

## Cytochalasin Synthesis: Total Synthesis of Cytochalasin G

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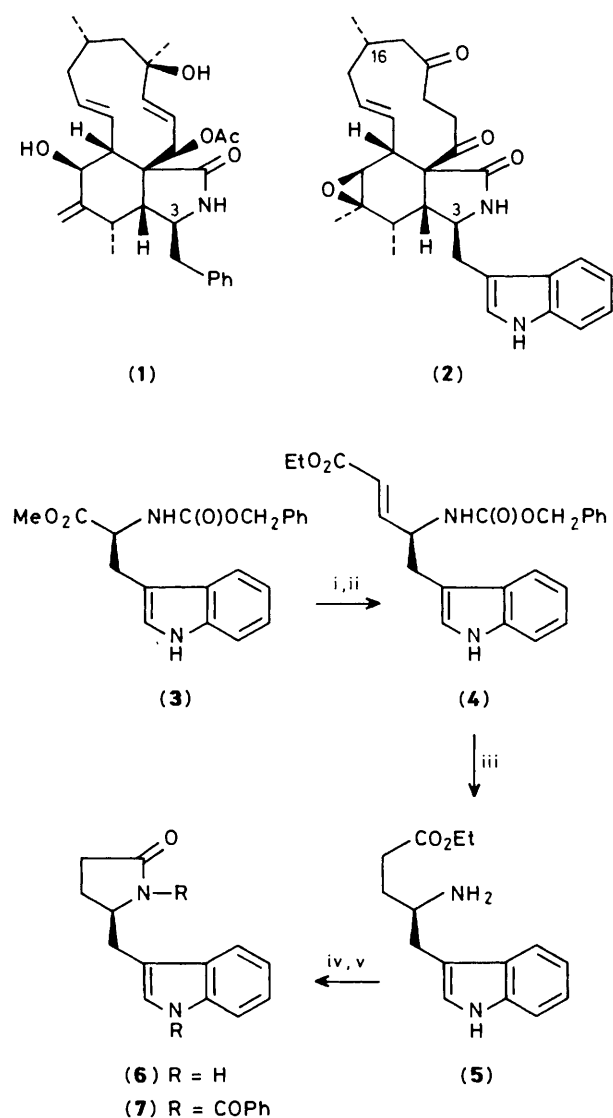
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Cytochalasin G (**2**), an [11]cytochalasin with a tryptophan derived indolylmethyl substituent at C(3) has been synthesized using an intramolecular Diels–Alder reaction to form the 11-membered ring.

The cytochalasins, a group of biologically active, fungal metabolites, present a considerable synthetic challenge.<sup>1,2</sup> To date several approaches to the [11]cytochalasins have been reported,<sup>3</sup> and a total synthesis of cytochalasin H (**1**) using an intramolecular Diels–Alder reaction has been described.<sup>4</sup> However synthetic work in this area has been limited so far to cytochalasins derived from phenylalanine which possess a phenylmethyl substituent at C(3), *e.g.* (**1**). We now report the first synthesis of cytochalasin G (**2**) which is an [11]cytochalasin with a tryptophan derived C(3) indolylmethyl substituent.<sup>5</sup>

Our approach involved the acylation of the (5*R*)-*N*-benzoyl-5-indolylmethylpyrrolidinone (**7**) using long-chain imidazole (**13**), followed by oxidation and Diels–Alder cyclization. The synthesis of pyrrolidinone (**7**) is outlined in Scheme 1.

