Cytochalasan Synthesis: Total Synthesis of Cytochalasin H

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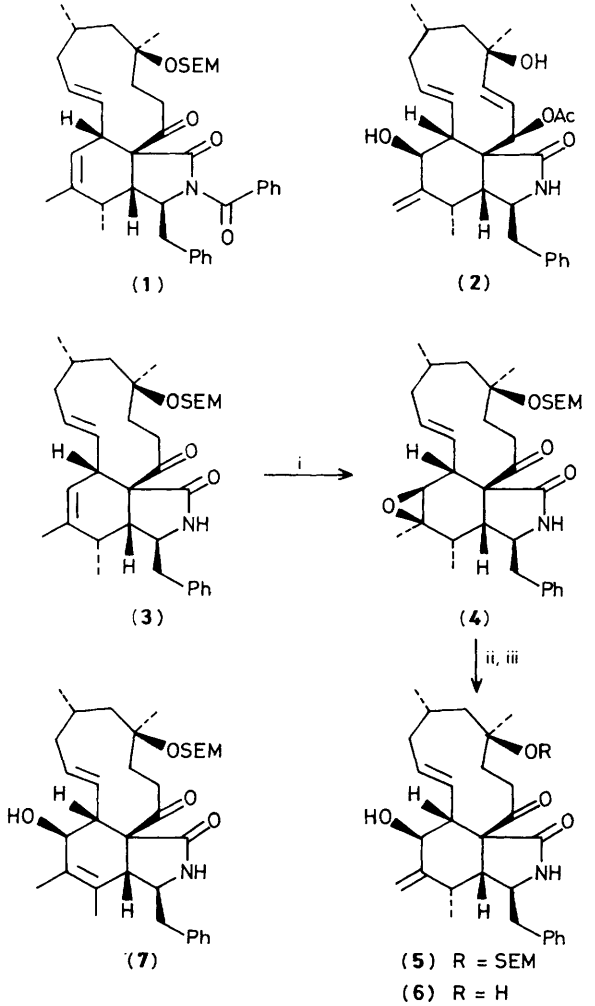
The final stages of a total synthesis of cytochalasin H are described.

Synthesis of the cytochalasans,[1] an important group of biologically active, fungal metabolites, is an area of considerable interest at the present time.[2] In the preceding communication we described the total synthesis of the [11]cytochalasan (**1**) using an intramolecular Diels–Alder reaction to close the 11-membered ring.[2] We now report the conversion of this adduct into cytochalasin H (**2**),[3] so completing the first total synthesis of a naturally occurring [11]cytochalasan.

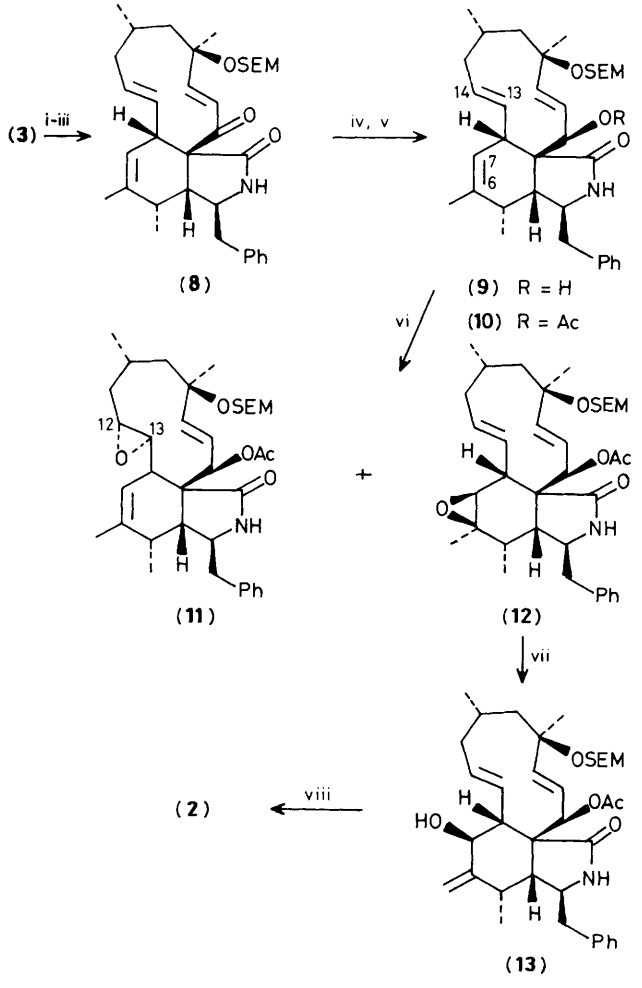
Preliminary studies on the cyclohexene ring modification were carried out on the *N*-deprotected Diels–Alder adduct (**3**), and are summarized in Scheme 1. Epoxidation using *m*-chloroperoxybenzoic acid (MCPBA) was both regio- and stereo-selective, and provided the cyclohexene oxide (**4**) (70%) *via* attack on the trisubstituted double bond from its less hindered face, no other epoxides being isolated. Rearrangement of the epoxide (**4**) was effected by treatment with aluminium isopropoxide in xylene at 125 °C,[4] and gave two products which were separated by flash chromatography. The major product was identified as the desired methylenecyclohexanol (**5**) (60%), which was treated with 5% aqueous hydrogen fluoride in acetonitrile to deprotect the C(18) alcohol, whilst the minor product was provisionally identified as the endocyclic alkene (**7**). Next the introduction of the C(19)—C(21) allylic acetate moiety was investigated, and this work is outlined in Scheme 2.

