

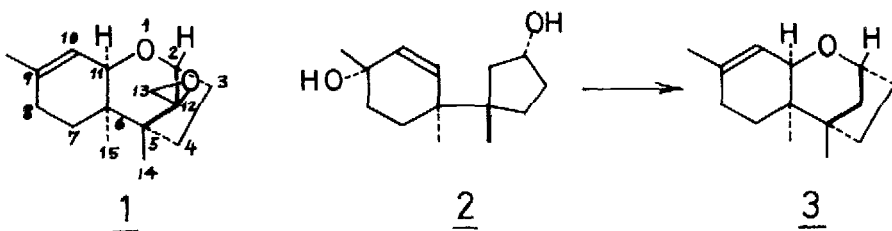
A SYNTHESIS OF 12,13-EPOXYTRICHOHEC-9-ENE

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12,13-Epoxytrichothec-9-ene 1 is a metabolite isolated from *Trichothecium roseum* by Nozoe et al ¹ and its structure was synthetically confirmed by Tatsuno et al ² In a previous paper,³ we reported that the model compound 2 was stereoselectively cyclised to 3 by the similar way as predicted for the biosynthesis of trichodermin ⁴

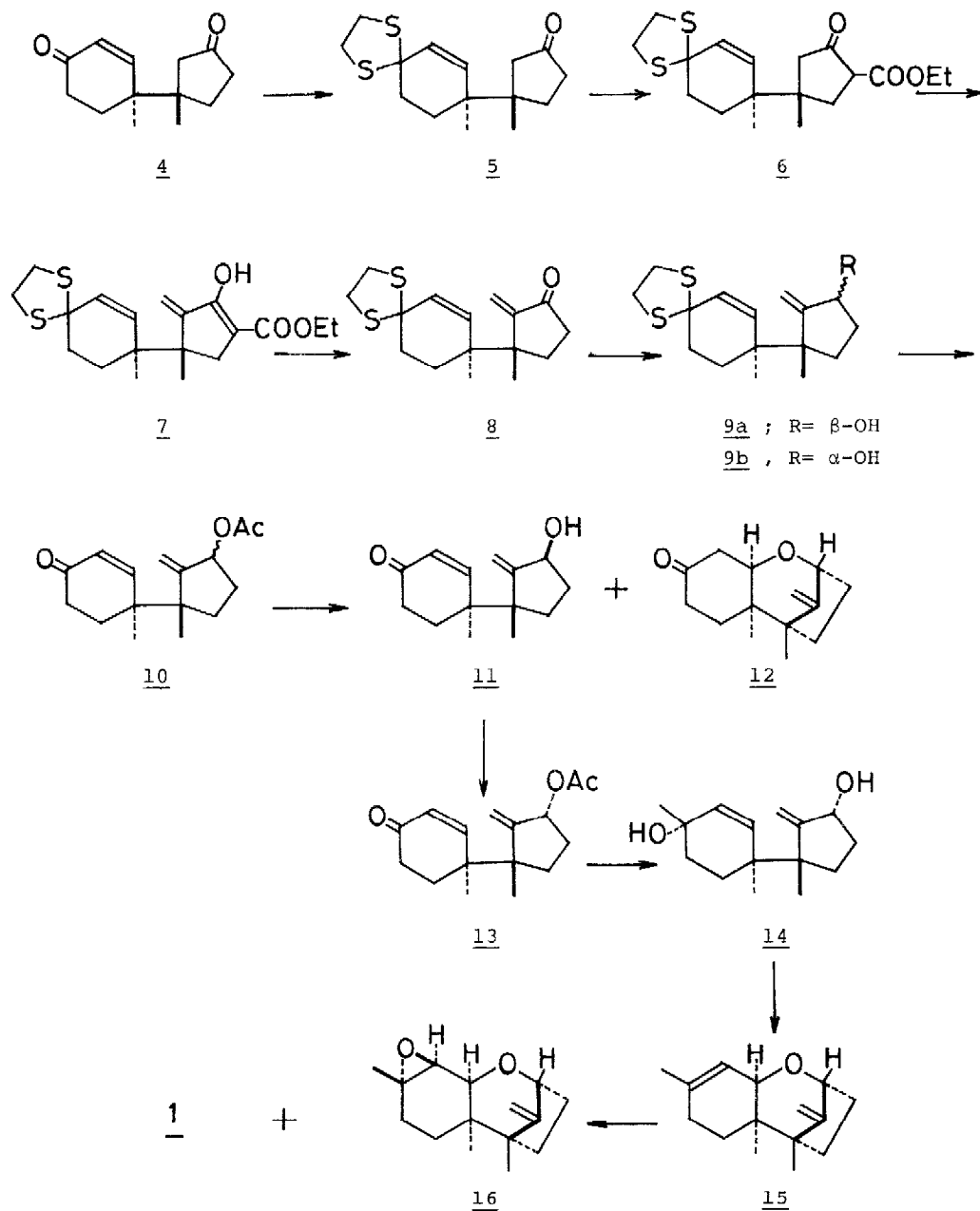


We now wish to report the first biomimetic synthesis of 1 from the enedione 4.³

Selective thioketalization of 4 with 1,2-ethanedithiol and BF_3 ether in methanol⁵ gave the monothioketal 5, mp 104-105°, ν_{max} (CHCl_3) 1740 cm^{-1} , in 72% yield. Various attempts to introduce a methyl group at C-12⁶ of 5 were unsuccessful. We then carried out the direct methylenation at C-12 after the method of Miller and Smith⁷. Thus the carboethoxy ketone 6, obtained by the usual method (Et_2CO_3 , NaH, 87%), was treated with formaldehyde, Et_2NH and $\text{Et}_2\text{NH HCl}$ in dioxane at 50° to give the olefin 7, mp 110-111°, ν_{max} (CCl_4) 3200, 1660, 1610 and 905 cm^{-1} , $\lambda_{\text{max}}^{\text{EtOH}}$ 289 nm and $\lambda_{\text{max}}^{\text{EtOH-OH}^-}$ 328 nm, δ (CCl_4) 1.10, 1.18 (6H, two s), 5.17 (1H, s), 5.65 (1H, s), 5.60 (1H, dd, $J=1.5^8$ and 10.0 Hz) and 5.82 (1H, d, $J=10.0$ Hz), in 37% yield. Decarboethoxylation of 7 with boric acid in xylene under reflux gave the dienone 8

as an oil, ν_{\max} (CCl_4) 1730, 1620 and 950 cm^{-1} , δ (CCl_4) 1.00, 1.20 (6H, two s), 5.24 (1H, d, $J=1.5\text{ Hz}$), 5.54 (1H, dd, $J=1.5$ and 9.2 Hz), 5.80 (1H, d, $J=9.2\text{ Hz}$) and 6.04 (1H, d, $J=1.5\text{ Hz}$). Reduction of 8 with NaBH_4 in methanol at -78° gave a mixture of epimeric alcohols 9a and 9b in the ratio of 5 : 1 in 76% yield from 7.⁹ The mixture was acetylated and desulfurization of the acetate with $\text{HgCl}_2\text{-CdCO}_3$ gave the dienone acetate 10, which on hydrolysis with alkali gave the hydroxy dienone 11 as an oil, ν_{\max} (CCl_4) 3400, 1685 and 905 cm^{-1} , δ (CCl_4) 1.16 (6H, s), 4.16 (1H, m, $W^{1/2}$ 18 Hz), 4.96 (1H, d, $J=2.6\text{ Hz}$), 5.16 (1H, d, $J=2.6\text{ Hz}$), 5.76 (1H, d, $J=10.5\text{ Hz}$) and 6.79 (1H, dd, $J=1.8$ and 10.5 Hz), and the enone 12, mp $95\text{-}96.5^\circ$, ν_{\max} (CHCl_3) 1720 and 900 cm^{-1} , δ (CDCl_3) 1.05, 1.11 (6H, two s), 3.95 (1H, quint, $W^{1/2}$ 8.8 Hz, H_{11}), 4.28 (1H, broad d, $J=4.2\text{ Hz}$, H_2), 4.59 (1H, s) and 4.93 (1H, s), in 60 and 12% yields, respectively. Only the α -alcohol can add to the α,β -unsaturated ketone under acidic or basic condition as pointed out in the model reaction.