Cytochalasan Synthesis: Total Synthesis of Cytochalasin D

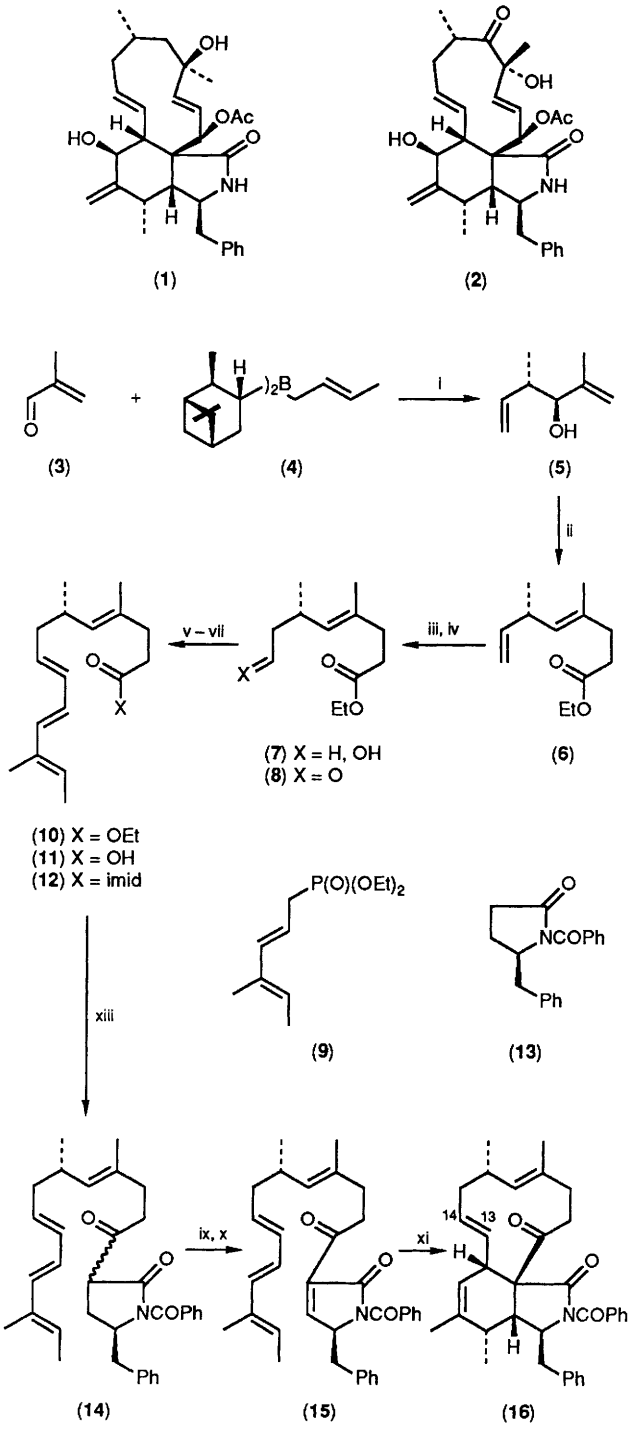
Eric Merifield and Eric J. Thomas*

The Department of Chemistry, The University of Manchester, Manchester M13 9PL, U.K.

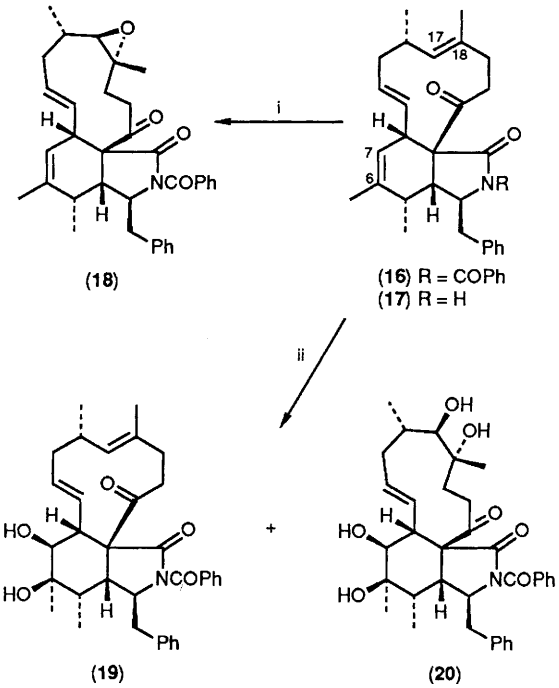
Cytochalasin D has been synthesized using an intramolecular Diels–Alder reaction to form the eleven-membered ring.

