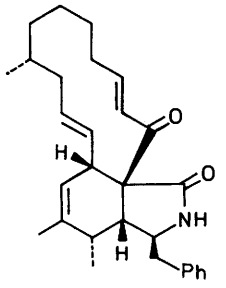
Cytochalasan Synthesis: Total Synthesis of Cytochalasin H

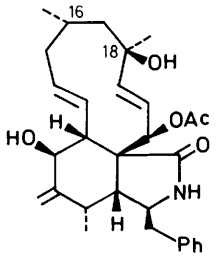
Eric J. Thomas *,† **and John W. F. Whitehead**
The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY

Cytochalasin H (**2**) has been synthesized using an intramolecular Diels–Alder reaction to form the [11]cytochalasan skeleton. This was highly stereoselective and gave adduct (**49**) with the correct configurations at all chiral centres. The later stages of the synthesis involved stereoselective cyclohexene epoxidation–epoxide rearrangement, introduction of the C-19–C-20 double bond, and stereoselective reduction of the C-21 ketone.

An approach to the synthesis of carbocyclic cytochalasans has been developed which makes use of an intramolecular Diels–Alder reaction of a long chain 3-(2-oxotrienyl)pyrrol-2(5*H*)-one to form the cytochalasan skeleton, and has been applied to a synthesis of the naturally occurring [13]cytochalasan, proxiphomin (**1**).[1] We now describe a total synthesis of the [11]cytochalasan, cytochalasin H (**2**) using this stragegy.[2,3]



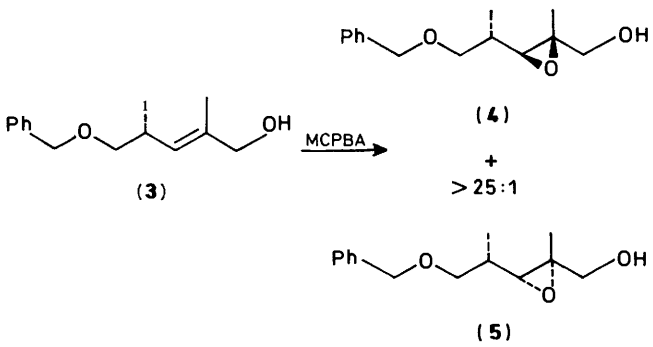
(**1**)



(**2**)

Results and Discussion

Synthesis and Cyclization of the 3-(1-*Oxotrienyl*)*pyrrol*-2-(5H)-*one* (**48**).—The method chosen for the introduction of the desired stereochemistry at C-16 and -18 was based on the stereoselective peracid epoxidation of the open chain allylic alcohol (**3**), which has been shown by Kishi to provide a > 25:1 mixture of hydroxy epoxides (**4**) and (**5**).[4] Thus treatment of



(**3**) (**4**) + > 25:1 (**5**)

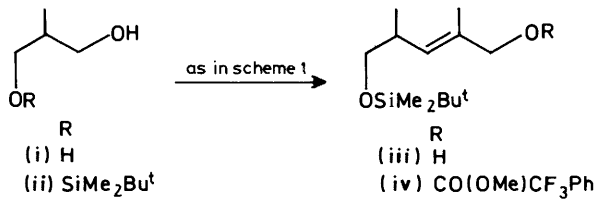
hydroxy ester (**6**) with dimethyl-t-butylsilyl chloride–imidazole gave the silylated ester (**7**) which was reduced with di-isobutylaluminium hydride to provide alcohol (**8**). Swern oxidation and condensation of aldehyde (**9**) with the ethoxycarbonylphosphorane (**10**) gave the α,β-unsaturated ester (**11**) (73%), which was reduced using lithium aluminium hydride to allylic alcohol (**12**), the optical purity of which was checked by conversion into the Mosher's ester (**13**) (Scheme 1) and found to correspond to an e.e. of at least 95‡. Epoxidation of the allylic alcohol (**12**) with *m*-chloroperoxybenzoic acid then gave a single epoxide which was homogeneous by high-field n.m.r., and which was identified as the desired isomer (**14**) by analogy with the work of Kishi. Reduction of the epoxide (**14**) using lithium aluminium hydride was regioselective, and gave the diol (**15**) (65%). The functionality and stereochemistry of this diol corresponds to that of the C-15–C-19 fragment of cytochalasin H (**2**).

