Cytochalasan Synthesis: Total Synthesis of Cytochalasin G

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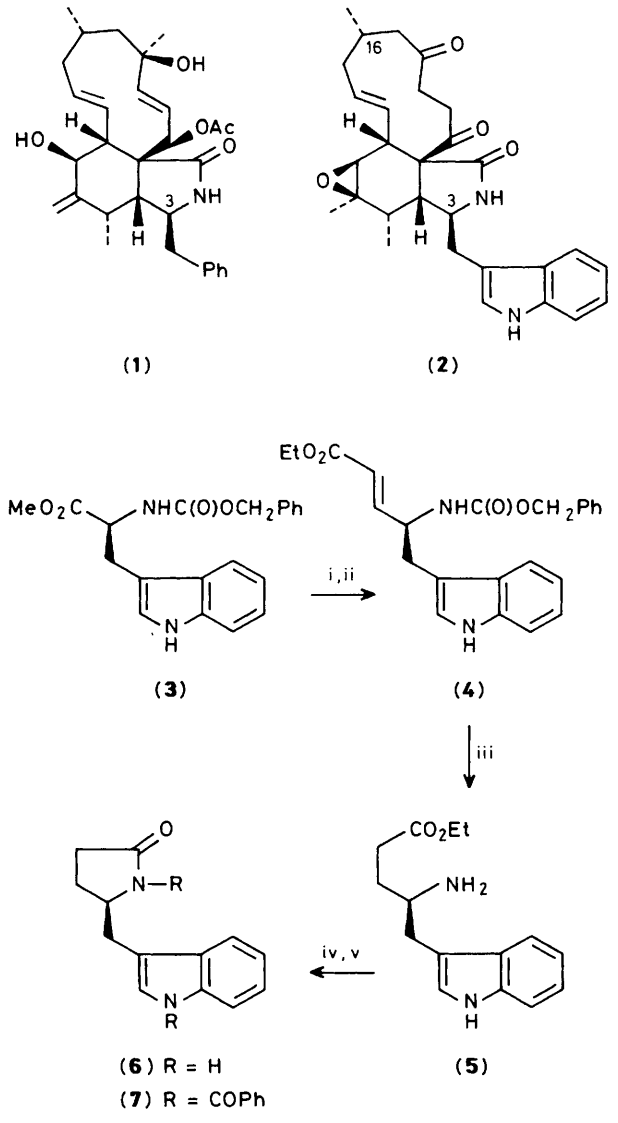
Cytochalasin G (**2**), an [11]cytochalasan with a tryptophan derived indolylmethyl substituent at C(3) has been synthesized using an intramolecular Diels–Alder reaction to form the 11-membered ring.

The cytochalasans, a group of biologically active, fungal metabolites, present a considerable synthetic challenge.[1,2] To date several approaches to the [11]cytochalasans have been reported,[3] and a total synthesis of cytochalasin H (**1**) using an intramolecular Diels–Alder reaction has been described.[4] However synthetic work in this area has been limited so far to cytochalasans 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]cytochalasan with a tryptophan derived C(3) indolylmethyl subsituent.[5]

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

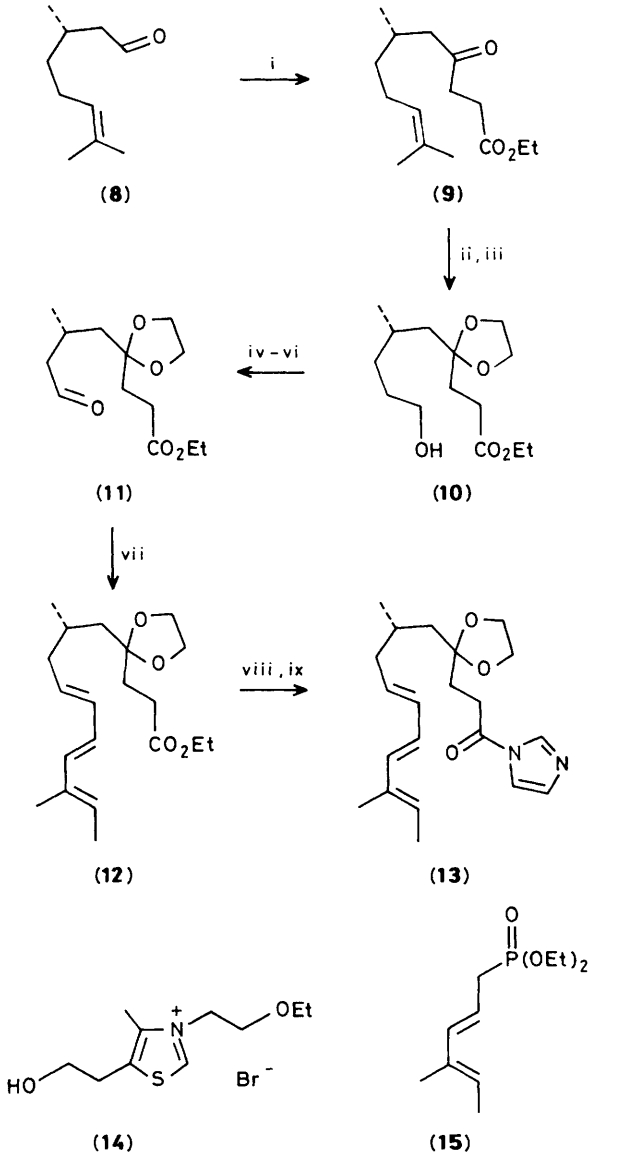
Reduction of *N*-benzyloxycarbonyltryptophan methyl ester (**3**) by di-isobutylaluminium hydride gave the corresponding aldehyde[6] which, without purification, was immediately treated with the lithium salt of triethylphosphonoacetate to provide the unsaturated ester (**4**) [50% from ester (**3**)].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