³ Hence the major alcohol 9a, mp $116.5\text{-}118^\circ$, ν_{\max} (CHCl_3) 3440, 1650 and 900 cm^{-1} , δ (CDCl_3) 0.98, 1.10 (6H, two s), 4.29 (1H, m, $W^{1/2}$ 22 Hz), 4.99 (1H, d, $J=2.7\text{ Hz}$), 5.15 (1H, d, $J=2.7\text{ Hz}$), 5.58 (1H, dd, $J=1.4$ and 10.0 Hz) and 5.78 (1H, d, $J=10.0\text{ Hz}$) was assigned as β -quasi-equatorial conformation. MDR experiments of 12 showed that the coupling constants $J_{10\alpha,11}$, $J_{10\beta,11}$, and $J_{7\alpha,11}$ (W -form coupling) were 4.2, 2.3 and 2.3 Hzs, respectively, suggesting the cis A/B ring juncture. The hydroxy dienone 11 was transformed into the 2α -acetate 13 in 61% yield, as previously reported,³ via the following sequence of reagents (a) mesyl chloride in pyridine and (b) tetraethylammonium acetate in refluxing acetone. Treatment of 13 with methyl magnesium iodide followed by alkaline hydrolysis gave the diol 14, which without further purification was treated with acid gave the diene 15 as a single product in 40% yield from 13. The synthetic diene 15 exhibited ir and nmr spectra identical with those of an authentic sample.² Oxidation of 15 with *m*-chloroperbenzoic acid and Na_2HPO_4 gave 12,13-epoxytrichothec-9-ene 1, mp $54\text{-}57^\circ$ (from aq MeOH),¹⁰ identical with the natural product (ir, nmr), and the isomeric epoxide 16 as an amorphous product, ν_{\max} (CHCl_3) 1050 and 890 cm^{-1} , δ (CCl_4) 0.68 (3H, s), 0.91 (3H, s), 1.24 (3H, s), 2.74 (1H, d, $J=5.2\text{ Hz}$), 3.50 (1H, dd, $J=2.3$ and 5.2 Hz), 4.22 (1H, broad d, $J=3.8\text{ Hz}$), 4.46 (1H, d, $J=1.5\text{ Hz}$) and 4.89 (1H, d, $J=1.5\text{ Hz}$) in the ratio of 1 : 1. The easy and stereoselective formation of trichothecane skeleton by this method would demonstrate the validity of the proposed biosynthetic hypothesis.

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References and Footnotes

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- 8 This proton also couples with $H_{7\alpha}$
- 9 Other reducing agents, such as $NaAl(OCH_2CH_2OCH_3)_2H_2$ or $LiAl(OCH_3)_3H$ gave 9a and a saturated alcohol. Reduction with AlH_3 gave 9a and 9b in the ratio of 2 1
10. The natural product was reported as an oil