

Total Synthesis of the Macrolide Antibiotic (\pm)-Pyrenophorin

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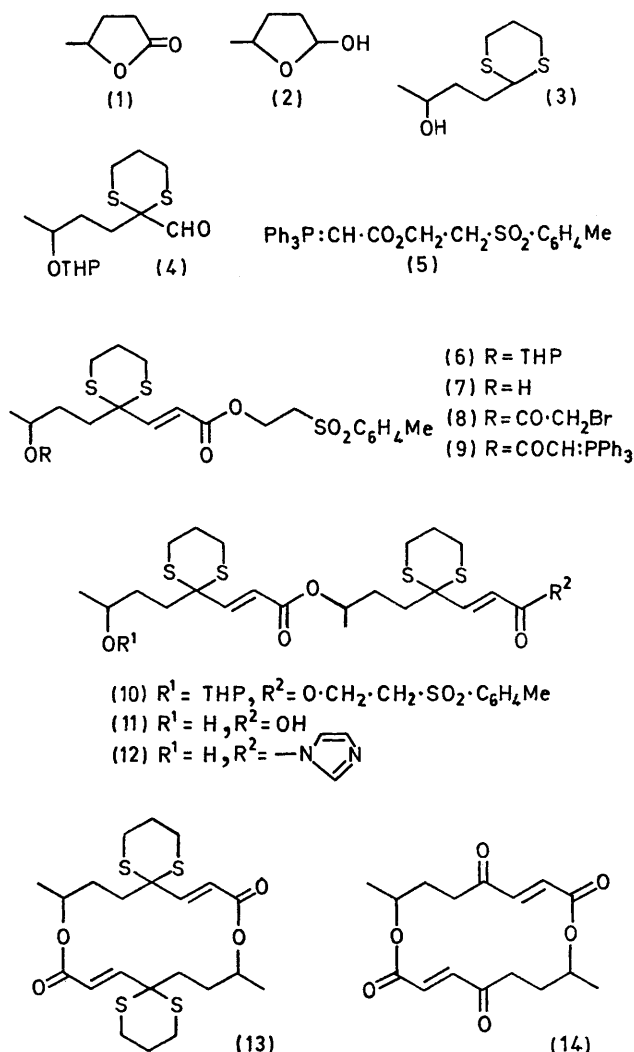
Summary The total synthesis of the macrolide antibiotic pyrenophorin (**14**) is described.

THE construction of large ring compounds has always posed a problem, and this challenge, frequently exacerbated by complex stereochemistry, has engendered a continuous interest in the chemistry and synthesis¹ of the macrolide group of antibiotics. We now record the total synthesis, in racemic form, of pyrenophorin² (**14**), a sixteen-membered bis-lactone antifungal and cytostatic metabolite of the

plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum*.

Reduction (NaAlH_4)³ of γ -valerolactone (**1**) afforded the lactol (**2**), which gave the substituted dithian (**3**) on treatment with propane-1,3-dithiol and $\text{BF}_3\text{-Et}_2\text{O}$. Protection of the alcohol function of (**3**) as its tetrahydropyranyl ether followed by sequential exposure to *n*-butyl-lithium and ethyl formate⁴ yielded the aldehyde (**4**). This aldehyde (**4**), on reaction with the phosphonium ylide (**5**) derived from the bromoacetate of toluene-*p*-sulphonylethanol,⁵ gave the olefin (**6**) as sole product; the *trans*-stereochemistry

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THP = tetrahydropyranyl

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of the olefinic linkage was defined by the n.m.r. spectrum (olefinic coupling constant of 16 Hz). Removal of the tetrahydropyranyl ether group with mineral acid liberated the alcohol (7), whose bromoacetate (8), on treatment with PPh_3 and deprotonation of the resulting phosphonium salt with aqueous NaOH , was transformed into the ylide (9). Condensation of (9) with the aldehyde (4) in hot benzene gave the all-*trans* bis-olefin (10) as the only product. After cleavage of the tetrahydropyranyl ether with acid, the toluene-*p*-sulphonylethyl protecting group was easily and quantitatively removed at ambient temperature with 1,5-diazabicyclo[4,3,0]non-5-ene in benzene to yield the hydroxy-acid (11) as a glass. This mild method of selectively removing the toluene-*p*-sulphonylethyl protecting group was an essential feature, as use of stronger bases⁵ resulted in extensive cleavage of the central ester linkage (other organic bases proved ineffective). This acid was converted into the corresponding imidazolid (12) by the action of bisimidazol-1-yl ketone according to the method of Staab.⁶ Dilution with benzene and treatment with a catalytic amount of 1,5-diazabicyclo[4,3,0]non-5-ene effected a smooth cyclisation to yield a 1:1 mixture (n.m.r.) of the diastereoisomeric bis-lactone (13) in a total yield of 60%. Removal of the thioacetal protecting groups by reaction with *N*-chlorosuccinimide⁷ in the presence of AgNO_3 gave two compounds, again as a 1:1 mixture, the less polar of which, m.p. 124–125°, was identical in all respects (n.m.r., i.r., mass spectrum, t.l.c. and g.l.c. behaviour under a variety of conditions) save rotation with the naturally occurring (–)-pyrenophorin (14). The more polar compound, m.p. 118–119°, although chromatographically different, showed a mass spectrum indistinguishable from that of the less polar compound; since other spectral properties were virtually identical, it is assigned the structure of the *meso*-diastereoisomer.

Repetition of the synthetic route using resolved γ -valerolactone is under active investigation.

Analytical and spectroscopic data for all compounds were in full accordance with the structures assigned.

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