Cytochalasan Synthesis: an Alternative Approach to Cytochalasin D

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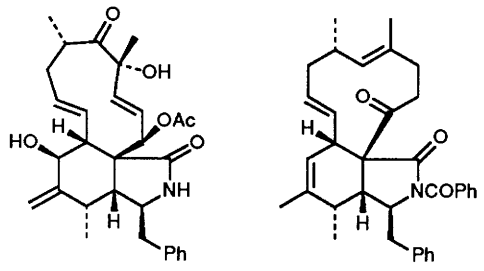
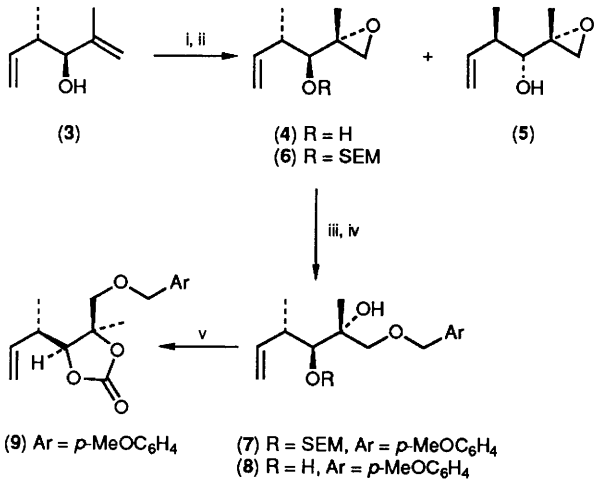
The stereoselective synthesis of an advanced intermediate for a proposed synthesis of cytochalasin D is described.

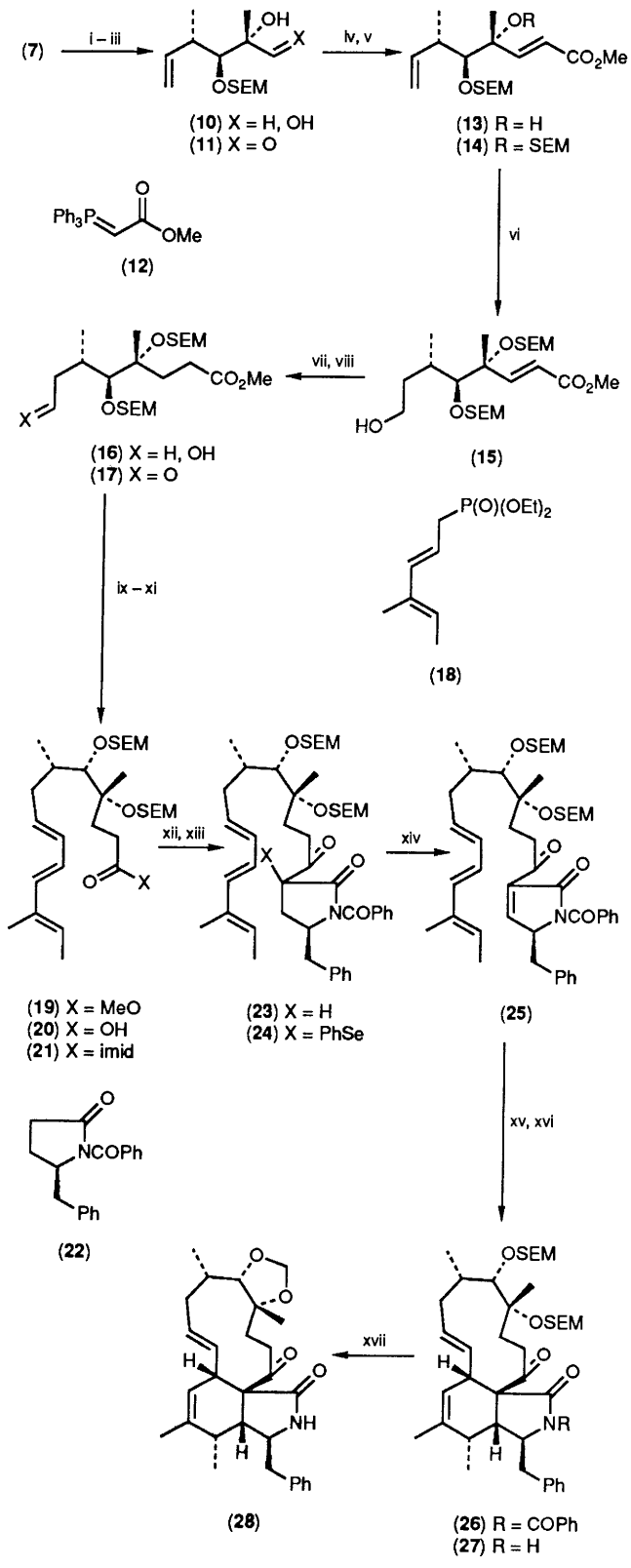
A total synthesis of cytochalasin D (**1**) using an intramolecular Diels–Alder reaction to form the eleven-membered ring is described in the preceding communication.[1] One aspect of this synthesis is the use of the conformational preferences of the eleven-membered ring to control the configurations of the



