Cytochalasan Synthesis: An Alternative Approach to Cytochalasin H

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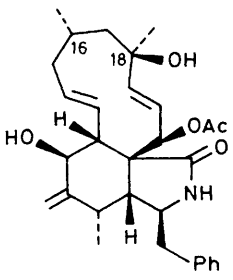
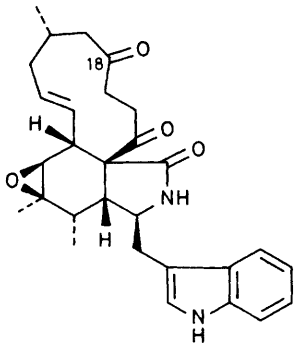
The cytochalasin H precursor (**3**) has been obtained regio- and stereo-selectively from the diketone (**2**) using methylmagnesium chloride in tetrahydrofuran.

The cytochalasans comprise an important group of biologically active fungal metabolites.[1] Recently a synthesis of cytochalasin H (**1**) was described which involved closure of the 11-membered ring *via* an intramolecular Diels–Alder reaction,[2] 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.[3] 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,[4] 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**)[5] with imidazolide (**4**)[3] 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**)



(1)



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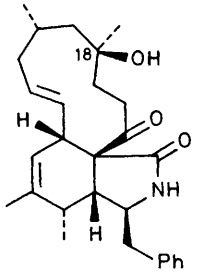

(3)

(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 °C was similarly selective but gave significantly lower yields. Since the C(18)-silylethoxymethyl ether of hydroxyketone (**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.

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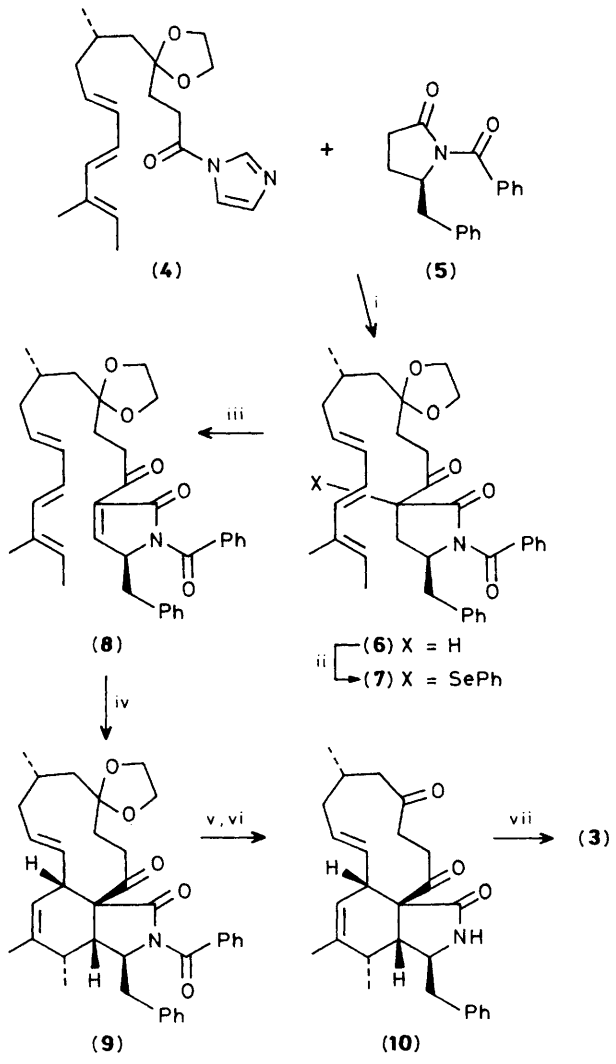

Scheme 1. *Reagents:* i, $LiN(SiMe_3)_2$, THF, −70 °C for 6 h, 20 °C for 1 h; ii, $LiN(SiMe_3)_2$, THF, PhSeCl, −70 °C, 4 h [78% from (**4**)]; iii, *m*-chloroperbenzoic acid, excess of H_2O_2, −50 °C, 15 min, 0 °C, 5 min; iv, toluene, 80 °C [58% from (**7**)]; v, NaOH, MeOH, H_2O; vi, 5% aqueous HCl, THF [66% from (**9**)]; vii, MeMgCl, THF (84%).

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