Scheme 1. *Reagents:* i, Bu^i_2AlH (73%); ii, $(EtO)_2P(O)CH_2CO_2Et$, lithium di-isopropylamide (70%); iii, H_2, Pd–C, AcOH, EtOH (81%); iv, NaOEt, EtOH (95%); v, PhCOCl, Et_3N, DMAP (77%).

(**6**), using a catalytic amount of base in ethanol. Bis-benzoylation using benzoyl chloride [triethylamine, dimethylaminopyridine (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, $[\alpha]_D^{20} + 51 \pm 2°$ (*c* 0.87, CH_2Cl_2), although its optical purity was not established at this stage.

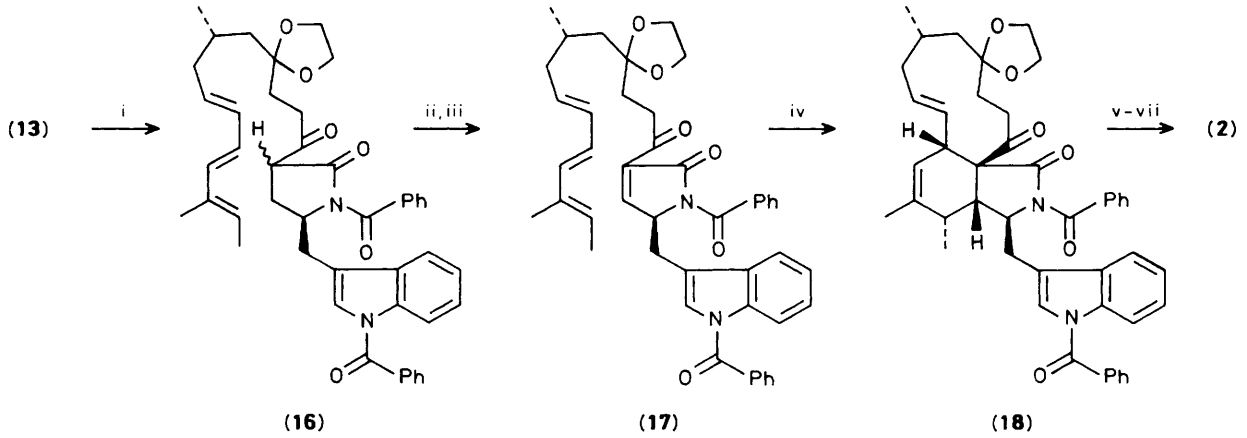
The synthesis of long-chain triene imidazolide (**13**) is outlined in Scheme 2. The asymmetric centre at C(16) was introduced *via* (*S*)-citronellal (**8**) which was treated with an excess of ethyl acrylate and the thiazolium salt (**14**),[7] to provide keto-ester (**9**), isolated by distillation (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, $HOCH_2CH_2OH$, *p*-$MeC_6H_4SO_2OH$ (70%); iii, O_3, then $NaBH_4$ (57%); iv, *o*-$NO_2C_6H_4SeCN$, Bu^n_3P (82%); v, H_2O_2 (81%); vi, O_3, then dimethyl sulphide (73%); vii, (**15**)–Li (87%); viii, NaOH, H_2O, 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 °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}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, $LiN(SiMe_3)_2$, PhSeCl (84%), iii, H_2O_2, *m*-chloroperoxybenzoic acid, −40 °C then 0 °C; iv, toluene, 80 °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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