The next phase of the synthesis involved chain extension of the diol to incorporate the ester and trienyl groups required for pyrrolidinone acylation and Diels–Alder cyclization. Preliminary attempts to achieve this using the epoxide (**17**), prepared from diol (**15**) by cyclization of the toluene-*p*-sulphonate (**16**), were unsuccessful, no epoxide ring opened products being obtained using dilithiated acetic acid (50 °C, 2 days) or various acetic acid enolate equivalents. However, selective oxidation of the diol (**15**) using *N*-chlorosuccinimide–dimethyl sulphide[5] gave an excellent yield of hydroxy aldehyde (**18**), which on treatment with the methoxycarbonylphosphorane (**19**) gave the α,β-unsaturated hydroxy ester (**20**) (65%).

The next step was to deprotect the primary alcohol followed by chain extension using a Wittig reagent. However, treatment of the dimethyl-t-butylsilyl ether (**20**) with anhydrous tetrabutylammonium fluoride in tetrahydrofuran did not give the desired alcohol. Instead two products were isolated, both of which had lost the double bond, and which were identified as the bicyclic lactone (**24**) together with hydroxy ester (**25**); (**24**):(**25**) = 4:1. The cyclic products (**24**) and (**25**) must have been formed during the attempted deprotection by base-catalysed conjugate addition of the primary alcohol onto the electron deficient α,β-unsaturated ester, and so acidic conditions for the silyl deprotection were investigated. It was found that acid-catalysed deprotection using Dowex 50W-X8 in methanol

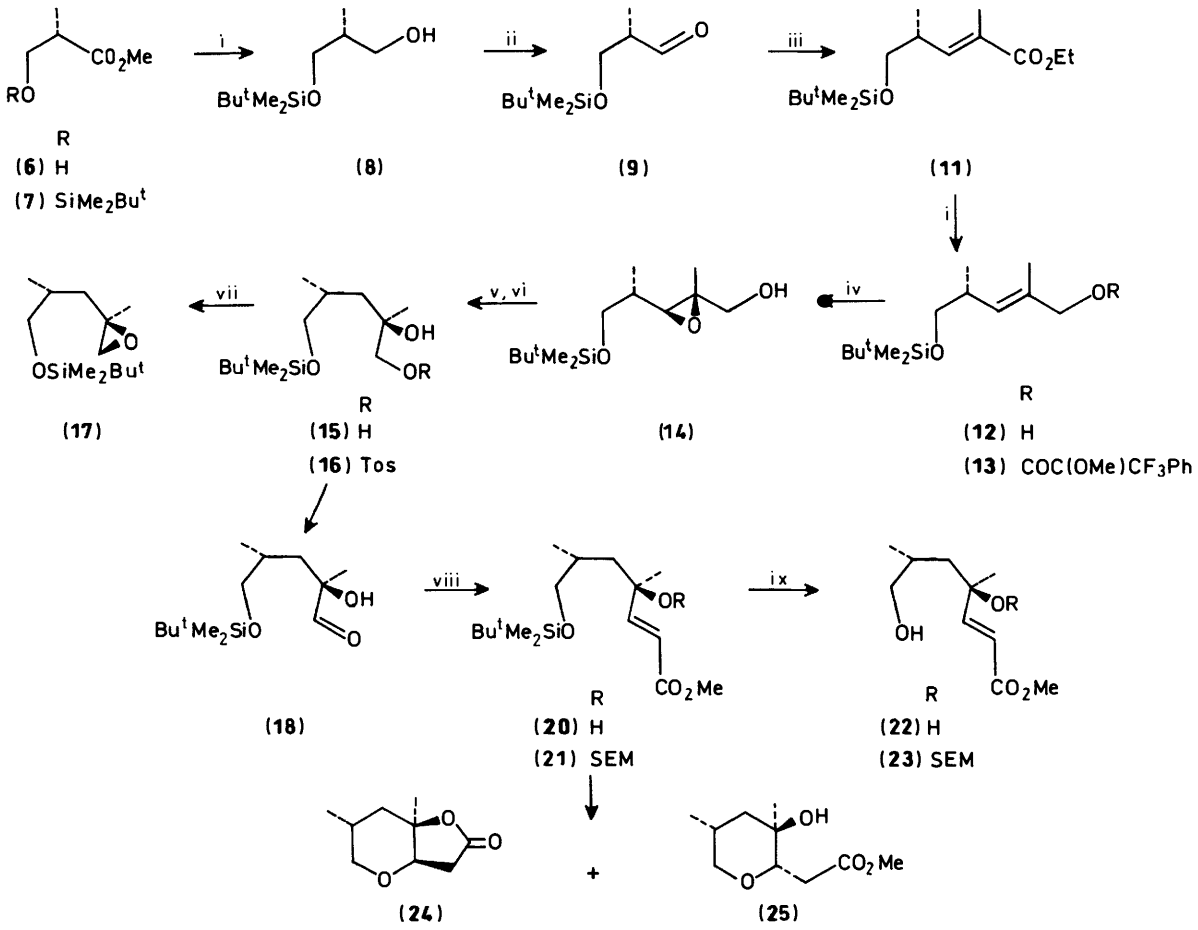
† *Present address:* Department of Chemistry, The Victoria University of Manchester, Manchester, M13 9PL.