The C(19)–C(20) (*E*)-double bond was introduced into the *N*-deprotected Diels–Alder adduct (**3**) by conversion of the ketone into its enol trimethylsilyl ether, phenylselenenylation, and oxidative elimination. The ketone was then reduced using sodium borohydride to provide a single alcohol which was

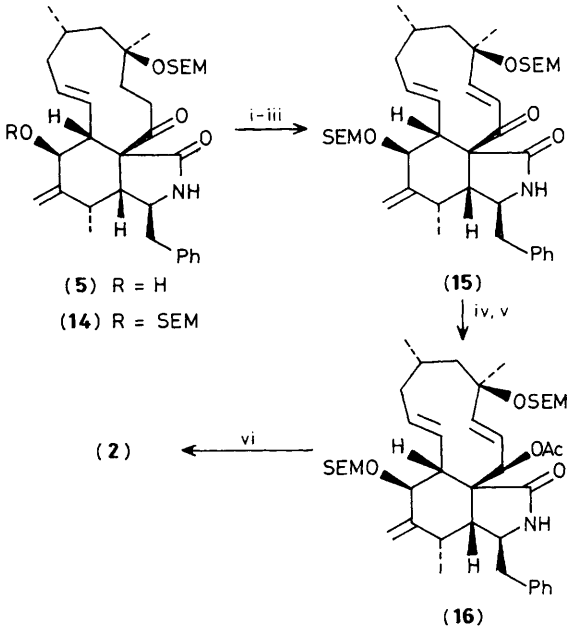


SEM = $CH_2OCH_2CH_2SiMe_3$

Scheme 1. *Reagents:* i, MCPBA (72%); ii, $Al(OPr^i)_3$, xylene, 125 °C, 5—8 h (60%); iii, 5% aqueous HF in acetonitrile (85%).



Scheme 2. *Reagents:* i, lithium di-isopropylamide (LDA), Me_3SiCl; ii, Bu^n_4NF, PhSeCl [78% from (**3**)]; iii, H_2O_2, pyridine (75%); iv, $NaBH_4$ (78%); v, excess of Ac_2O, pyridine, 4-*N*,*N*-dimethylaminopyridine (DMAP) (90%); vi, MCPBA (70—80%); vii, $Al(OPr^i)_3$, xylene, reflux (65%); viii, 5% aqueous HF, acetonitrile (70%).



Scheme 3. *Reagents:* i, LDA, Me_3SiCl; ii, Bu^n_4NF, PhSeCl [21% from (**14**)]; iii, H_2O_2, pyridine (65%); iv, $NaBH_4$ (71%); v, Ac_2O, pyridine, DMAP (90%); vi, 5% aqueous HF in acetonitrile (60%).

identified as the desired isomer (**9**) by comparison of its ^1H n.m.r. spectrum with that of cytochalasin H (**2**). The fairly rigid conformation imposed on the 11-membered ring would appear to control the diastereoface selectivity of this reduction very efficiently as has been observed in the aspochalasan series.[5] The C(21) hydroxy group was then acetylated, and the acetate (**10**) subjected to the epoxidation–rearrangement sequence developed earlier to introduce the methylenecyclohexanol system. However on treatment of the acetate (**10**) with a slight excess of *m*-chloroperoxybenzoic acid, two mono-epoxides were formed which were separated and identified as (**11**) and (**12**), ratio 2 : 1, in which the epoxidation had occurred preferentially on the C(13)–C(14) disubstituted double bond. Nevertheless the desired cyclohexene oxide (**12**) was isolated in a 25% yield, and was isomerized to the allylic alcohol (**13**) (65%) by aluminium isopropoxide in xylene at 125 °C, only traces of the possible endocyclic allylic alcohol being detected in this case. Deprotection of the C(18) hydroxy group finally provided cytochalasin H (**2**) identical (^1H n.m.r., i.r., and mass spectra, optical rotation,† m.p. *etc.*) with an authentic sample.[6]

An alternative route to cytochalasin H which avoided the unfavourable epoxidation of acetate (**10**) was briefly investigated. The methylenecyclohexanol (**5**) prepared during the initial studies of the cyclohexene oxidation was protected ($ClCH_2OCH_2CH_2SiMe_3$, Et_2NPr^i), and the bis-SEM ether (**14**) taken through the silylation, phenylselenenylation, and oxidative elimination procedure to provide the α,β-unsaturated ketone (**15**). Reduction ($NaBH_4$) and acetylation, as before, provided the bis-SEM derivative of cytochalasin H which was converted into cytochalasin H (**2**) by treatment with dilute aqueous HF in acetonitrile.

This work completes the first synthesis of a fully functionalized [11]cytochalasan, and confirms the usefulness of the intramolecular Diels–Alder reaction as a synthetic approach to compounds in this area.

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6 Purchased from Sigma Chemical Company, catalogue no. C 0889.

† $[\alpha]_{20}^{D}$ (commercial) −13.3° (*c* 0.075, $CHCl_3$); $[\alpha]_{20}^{D}$ (synthetic) −14.5° (*c* 0.265, $CHCl_3$).