(**1**) (**2**)



Scheme 1. *Reagents and conditions*: i, (+)-DET, $Ti(OPr^i)_4$, 4 Å sieves, Bu^tO_2H, −20 °C, 60 h then $FeSO_4$, tartaric acid, 57%; ii, Pr^i_2NEt, SEMCl, CH_2Cl_2, 97%; iii, *p*-$MeOC_6H_4CH_2OH$, NaOH, 80 °C, 3 days, 71%; iv, aq. HF, MeCN, 1 h, 63%; v, $CO(imidazole)_2$, benzene, heat, 2 days, 76%.



Scheme 2. *Reagents and conditions*: i, dichlorodicyanoquinone, CH_2Cl_2, H_2O, 20 min, 97%; ii, NaOH, H_2O, MeOH, 88%; iii, DMSO, oxalyl chloride, CH_2Cl_2 −50 °C, then Et_3N, 77%; iv, (**12**) benzene, 80 °C, 4 h, 95%; v, Pr^i_2NEt, SEMCl, CH_2Cl_2, 48 h, heat, 92%; vi, 9-BBN, tetrahydrofuran (THF), heat, 1.5 h, then NaOH, H_2O_2, 1 h, 76%; vii, Pd–C, H_2, MeOH, 80%; viii, DMSO, oxalyl chloride, CH_2Cl_2, −50 °C, then Et_3N, 78%; ix, (**18**)-Li, THF, −70 °C, 1 h, then hexamethylphosphoramide, 3 h, 79%; x, NaOH, H_2O, EtOH, 6 h; xi, $CO(imidazole)_2$, THF, 16 h, 94% from (**19**); xii, (**22**)-Li, −72 °C, THF, 2 h, then 1 h, room temp., 92%; xiii, $LiN(SiMe_3)_2$, PhSeCl, −72 °C, 2.5 h, 81%; xiv, H_2O_2. *m*-chloroperbenzoic acid, −50 °C, 15 min, then 0 °C, 10 min; xv, toluene, 80 °C, 16 h, 53% from (**24**); xvi, NaOH, MeOH, H_2O, 2.5 h, 89%; xvii, aq. HF, MeCN, 6 h, 55%.

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chiral centres at C(18) and C(21). Indeed of the five chiral centres present in the eleven-membered ring only that at C(16) is present before the Diels–Alder step. A consequence of this approach is that the formation of the cytochalasan nucleus is completed early in the synthesis, only eleven steps being required to form the key intermediate (**2**). However the conversion of this intermediate into cytochalasin D is quite lengthy. An alternative approach would be to introduce more of the functionality before effecting the Diels–Alder step. We now report a stereoselective synthesis of an advanced intermediate for a proposed synthesis of cytochalasin D (**1**) by a route in which the chiral centres at C(16) and C(18) are both introduced before the Diels–Alder reaction.