‡ The ^{1}H n.m.r. of the Mosher's derivative from the optically active alcohol (**12**) was compared with that obtained from the racemic material (**iii**) prepared from the achiral diol (**i**) by monosilylation (Bu^tMe_2SiCl, imidazole, 20 °C; 95%), and conversion of the monosilyl ether (**ii**) into the allylic alcohol (**iii**) as outlined in the text.



R
(i) H
(ii) $SiMe_2Bu^t$

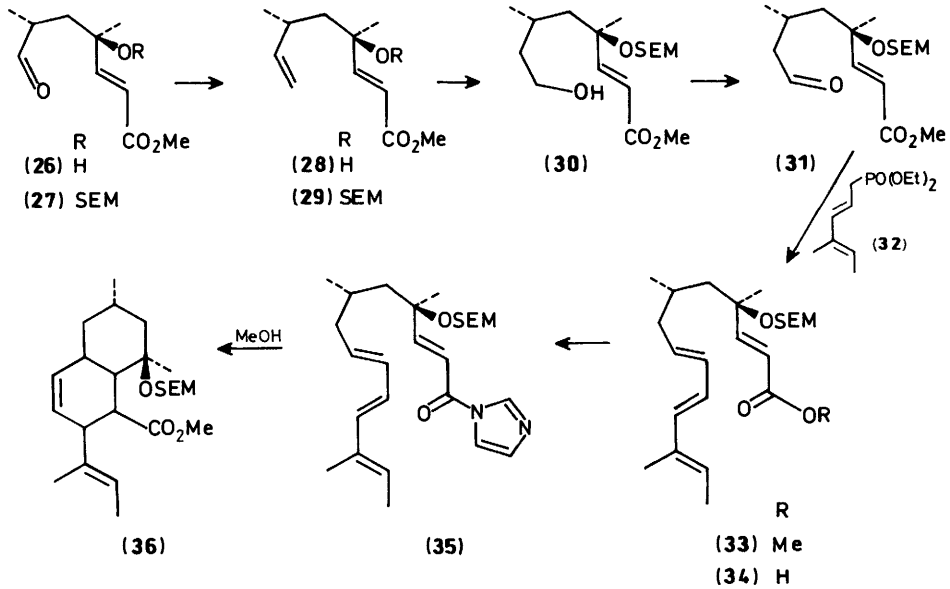
R
(iii) H
(iv) CO(OMe)CF_3Ph



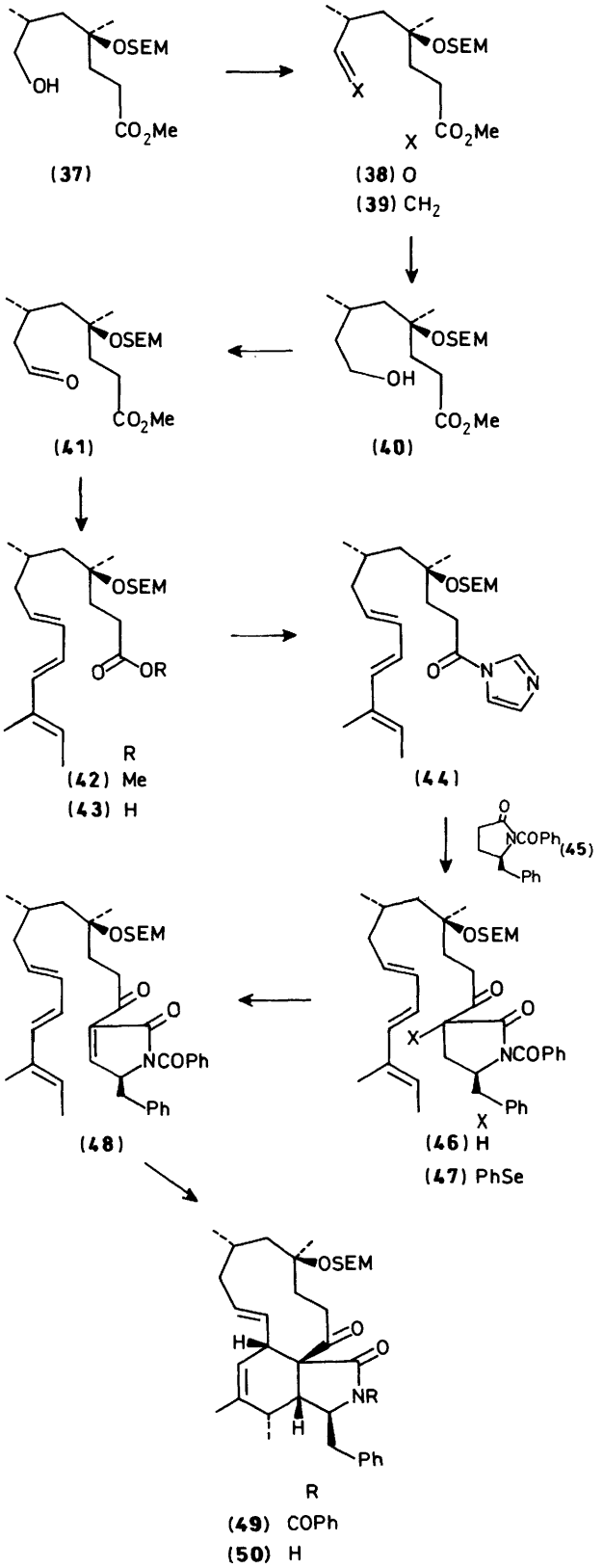
Scheme 1. *Reagents and conditions:* i, DIBAL; ii, Swern; iii, $Ph_3P{=}CMeCO_2Et$ (**10**); iv, MCPBA; v, $LiAlH_4$; vi, TosCl (Tos = *p*-$MeC_6H_4SO_2$); vii, base; viii, $Ph_3P{=}CHCO_2Me$ (**19**); ix, Dowex. SEM = $CH_2OCH_2CH_2SiMe_3$

at room temperature was effective, and the desired alcohol (**22**) was isolated in good yield (85%).

Selective oxidation of the diol (**22**) gave the aldehyde (**26**) but Wittig reactions of this with methylenetriphenylphosphorane were inefficient and gave only modest yields (30%) of diene (**28**). It was decided to protect the tertiary alcohol, and this was effected at the dimethyl-t-butylsilyl ether stage by treatment with (2-trimethylsilylethoxy)methyl chloride (SEM Cl) which gave the bis-protected diol (**21**) (89%).[6] Treatment with the Dowex resin again cleanly removed the dimethyl-t-butylsilyl group, and gave the primary alcohol (**23**) (75%), which was oxidized to the aldehyde (**27**) under Swern conditions, and



Scheme 2.



