Total Synthesis of the Macrolide Antibiotic (±)-Pyrenophorin

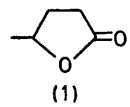
By E. W. COLVIN,* T. A. PURCELL, and R. A. RAPHAEL*†
(*Department of Chemistry, University of Glasgow, Glasgow* G12 8QQ)

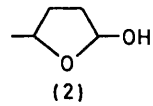
Summary The total synthesis of the macrolide antibiotic pyrenophorin (**14**) is described.

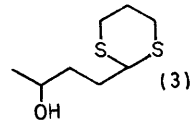
THE construction of large ring compounds has always posed a problem, and this challenge, frequently exacerbated by complex stereochemistry, has engendered a continuous interest in the chemistry and synthesis[1] of the macrolide group of antibiotics. We now record the total synthesis, in racemic form, of pyrenophorin[2] (**14**), a sixteen-membered bis-lactone antifungal and cytostatic metabolite of the plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum*.

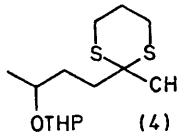
Reduction ($NaAlH_4$[3]) of γ-valerolactone (**1**) afforded the lactol (**2**), which gave the substituted dithian (**3**) on treatment with propane-1,3-dithiol and BF_3–Et_2O. Protection of the alcohol function of (**3**) as its tetrahydropyranyl ether followed by sequential exposure to n-butyl-lithium and ethyl formate[4] 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

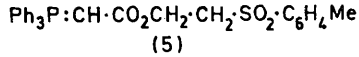
† Present address: University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

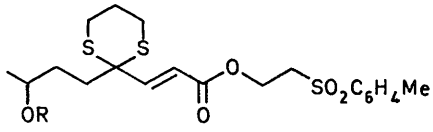

(1)


(2)

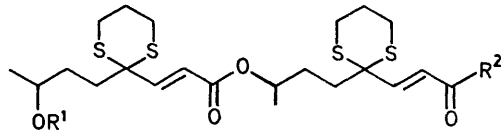

(3)


(4)

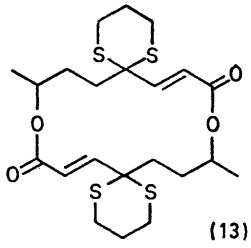

(5)

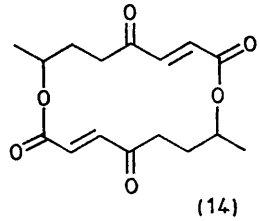


(6) R = THP
(7) R = H
(8) R = CO·CH$_2$Br
(9) R = COCH:PPh$_3$



(10) R^1 = THP, R^2 = O·CH$_2$·CH$_2$·SO$_2$·C$_6$H$_4$Me
(11) R^1 = H, R^2 = OH
(12) R^1 = H, R^2 = —N⟨imidazole⟩


(13)


(14)

THP = tetrahydropyranyl

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 bases[5] resulted in extensive cleavage of the central ester linkage (other organic bases proved ineffective). This acid was converted into the corresponding imidazolide (**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*-chlorosuccinimide[7] 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.

We thank Professor Shigeo Nozoe for a sample of (—)-pyrenophorin and the S.R.C. for a studentship (to T.A.P.).

(*Received, 7th August*, 1972; *Com.* 1379.)

[1] D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, 1968, **24**, 2443.
[2] S. Nozoe, K. Hitai, K. Tsuda, K. Ishibashi, M. Shirasaka, and J. F. Grove, *Tetrahedron Letters*, 1965, 4675; J. F. Grove, *J. Chem. Soc.* (*C*), 1971, 2261.
[3] L. I. Zakharkin, V. V. Gavrilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Letters*, 1963, 2087.
[4] E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1965, **4**, 1077.
[5] A. W. Miller and C. J. M. Stirling, *J. Chem. Soc.* (*C*), 1968, 2612.
[6] H. A. Staab and A. Mannschreck, *Chem. Ber.*, 1962, **95**, 1284.
[7] E. J. Corey and D. Crouse, *J. Org. Chem.*, 1968, **33**, 298.