Epoxidation of the *anti*-alcohol (**3**) [enantiomeric excess (e.e.) 84%, Mosher's derivative][1,2] containing 15% of its *syn*-diastereoisomer, with Bu^{t}OH–(+)-diethyl tartrate [(+)-DET]–Ti(OPr^i)$_4$ gave a 55% yield of the required hydroxyepoxide (**4**) together with *ca.* 10% of a mixture of diastereoisomeric epoxides and a small amount of starting material.[3]‡ The e.e. of the hydroxyepoxide (**4**) was found to be 98%, significantly larger than that of the starting alcohol due to preferential formation of hydroxyepoxide (**5**), a diastereoisomer of (**4**), from epoxidation of the enantiomer of alcohol (**3**).

After protection of the hydroxyepoxide as its trimethylsilylethoxymethoxy (SEM) ether, epoxide opening was achieved using neat *p*-methoxybenzyl alcohol in the presence of powdered sodium hydroxide at 80 °C for three days giving the *p*-methoxybenzyl ether (**7**). The stereochemistry of the epoxidation step was confirmed at this stage by removal of the SEM group using dilute aqueous HF in acetonitrile, and conversion of the diol (**8**) into the cyclic carbonate (**9**) which was examined by NOE spectroscopy (Scheme 1).

Removal of the *p*-methoxybenzyl group from (**7**) was achieved using dichlorodicyanoquinone followed by saponification of the intermediate *p*-methoxybenzoates to give the diol (**10**).[4] Oxidation using oxalyl chloride–dimethyl sulphoxide (DMSO) gave the hydroxyaldehyde (**11**) which was condensed with the methoxycarbonylmethylenephosphorane (**12**) to give the dienyl ester (**13**). This was further protected as its bis-SEM derivative and hydroborated using 9-borabicyclo[3.3.1]nonane (9-BBN) to give the primary alcohol (**15**) after oxidation. Hydrogenation gave the saturated hydroxyester (**16**).

Further oxidation gave the aldehyde (**17**) which was condensed with the dienyl phosphonate (**18**) using the procedure developed earlier[5] to give the conjugated triene (**19**). Ester hydrolysis and treatment of the free acid with carbonyl 1,1′-di-imidazole gave the long-chain acyl imidazolide (**21**) which was used to acylate the lithium enolate of the (5*R*)-5-benzylpyrrolidinone (**22**).[6] Phenylselenenylation and oxidative elimination gave the unstable pyrrol-2(5*H*)-one (**25**), which was not isolated[5] but which was heated in solution in toluene to provide a good yield [53% based on phenylselenopyrrolidinone (**24**)] of the required Diels–Alder product (**26**). Treatment with potassium hydroxide in methanol gave the *N*H pyrrolidinone (**27**), and preliminary attempts to remove the two vicinal SEM-ethers gave the methylenedioxy compound (**28**) (Scheme 2).

The stereochemistry shown was assigned to the Diels–Alder product (**26**) by analogy with earlier work[1] and was supported by extensive NMR spectroscopic studies including NOE experiments. It has the stereochemistry that would be required for a synthesis of cytochalasin D (**1**) at seven of its chiral centres, the remaining hydroxy bearing chiral centre at C(17) being suitably functionalized for conversion into the C(17) ketone.

This work complements the approach to cytochalasin D (**1**) described in the preceding communication in that the chiral centres at C(16) and C(18) are established early in the synthesis, indeed both are present after the second step. The combination of allylborane chemistry and a Sharpless epoxidation would appear to be powerful strategy for the asymmetric synthesis of aliphatic compounds containing three contiguous chiral centres.

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‡ All new compounds were thoroughly characterized by spectroscopic methods.

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