Scheme 3.

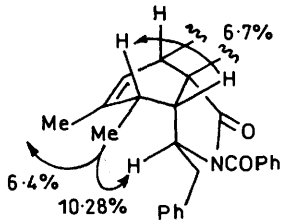


Figure. N.O.e. data for adduct (49)

condensed with methylenetriphenylphosphorane to provide the SEM diene (29) (65%). Regioselective hydroboration–oxidation using 9-bicycloboranonane gave the hydroxy ester (30) (83%) ready for conversion into the triene for the Diels–Alder step (Scheme 2).

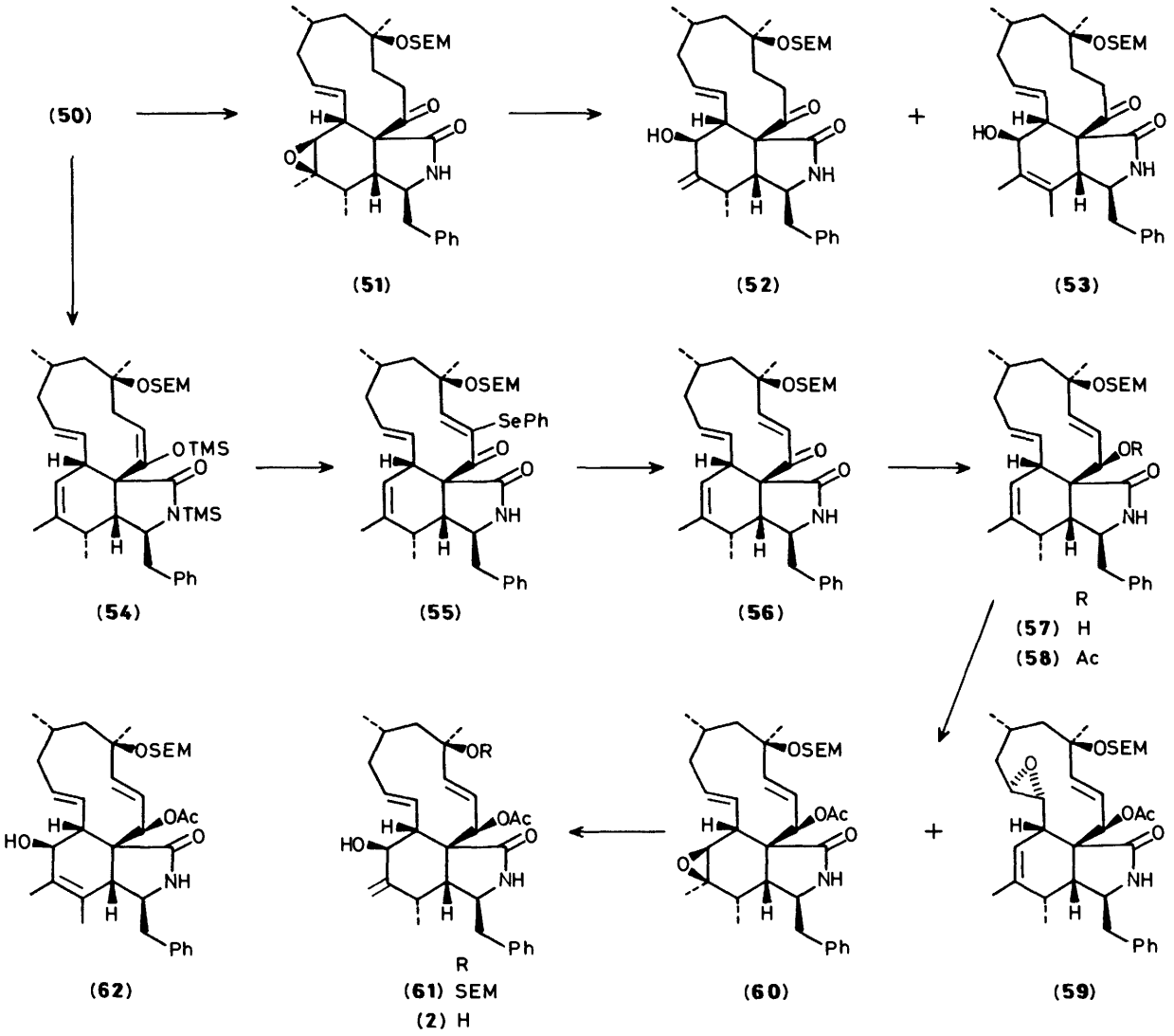
Alcohol (30) was then oxidized to the aldehyde (31), and the aldehyde condensed with the dienylphosphonate (32), using the conditions developed previously,[7] to give the (*E*,*E*,*E*)-triene (33) (48%). Ester hydrolysis gave the acid (34) which was treated with 1,1′-carbonyldi-imidazole. However, this did not give the desired imidazolyltetraene (35). Instead a complex mixture of products was obtained which, after treatment with methanol, gave a methyl ester tentatively identified as the bicyclic ester (36) on the basis of its n.m.r. spectrum. Although this product was not fully characterized or its stereochemistry established, its formation suggested that the imidazolyltetraene (35) is unstable with respect to an undesired intramolecular Diels–Alder reaction. Rather than investigate this process is more detail, it was decided to remove the C-2–C-3 double bond, which would then have to be reintroduced at the end of the synthesis.

