Cytochalasan Synthesis: Synthesis of an [11]-Membered Ring Precursor of Cytochalasin H

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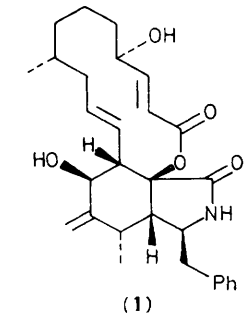
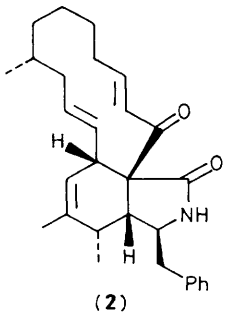
The cytochalasin H precursor (**20**) has been synthesized using an intramolecular Diels–Alder reaction to control stereochemistry and to form the 11-membered ring.

The cytochalasans,[1] an important group of biologically active fungal metabolites, have been the targets of much synthetic endeavour. To date total syntheses of the macrolide cytochalasan, cytochalasin B (**1**),[2] and the [13]cytochalasan, proxiphomin (**2**),[3] have been described, together with several novel ring-expansion and fragmentation approaches to cytochalasin D (**3**).[4,5] We now describe the synthesis of an 11-membered ring precursor of cytochalasin H (**4**),[6] a cytochalasan which differs from cytochalasin D in having no carbonyl function at C(17), and the opposite configuration at C(18). Our synthesis is based on the use of an intramolecular Diels–Alder reaction, which has been shown previously to provide rapid access to the [11]cytochalasan skeleton.[7]

The first phase of the synthesis was concerned with the preparation of the long-chain triene-imidazolide (**12**), and is outlined in Scheme 1. Thus the protected hydroxy aldehyde



(1)



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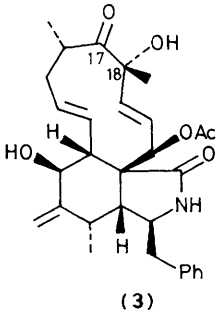

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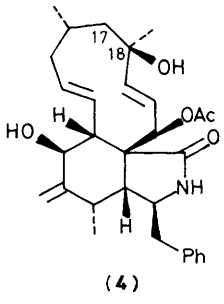


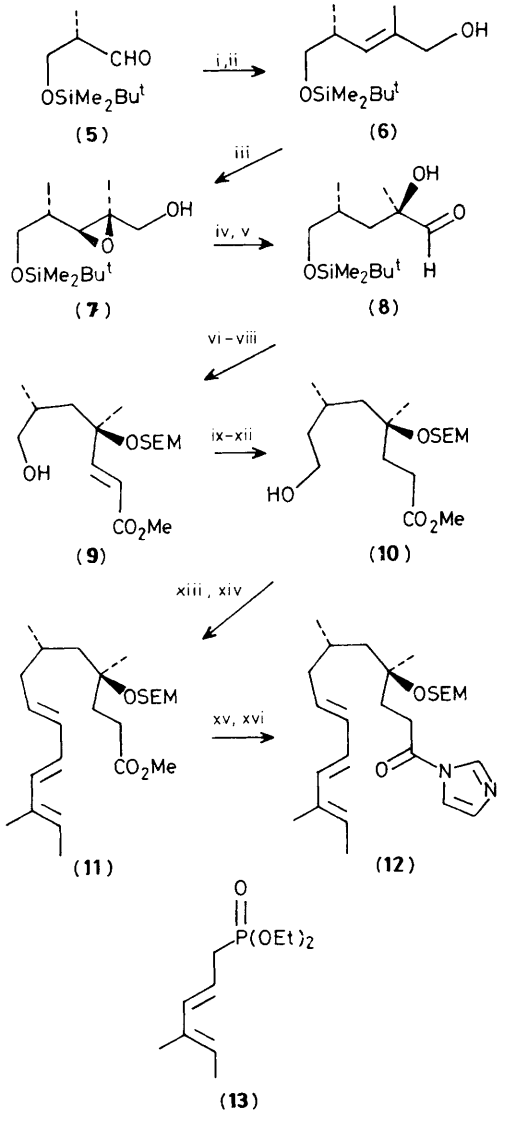
(4)