Total synthesis of the cytochalasans, a group of complex, biologically active fungal metabolites, is of considerable interest.[1,2] One approach to this system involves the use of an intramolecular Diels–Alder reaction to form the reduced isoindolone and large ring fragments simultaneously, and this approach has been used to synthesize several naturally occurring cytochalasans including cytochalasin H (**1**).[3,4] We now report the use of this strategy to synthesize cytochalasin D (**2**), one of the first fully functionalized cytochalasans to be characterized and one which has potent biological activity.[5]

The synthesis of the cytochalasan nucleus is outlined in Scheme 1. Treatment of methacrolein (**3**) with the (*E*)-but-2-enyldi-isopinocampheylborane (**4**) derived from (+)-pinene[6] gave the *anti*-homoallylic alcohol (**5**) after oxidative work-up, together with a small amount (<10%) of its *syn*-diastereoisomer. These were not separated, rather the mixture was converted *via* a Claisen rearrangement using triethyl orthoacetate and propanoic acid into the dienyl ester (**6**). Regioselective hydroboration using 9-bicycloboranonane followed by oxidation, gave the 1° alcohol (**7**), which was



Scheme 1. *Reagents and conditions*: i, −78 °C, 3 h, then H_2O_2; ii, $MeC(OEt)_3$, propanoic acid, 140—170 °C, 52% from (**3**); iii, 9-borabicyclo[3.3.1]nonane then H_2O_2, 77%: iv, $(COCl)_2$, DMSO, 80%; v, (**9**)-Li, tetrahydrofuran (THF), hexamethylphosphoramide, 85%; vi, NaOH, EtOH, H_2O, 100%; vii, CO(imidazole)$_2$, THF, 100%; viii, (**13**)-Li, 92%; ix, $LiN(SiMe_3)_2$, PhSeCl, 86%; x, *m*-chloroperoxybenzoic acid, H_2O_2, −50 °C to 0 °C; xi, toluene, 80 °C, 25—30% from (**14**).



Scheme 2. *Reagents and conditions*: i, *m*-chloroperoxybenzoic acid, −25 °C, 95%; ii, OsO_4, (**19**) 55%, (**20**) 15%, and (**16**) 20%.

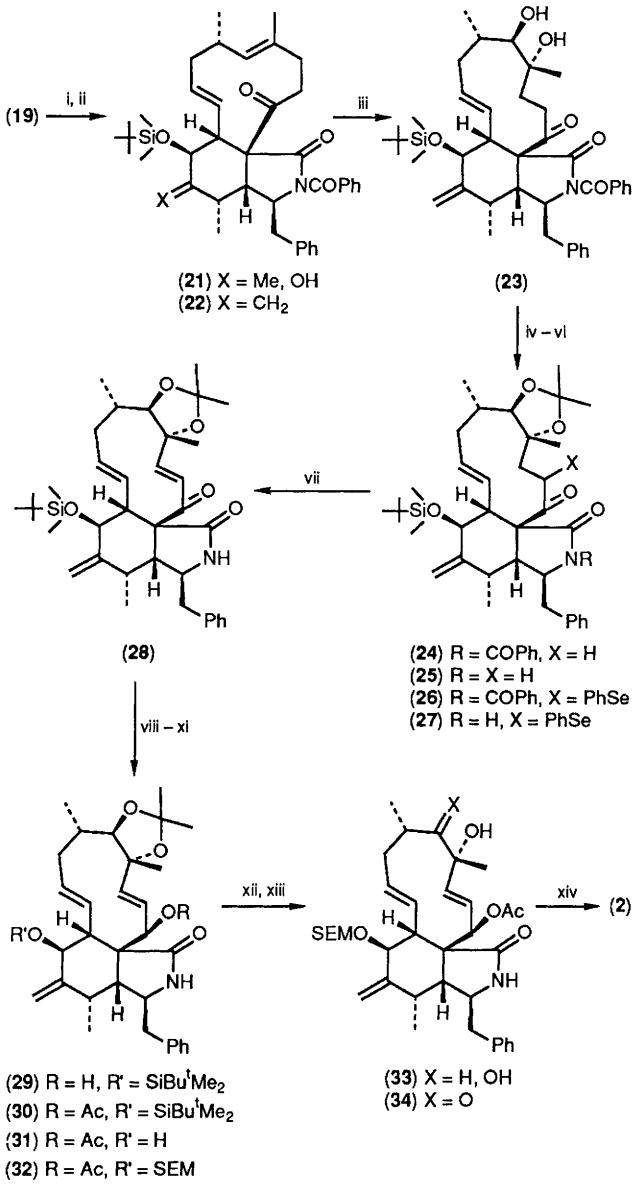
estimated to have an enantiomeric excess (e.e.) of 70% from the NMR spectrum of its Mosher's derivative. Oxidation using oxalyl chloride–dimethyl sulphoxide (DMSO) gave the aldehyde (**8**). Coupling this aldehyde to the dienyl phosphonate (**9**) using the conditions developed earlier,[7] gave the conjugated triene (**10**) which was hydrolysed and the acid (**11**) so formed converted into the acyl imidazolide (**12**) using carbonyl 1,1′-di-imidazole. The imidazolide was then used to acylate the lithium enolate of the (5*R*)-5-phenylmethylpyrrolidinone (**13**),[8] and the product converted into the unstable 3-acylpyrrol-2(5*H*)-one (**15**) by phenylselenenylation and oxidative elimination. The pyrrol-2(5*H*)-one was not isolated.[7] Rather it was heated in solution to give the Diels–Alder adduct (**16**) (25—35%) together with a small amount of a minor diastereoisomeric product (*ca.* 4%). The structure and stereochemistry of the adduct (**16**) was consistent with spectroscopic and analytical data,† and was confirmed by its conversion into cytochalasin D, *vide infra*.