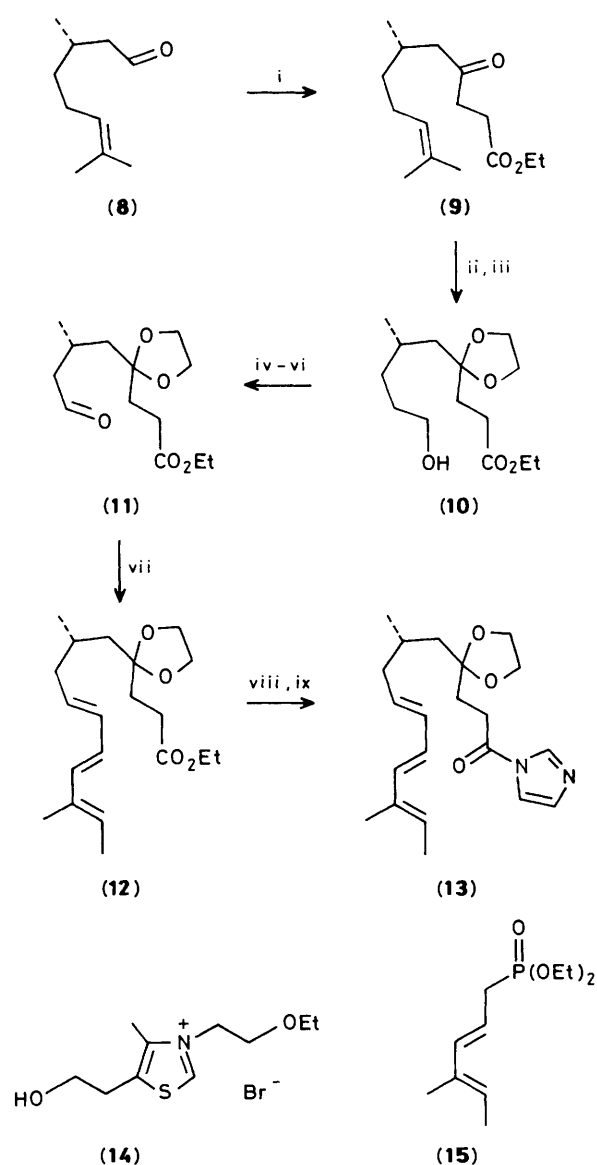
Reduction of *N*-benzyloxycarbonyltryptophan methyl ester (**3**) by di-isobutylaluminium hydride gave the corresponding aldehyde<sup>6</sup> which, without purification, was immediately treated with the lithium salt of triethylphosphonoacetate to provide the unsaturated ester (**4**) [50% from ester (**3**)]. This was hydrogenolysed in acidic ethanol, the saturated amino-ester (**5**) being isolated (81%) and cyclized to pyrrolidinone



**Scheme 1.** Reagents: i,  $\text{Bu}^i_2\text{AlH}$  (73%); ii,  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ , lithium di-isopropylamide (70%); iii,  $\text{H}_2$ , Pd-C, AcOH, EtOH (81%); iv, NaOEt, EtOH (95%); v,  $\text{PhCOCl}$ ,  $\text{Et}_3\text{N}$ , DMAP (77%).

(6), using a catalytic amount of base in ethanol. Bis-benzoylation using benzoyl chloride [triethylamine, dimethylamino-pyridine (DMAP)] then gave the desired pyrrolidinone (7) (77%). During this sequence care was taken to avoid racemization and the *N*-benzoylpyrrolidinone (7) so obtained was optically active,  $[\alpha]_D^{20} + 51 \pm 2^\circ$  (*c* 0.87,  $\text{CH}_2\text{Cl}_2$ ), although its optical purity was not established at this stage.