(**5**), readily available from methyl (2*S*)-3-hydroxy-2-methylpropanoate, was converted into the (*E*)-allylic alcohol (**6**) *via* a Wittig reaction followed by reduction, the optical purity of alcohol (**6**) being checked using Mosher's reagent (enantiomeric excess >98%). The allylic alcohol (**6**) was epoxidized using *m*-chloroperoxybenzoic acid (MCPBA) and the stereoselectivity of epoxidation found to follow that observed by Kishi on the corresponding benzyl ether,[8] so providing the epoxy-alcohol (**7**) containing less than 0.5% of the alternative diastereoisomer.

Regioselective reduction of the epoxide (**7**) using lithium aluminium hydride gave a diol which was oxidized (*N*-chlorosuccinimide, dimethyl sulphide[9]) to the α-hydroxy-aldehyde (**8**) (95%). Chain extension was effected by condensation with methoxycarbonylmethylenetriphenylphosphorane (70%), and protection–deprotection gave the primary alcohol (**9**) which was hydrogenated† and homologated *via* an oxidation, Wittig condensation, and hydroboration sequence. A Swern oxidation of the homologated alcohol (**10**), followed by condensation with the phosphonate (**13**) gave the triene ester (**11**) stereoselectively, which was hydrolysed and the acid treated with carbonyl-1,1′-di-imidazole, to provide the triene imidazolide (**12**). Although slightly long, this synthesis provided the desired imidazolide in gram quantities for further studies.

The conversion of the triene-imidazolide (**12**) into the Diels–Alder precursor (**17**), and the subsequent cyclization, are outlined in Scheme 2. Acylation of the pyrrolidinone (**14**)[10] by the imidazolide (**12**) was achieved using lithium hexamethyldisilazide as base (80—90%), and oxidation to the pyrrolinone (**17**) was carried out *via* phenylselenenylation followed by oxidative elimination. The triene-pyrrolinone (**17**) was handled in solution, since previous experience had

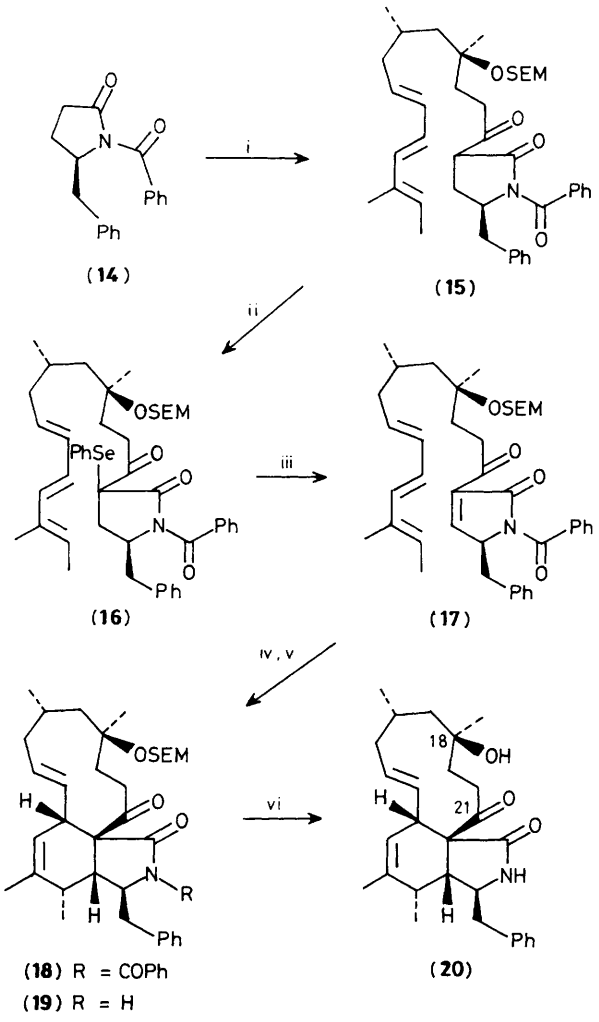
† Preliminary attempts to carry the C(19)–C(20) (cytochalasan numbering) double-bond through the synthesis were thwarted by an intramolecular Diels–Alder cyclization at the triene-imidazolide stage.