Hydrogenation of the unsaturated hydroxy ester (23) gave the saturated ester (37) (96%) which, after oxidation to aldehyde (38), Wittig coupling with methylenetriphenylphosphorane, and hydroboration, gave the alcohol (40) (Scheme 3). This was oxidized to the aldehyde (41) using a Swern oxidation, and coupling with the dienylphosphonate (32) under the usual conditions[7] gave the (*E*,*E*,*E*)-triene (42) which was isolated in good yield (75—87%) after chromatography on base washed silica. Ester hydrolysis then gave the acid (43), and treatment with 1,1′-carbonyldi-imidazole gave the imidazolyl trienone (44).

Conversion of the imidazolyltrienone (44) into the Diels–Alder precursor was carried out using procedures developed previously.[7] Thus coupling with the benzoyl pyrrolidinone (45) was achieved using lithium hexamethyldisilazide as base, and the 3-(1-oxotrienyl)pyrrolidinone (46) converted into the corresponding pyrrol-2-(5*H*)-one (48) *via* phenylselenation–oxidation elimination. No attempts were made to isolate the 3-(1-oxotrienyl)pyrrol-2-(5*H*)-one (48) since earlier work had indicated that such compounds polymerized very easily. Instead the solution of pyrrol-2(5*H*)-one was diluted with anhydrous toluene, and heated at 100 °C for 5 h. Flash chromatography of the product gave a single Diels–Alder product [38% based on selenide (47)] which was identified as the desired adduct (49) using ^{1}H n.m.r. data including the n.O.e. difference data outlined in the Figure. Minor products (< 5%) were detected in the crude reaction mixtures from these cyclizations, but were not isolated or characterized.

The isolation of a single Diels–Alder product from the cyclization of pyrrol-2(5*H*)-one (48) is consistent with the stereoselective formation of [11]cytochalasans during model intramolecular Diels–Alder reactions, and contrasts with the non-stereoselective formation of [13]cytochalasans under these conditions.[1] As before the isolation of essentially a single diastereoisomer implies that both of the chiral components used in the synthesis of the Diels–Alder precursor had been of high optical purity.

The 1-benzoyl Diels–Alder product (49) was treated with potassium hydroxide in methanol to give the corresponding NH compound (50) (90%). The conversion of this into cytochalasin H (2) was now examined.

