3-methylcyclopent-2-en-1-one 4 containing a sixteenfold excess of 4-methylcyclohex-3-en-1-one ethylene ketal 5 with a 100w high-pressure mercury lamp using a Pyrex filter at -23° for 5 hours gave the crystalline adduct 6 [16% based on 5, m.p. 161.5-162°, m/e 250, δ 1.02 (3H, s), 1.07 (3H, s) and 2.74 (d, J=9.2Hz, H_2)], the crystalline adduct 7 [m.p. 54.5-55.5°, m/e 250, δ 0.99 (3H, s), 1.30 (3H, s) and 2.00 (br. s, H_6)] and a complex mixture of at least four products. The Baeyer-Villiger oxidation of 6 gave the δ-lactone 8.

The lactone 8 was transformed, employing the following sequence of reagents: 1) OH^-, 2) CH_2N_2 and 3) Jones' reagent, into the cyclobutanone 9 (ν_{max} 1775 and 1745 cm^{-1}). The stereochemistry of the ring junctures of 6 was tentatively assigned as a cis-anti-cis configuration from the analogy of similar photocycloaddition reactions and this was confirmed by a x-ray analysis.[5] The Baeyer-Villiger oxidation of 7 gave the δ-lactone 10.

Treatment of 6 with 50% aqueous acetic acid (2.5 hours at 80°) afforded the α,β-unsaturated ketone 11 [66%, m.p. 134°, ν_{max} 1745 and 1680 cm^{-1}, λ_{max}^{EtOH} 228nm (ε 11,600), δ 1.10 (3H, s), 1.21 (3H, s), 6.00 (1H, d, J=10.4Hz) and 6.84 (1H, dd, J=1.5 and 10.4Hz)], the hydroxy ketone 12 [12%, m.p. 155-157° (in a sealed capillary tube), ν_{max} 3490 and 1730 cm^{-1}, δ 1.13 (3H, s), 1.23 (3H, s), 1.90 (1H, br. s), 4.58 (1H, s, OH), 5.84 (1H, d, J=9Hz) and 6.00 (1H, d, J=9Hz)] and the diketone 13 [5%, m.p. 111.5-112.5°, ν_{max} 1750 and 1725 cm^{-1}, δ 1.16 (3H, s) and 1.09 (3H, s)]. Treatment of 12 with 50% aqueous acetic acid gave a 1:1 mixture of 11 and 12. The Baeyer-Villiger oxidation of 13 gave the keto δ-lactone 14 [m.p. 160.5-161.5°, ν_{max} 1730 cm^{-1}, δ 0.98 (3H, s), 1.06 (3H, s) and 4.57 (1H, quint, J=2.2 and 4Hz)]. When 6 was treated with 2N hydrochloric acid, the diketone 13 was obtained nearly quantitative yield. The genesis of these products may be accounted for by the following scheme.



Reduction of 11 with sodium borohydride followed by oxidation with manganese dioxide gave a mixture of epimeric hydroxy enones 15a and 15b [70%, oil, ν_{max} 3400 1685 and 1620 cm^{-1}, λ_{max}^{EtOH} 231 nm (ε 9600), δ 1.12 (3H, s), 1.16 (3H, s), 2.92 (1H, s, OH), 4.11 (1H, quint), 5.74 (1H, d, J=10Hz) and 6.62 (1H, dd, J=1.4 and 10Hz)]. Treatment of the mixture 15 with Triton B gave the saturated ketone 16 [m.p. 65.5-67°, ν_{max} 1720 cm^{-1}, m/e 208, 109 and 81 (base peak), δ 1.04 (3H, s), 1.07 (3H, s),


CO2Me
9
H H
8
10
5
4
H H
6
7
OH
11
12
13
R
15a R=β-OH
15b R=α-OH
17 R=α-OAc
H
16
14
HO
OH
19
16 10 H 1 H
9 11 2
8 6 5 12 3
7 15 14 4
20
H-O
18

3.77 (quint, W1/2 9.2Hz, H_{11}) and 4.25 (m, W1/2 5.8Hz, H_2)] in 10% yield (74% of the alcohol was recovered unchanged). Analysis of the NMR spectrum revealed the coupling constants $J_{10\beta,11}$ and $J_{10\alpha,11}$ to be 4.4 and 1.4 Hz, respectively, suggesting the cis A/B ring juncture. The poor yield of 16 probably due to the unfavourable orientation of the hydroxy group of the major alcohol 15a for the addition. Inspection of the model showed that only the α alcohol can add to the α,β-unsaturated ketone group. Then the major alcohol 15a was converted into the α alcohol 15b. Treatment of the mesylate of 15a with tetraethylammonium acetate gave the keto acetate 17 [δ 1.04 (C-Me), 1.15 (C-Me), 1.94 (OAc), 5.08 (oct, W1/2 12.6Hz), 5.84 (d, J=10.7Hz) and 6.78 (dd, J=1.8 and 10.7Hz)], which upon treatment with potassium carbonate in methanol gave the cyclic ether 16 in 76% yield, uncontaminated by the C-11 epimer. The highly stereospecific cyclisation results as a consequence of favourable orbital overlap during the addition (the intermediate 18).

The keto acetate 17 was treated with methyl magnesium iodide to give the diol (72%, m.p. 75-76°). Treatment of the diol 19 with 2N hydrochloric acid gave the title compound 20 [76%, oil, m/e 206, 107 and 81 (base peak), ν_{max} 1680, 1460, 1440 and 1050 cm^{-1}, δ 0.72 (15-Me), 0.96 (14-Me), 1.66 (d, J=1Hz, 16-Me), 3.35 (br. d, J=5.1Hz, H_{11}), 4.10 (m, H_2) and 5.19 (dq, J=1 and 5.1Hz, H_{10})[6]]. The chemical shifts and splitting patterns for 15-Me, 16-Me, H_{10} and H_{11} were very close to those of trichodermin suggesting to have similar steric environment. Total synthesis of trichodermin based on this synthetic strategy is in progress.

References and Footenotes

1. Y. Machida, S. Nozoe, Tetrahedron, 28, 5113 (1972); B. A. Achilladelis, P. M. Adams and J. R. Hanson, J.C.S.Perkin I, 1972, 1425.
2. E. W. Colvin, S. Malchenko, R. A. Raphael, J. S. Roberts, J.C.S.Perkin I, 1973, 1989; D. J. Goldsmith, A. J. Lewis and W. C. Still, Jr., Tetrahedron Letters, 4807 (1973); Y. Fujimoto, S. Yokura, T. Nakamura and K. Tatsuno, Abstracts of the 94th Annual Meeting of the Pharmaceutical Society of Japan, Vol. II, pp. 161 (1974).
3. K. Yamakawa, J. Kurita and R. Sakaguchi, Tetrahedron Letters, 3877 (1973).
4. When the irradiation was carried out in n-pentane, the adducts 6 and 7 were obtained in the ratio of 1:1. And when 5 was irradiated with fivefold excess of 4, the dimer of 4 together with 6 and 7 was obtained.
5. To be published elesewhere.
6. These assignments were confirmed by NMDR experiments. The H_{11} proton resonance is upfield, presumably as a result of the bond anisotropic effect of C_3-C_4.

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