SEM = $CH_2OCH_2CH_2SiMe_3$

Scheme 1. *Reagents:* i, $Ph_3PC(Me)CO_2Me$, C_6H_6, reflux (70%); ii, $LiAlH_4$ (90%); iii, MCPBA (95%); iv, $LiAlH_4$ (60%); v, *N*-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2, −20 °C (95%); vi, Ph_3PCHCO_2Me (70%); vii, $ClCH_2OCH_2CH_2SiMe_3$, Et_2NPr^i (85%); viii, Dowex 50W-X8 (70%); ix, H_2, Pd–C, MeOH (95%); x, Me_2SO, oxalyl chloride (90%); xi, $Ph_3P{=}CH_2$ (70%); xii, 9-borabicyclo[3.3.1]nonane (9-BBN) then H_2O_2, OH^- (85%); xiii, Me_2SO, oxalyl chloride (90%); xiv, (**13**)–Li (75—85%); xv, NaOH, H_2O–MeOH then tartaric acid (90%); xvi, carbonyl-1,1-di-imidazole (90%).

shown that similar compounds polymerized on attempted isolation, and the Diels–Alder cyclization was carried out by diluting the solution of the pyrrolinone (**17**) with dry toluene, and heating at 80—100 °C for 5 h. After flash chromatography a single Diels–Alder adduct was isolated (38%), and identified, by spectroscopic comparison with analogous adducts prepared previously,[3,7] as the desired stereoisomer (**18**) formed by addition of the triene onto the less hindered face of the pyrrolinone *endo* to the pyrrolinone ring (see Figure 1). This cyclization appeared to be very stereoselective, minor products, which were not characterized, only being detected



Scheme 2. *Reagents:* i, $LiN(SiMe_3)_2$, (**12**) (80—90%); ii, $LiN(SiMe_3)_2$, PhSeCl (95%); iii, MCPBA, H_2O_2, −40 °C (15 min), 0 °C; iv, toluene, 80—100 °C, 5 h [38% from (**16**)]; v, KOH, MeOH (85%); vi, 5% aqueous HF, MeCN (75%).

at the 2% level. Finally *N*-deprotection was carried out using methanolic potassium hydroxide, and the C(18)-alcohol deprotected using 5% aqueous hydrogen fluoride in acetonitrile to provide the [11]cytochalasan (**20**).

Having assembled the [11]cytochalasan skeleton it remained to modify the cyclohexene and C(18)–C(21) fragments to complete the first total synthesis of cytochalasin H. This work is described in the following communication.[11]

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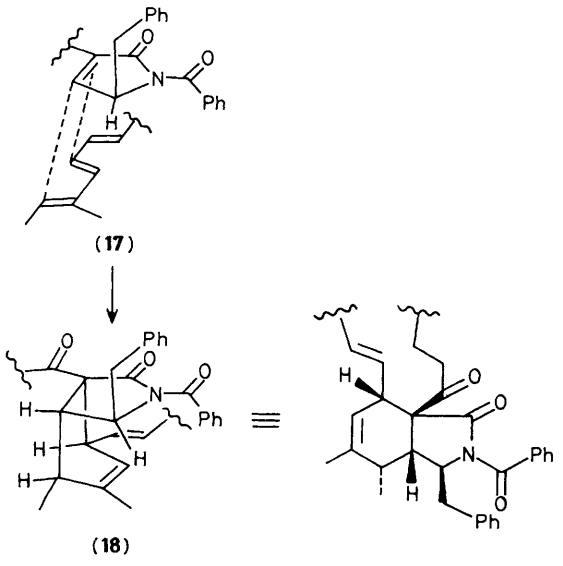

Figure 1

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