

## Cytochalasan Synthesis: An Alternative Approach to Cytochalasin H

Robert Sauter, Eric J. Thomas,\* and John P. Watts

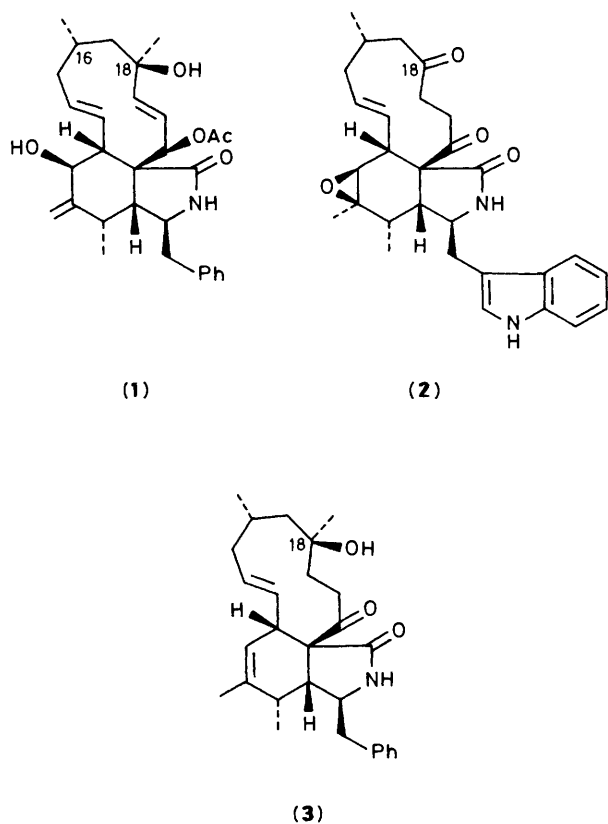
*The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K.*

The cytochalasin H precursor (**3**) has been obtained regio- and stereo-selectively from the diketone (**2**) using methylmagnesium chloride in tetrahydrofuran.

The cytochalasans comprise an important group of biologically active fungal metabolites.<sup>1</sup> Recently a synthesis of cytochalasin H (**1**) was described which involved closure of the 11-membered ring *via* an intramolecular Diels–Alder reaction,<sup>2</sup> the chiral centres at C(16) and C(18) being introduced prior to the cyclization step, and in the preceding communication a synthesis of cytochalasin G (**2**) is reported.<sup>3</sup> The *X*-ray crystal structure of cytochalasin G shows that one face of the C(18) ketone carbonyl is screened by the remainder of the 11-membered ring,<sup>4</sup> and suggests that nucleophilic attack should be highly stereoselective giving, with a methyl Grignard reagent for example, the cytochalasin H stereochemistry

at C(18). We now describe a synthesis of the cytochalasin H precursor (**3**) based on this idea.