It was intended to use the diastereofacial selectivity of reactions of the C(17)–C(18)‡ double bond to introduce the required stereochemistry at C(18). However first it was necessary to discriminate between the three carbon–carbon double bonds present in the adduct (**16**). It was found that epoxidation using *m*-chloroperoxybenzoic acid was both regio- and stereo-selective giving the 17,18-epoxide (**18**) as the only isolable product.[3] In contrast oxidation using one mole equivalent of osmium tetroxide was selective for the C(6)–C(7) double bond giving the diol (**19**)[9] together with the tetrol (**20**) and unchanged triene (**16**) (Scheme 2).

The synthesis of cytochalasin D (**2**) was completed using the diol (**19**). Selective protection using t-butyldimethylsilyl trifluoromethanesulphonate gave the mono-t-butyldimethylsilyl ether (**21**) which was dehydrated to provide the exocyclic alkene (**22**) using thionyl chloride–triethylamine. Further oxidation using osmium tetroxide gave the diol (**23**) which was protected as its acetonide (**24**). Phenylselenenylation at C(20) was best carried out on the *N*-benzoylcytochalasan (**24**) using

† All isolated new products were fully characterized spectroscopically and by either analytical or accurate mass data.

‡ For details of the cytochalasan numbering scheme, see ref. 11.



Scheme 3. *Reagents and conditions*: i, Bu^tMe_2SiOTf (Tf = trifluoromethylsulphonyl), 2,6-lutidine, 90%; ii, $SOCl_2$, triethylamine, 75%; iii, OsO_4, 75%; iv, 2,2-dimethoxypropane, $CHCl_3$, toluene-*p*-sulphonic acid, 100%; v, LDA, PhSeCl, 70%; vi, KOH, MeOH, 85%; vii, H_2O_2, H_2O, pyridine, 67%; viii, $NaBH_4$, $CeCl_3$, 90%; ix, Ac_2O, Et_3N, 4-dimethylaminopyridine, 80%; x, Bu_4NF, 90%; xi, SEMCl, Hunig's base, 75%; xii, H_3O^+, 80%; xiii, $(COCl)_2$, DMSO, 75%; xiv, HF, MeCN, H_2O, 70%.

lithium di-isopropylamide (LDA) and benzene selenenyl chloride at −35 °C, and was followed by hydrolysis of the *N*-benzoyl substituent and oxidative elimination to give the enone (**28**). Reduction of this enone using sodium borohydride or di-isobutylaluminium hydride gave mixtures of the required allylic alcohol (**29**) and the saturated ketone (**25**). However Luche's reagent, sodium borohydride–cerium(III) chloride,[10] was more regioselective and gave the allylic alcohol (**29**) exclusively; this was acetylated using acetic anhydride and triethylamine–4-dimethylaminopyridine (DMAP) to give the C(21) acetate (**30**) (Scheme 3).

Hydrolysis of the acetonide was accompanied by loss of the t-butyldimethylsilyl protecting group, and so this was first removed by treatment with tetrabutylammonium fluoride and the 7-OH reprotected as its trimethylsilylethoxymethyl (SEM) ether. Hydrolysis of the acetonide followed by oxidation using oxalyl chloride and DMSO then gave the hydroxyketone (**34**) which on deprotection using hydrogen fluoride in aqueous acetonitrile gave cytochalasin D (**2**) identical to an authentic sample of the natural product (300 MHz, NMR, IR, MS, TLC, optical rotation, *etc.*).

This synthesis of cytochalasin D (**2**) complements that reported earlier for cytochalasin H (**1**)[3] in that of the nine chiral centres, only those at C(16) and C(3) were present before the Diels–Alder cyclization. All the others were induced either during or subsequent to the Diels–Alder reaction. The different regioselectivity observed for the epoxidation and osmium tetroxide reactions of the Diels–Alder adduct (**16**) and its debenzoylated analogue (**17**) are of interest, and must reflect the different electronic and steric requirements of these reactions.

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