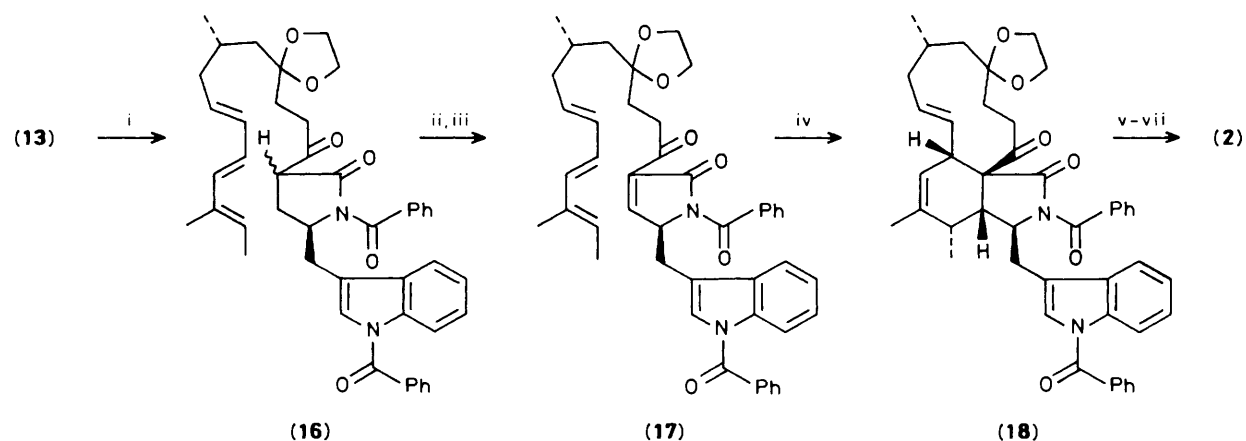
The synthesis of long-chain triene imidazolide (13) is outlined in Scheme 2. The asymmetric centre at C(16) was introduced *via* (*S*)-citronellal (8) which was treated with an excess of ethyl acrylate and the thiazolium salt (14),<sup>7</sup> to provide keto-ester (9), isolated by distillation (55%). Ketone protection and ozonolysis followed by a sodium borohydride reduction gave the hydroxy-acetal (10), which was converted into the aldehyde (11) *via* arylselenenylation, oxidative elimination, and ozonolysis. Condensation of this aldehyde with the lithium salt of dienylphosphonate (15) gave the long-chain triene ester (12). This was hydrolysed, and the carboxylic acid converted into the acylimidazolide (13) using carbonyl di-imidazole.



**Scheme 2.** Reagents: i, ethyl acrylate (4 equiv.), thiazolium salt (14) (55%); ii,  $\text{HOCH}_2\text{CH}_2\text{OH}$ , *p*- $\text{MeC}_6\text{H}_4\text{SO}_2\text{OH}$  (70%); iii,  $\text{O}_3$ , then  $\text{NaBH}_4$  (57%); iv, *o*- $\text{NO}_2\text{C}_6\text{H}_4\text{SeCN}$ ,  $\text{Bu}^n_3\text{P}$  (82%); v,  $\text{H}_2\text{O}_2$  (81%); vi,  $\text{O}_3$ , then dimethyl sulphide (73%); vii, (15)-Li (87%); viii, NaOH,  $\text{H}_2\text{O}$ , EtOH, then tartaric acid (90%); ix, carbonyl di-imidazole (95%).

Acylation of pyrrolidinone (7) by the long-chain triene imidazolide (13) was carried out using lithium hexamethyldisilazide as base, and gave the keto-pyrrolidinone (16) as a mixture of diastereoisomers (Scheme 3). Oxidation of the pyrrolidinone was then achieved by phenylselenenylation and oxidative elimination to give the unstable triene-pyrrolinone (17) which was immediately cyclized by heating in toluene ( $80^\circ\text{C}$ , 7 h). Only a single Diels-Alder product was isolated from this reaction (32% yield), and was assigned structure (18) by analogy with earlier work. Minor products were detected at the 2–3% level but were not identified.

Finally the Diels-Alder adduct (18) was converted into cytochalasin G (2) by a three step sequence involving acetal hydrolysis, epoxidation, and *N*-deprotection. The synthetic sample of cytochalasin G so obtained was identical ( $^1\text{H}$  n.m.r., m.p.,  $[\alpha]_D^{20}$ , etc.) with a sample of the natural material.



**Scheme 3.** Reagents: i, (7)-Li (68%); ii,  $\text{LiN}(\text{SiMe}_3)_2$ ,  $\text{PhSeCl}$  (84%), iii,  $\text{H}_2\text{O}_2$ , *m*-chloroperoxybenzoic acid,  $-40^\circ\text{C}$  then  $0^\circ\text{C}$ ; iv, toluene,  $80^\circ\text{C}$ , 7 h (32% from the intermediate selenide); v, 5% aqueous HCl, tetrahydrofuran, (71%); vi, *m*-chloroperoxybenzoic acid (39%); vii, NaOH, MeOH (62%).

This synthesis of cytochalasin G extends our earlier work, and confirms the usefulness of the intramolecular Diels–Alder approach for synthesis of natural products in this area.

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