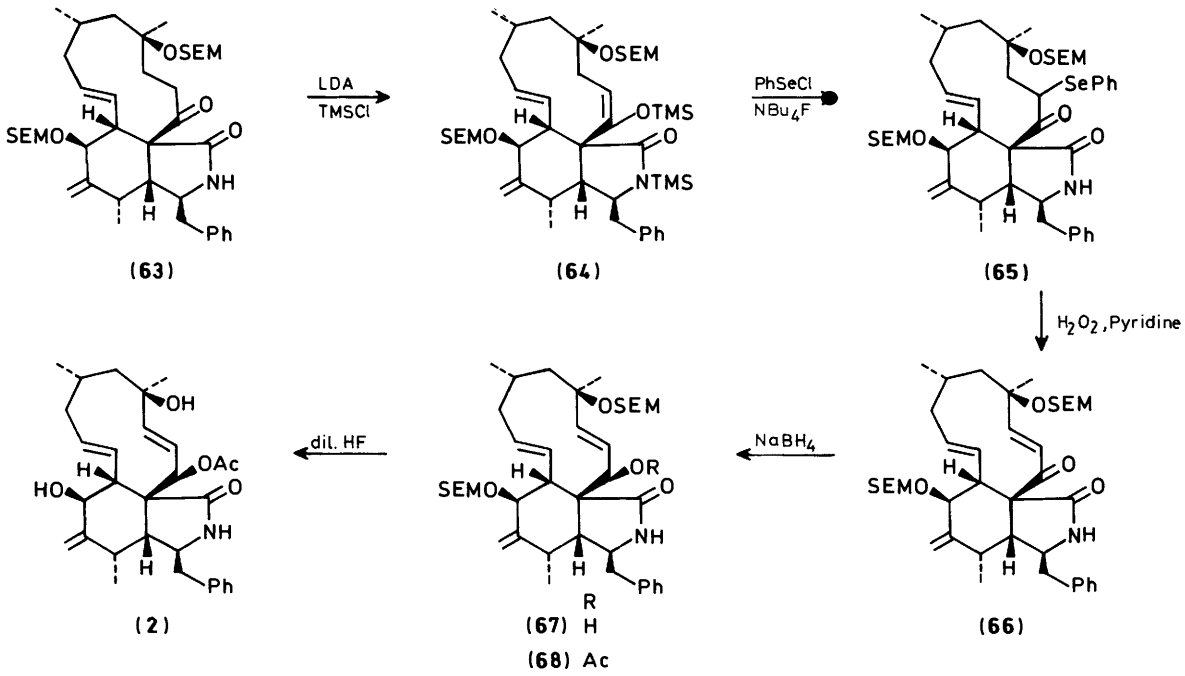


Scheme 4.

Modification of the Cyclohexene Ring.—Epoxidation of the 1-debenzoylated Diels–Alder adduct (**50**) using *m*-chloroperoxybenzoic acid in dichloromethane at −20 °C, was found to be both regio- and stereo-selective, and gave a single product identified as the epoxide (**51**) (Scheme 4). The regioselectivity of the epoxidation was apparent from the ^{1}H n.m.r. spectrum of the product which clearly showed the loss of the C-6–C-7 double bond. The stereochemistry of epoxidation was assumed to be as shown since molecular models indicated that the β-face of the C-6–C-7 double bond was much more accessible for attack. The epoxide (**51**) was then treated with aluminium isopropoxide[8] at 125 °C for several hours to effect isomerization into the allylic alcohols (**52**) and (**53**). The desired *exo*cyclic isomer (**52**) (60%) was the major product and was obtained together with a small amount of the *endo*cyclic isomer (**53**) (20%), the two products being separated by chromatography.

Synthesis of Cytochalasin H (**2**).—Having developed a procedure for the introduction of the methylenecyclohexanol fragment, attention was directed towards modification of the C-19–C-21 fragment of the macrocyclic ring. Treatment of the 1-debenzoylated Diels–Alder adduct (**50**) with lithium diisopropylamide and trimethylsilyl chloride gave the silyl enol ether (**54**), which with a slight excess of benzeneselenenyl chloride and tetrabutylammonium fluoride gave phenylseleno ketone (**55**) (Scheme 4). Selenoxide elimination was then effected using hydrogen peroxide in pyridine and gave the (*E*)-α,β-unsaturated ketone (**56**) which was reduced with sodium borohydride to give the required alcohol (**57**). This reduction was highly stereoselective; only alcohol (**57**) with the required configuration at C-21 was isolated. This stereoselectivity, which was crucial for a successful synthesis of cytochalasin H (**2**), has been observed in the aspochalasan series,[9] and can be explained by the shielding of one face of the carbonyl group by the 11-membered ring. The known preference for the reduction of an α,β-unsaturated ketone to take place from a direction orthogonal to the plane of the π-system also favoured formation of the observed product. The alcohol (**57**) was then acetylated using acetic anhydride in pyridine to give acetate (**58**).