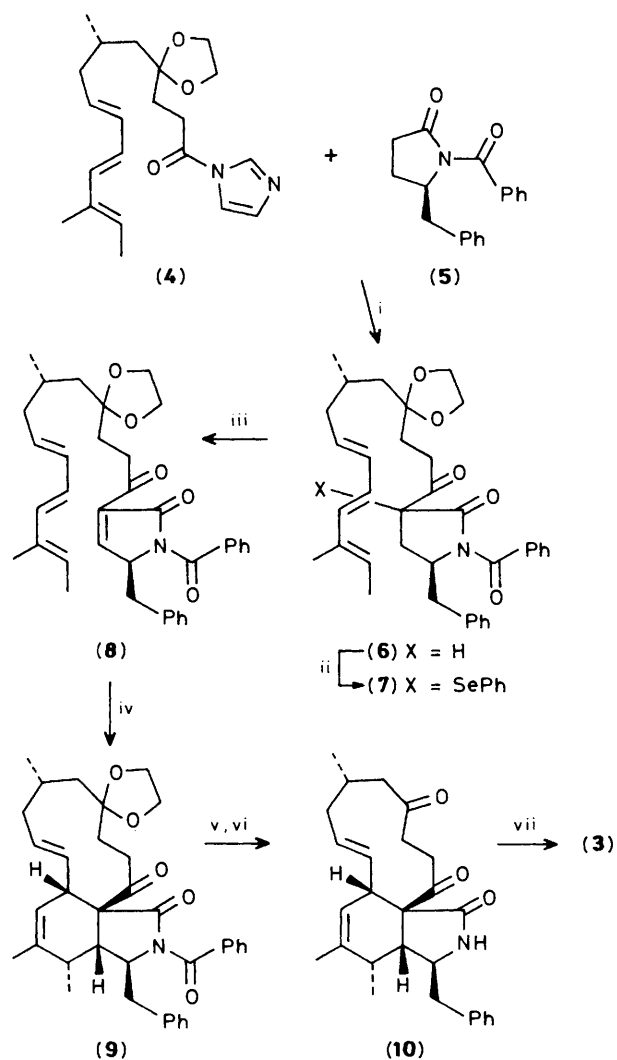
Acylation of the *N*-benzoyl pyrrolidinone (**5**)<sup>5</sup> with imidazole (**4**)<sup>3</sup> gave the ketopyrrolidinone (**6**) which was phenylselenenylated to provide the phenylselenyl ketone (**7**) [78% from (**4**)] (Scheme 1). Oxidation gave the unstable trienylpyrrolinone (**8**) which was cyclized by heating a dilute solution in toluene at 80 °C for 14 h, to give the Diels–Alder product (**9**) (58%), identified from spectroscopic data and by analogy with our earlier work. Deprotection gave the diketone (**10**) (66%) which was treated with methylmagnesium chloride in tetrahydrofuran (THF) at 20 °C to provide the hydroxyketone (**3**)



(84% after chromatography), identified as the expected C(18) diastereoisomer by comparison with an authentic sample prepared during the cytochalasin H synthesis. The methylmagnesium chloride reaction was found to be highly regio- and stereo-selective, no other product being isolated. The use of methyl lithium at  $-40^{\circ}\text{C}$  was similarly selective but gave significantly lower yields. Since the C(18)-silyloxy ketone (3) has been converted into cytochalasin H (1) this work constitutes a second formal synthesis of cytochalasin H and provides another example of medium-ring stereochemical control.

We thank the S.E.R.C. and I.C.I. Pharmaceuticals Division for support (to J. P. W.) under the CASE scheme. We also thank I.C.I. Pharmaceuticals for generous gifts of chemicals, Dr. A. E. Derome and Mrs. McGuinness for n.m.r. spectra, Dr. R. T. Aplin for mass spectra, and Dr. D. J. Tapolczay for helpful discussions. R. S. is on leave from Dr. Karl Thomas GmbH, Chemisch-pharmazeutische Fabrik, Biberach an der Riss, West Germany.

Received, 11th June 1986; Com. 800



**Scheme 1.** Reagents: i,  $\text{LiN}(\text{SiMe}_3)_2$ , THF,  $-70^{\circ}\text{C}$  for 6 h,  $20^{\circ}\text{C}$  for 1 h; ii,  $\text{LiN}(\text{SiMe}_3)_2$ , THF, PhSeCl,  $-70^{\circ}\text{C}$ , 4 h [78% from (4)]; iii, *m*-chloroperbenzoic acid, excess of  $\text{H}_2\text{O}_2$ ,  $-50^{\circ}\text{C}$ , 15 min,  $0^{\circ}\text{C}$ , 5 min; iv, toluene,  $80^{\circ}\text{C}$  [58% from (7)]; v, NaOH, MeOH,  $\text{H}_2\text{O}$ ; vi, 5% aqueous HCl, THF [66% from (9)]; vii, MeMgCl, THF (84%).

## References

- 1 M. Binder and C. Tamm, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 370.
- 2 E. J. Thomas and J. W. F. Whitehead, *J. Chem. Soc., Chem. Commun.*, 1986, 727.
- 3 H. Dyke, R. Sauter, P. Steel, and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1986, previous communication.
- 4 A. F. Cameron, A. A. Freer, B. Hesp, and C. J. Strawson, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1741.
- 5 C. C. Tseng, S. Terashima, and S.-i. Yamada, *Chem. Pharm. Bull.*, 1977, **25**, 29.