All that now remained to complete a synthesis of cytochalasin H (**2**), was the conversion of the cyclohexene fragment of acetate (**58**) into a methylenecyclohexanol unit using the chemistry developed for the preparation of the allylic alcohol (**52**). However, peracid epoxidation of the trienyl acetate (**58**) was not regioselective. Two epoxides were obtained which were identified as the desired isomer (**60**) together with the regioisomer (**59**), formed by epoxidation of the disubstituted



Scheme 5.

C-13–C-14 double bond, (**59**):(**60**) = 65:35. The regioselectivity of this epoxidation was disappointing especially in view of the regioselective epoxidation of the dienyl ketone (**50**). However, the two epoxides could be separated, and treatment of the cyclohexene epoxide (**60**) with aluminium isopropoxide at 125 °C effected epoxide rearrangement and gave the *exo*cyclic allylic alcohol (**61**) together with a small amount of the *endo*cyclic isomer (**62**). Removal of the SEM-protecting group using dilute aqueous hydrogen fluoride in aqueous acetonitrile then gave cytochalasin H (**2**), identical within experimental limits, with a sample of the natural product[10] by high-field ^1H and ^{13}C n.m.r., i.r., m.s., t.l.c., m.p., and optical rotation.

Preliminary studies were carried out to develop a synthesis of cytochalasin H which avoided the unfavourable epoxidation of the acetate (**58**). Thus protection of the methylenecyclohexanol (**52**) gave the bis-SEM ether (**63**) which was taken through to the allylic acetate (**68**) *via* phenylselenation, oxidative elimination, reduction, and acetylation (Scheme 5). Double deprotection then gave cytochalasin H(**2**) identical with the material prepared earlier.

This work completed the first synthesis of a naturally occurring [11]cytochalasan, and demonstrates the suitability of the intramolecular Diels–Alder approach for the synthesis of complex natural products in this area.

Experimental

For general experimental details see the first paper in this series.[7]

(2R)-3-(*Dimethyl-t-butylsiloxy*)-2-*methylpropan*-1-*ol* (**8**).—Imidazole (14.4 g, 0.21 mol) and dimethyl-t-butylsilyl chloride (14.4 g, 92 mmol) were added to a solution of (2*S*)-methyl 3-hydroxy-2-methylpropanoate (**6**) (10 g, 84.7 mmol) in anhydrous *N*,*N*-dimethylformamide (50 ml), and the mixture was stirred at room temperature, under a nitrogen atmosphere, for 12 h, before being poured into ether (200 ml). The ethereal solution was washed with water (2 × 200 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave (2S)-*methyl* 3-(*dimethyl-t-butylsiloxy*)-2-*methylpropanoate* (**7**) (19.8 g, 98%), a colourless oil; $[\alpha]_D^{20}$ +18.1° (*c* 4.03 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 720, 1 360, and 1 250 cm^{-1}; δ_H(60 MHz) 0.08 (6 H, s, 2 × SiMe), 0.92 (9 H, s, CMe_3), 1.18 (3 H, d, *J* 7.5 Hz, CH*Me*), 2.75 (1 H, m, C*H*Me), 3.70 (3 H, s, OMe), and 3.75 (2 H, m, OCH_2); *m*/*z* (c.i.) 233 (M^+ + 1, 100%).

A 1M solution of di-isobutylaluminium hydride in toluene (156 ml) was added to the siloxy ester (**7**) (16.5 g, 71.1 mmol) in THF (200 ml) at −78 °C under argon, and the mixture was stirred at −78 °C for 2 h, and at room temperature for 2 h. After recooling to −78 °C, methanol (20 ml) was added, followed by brine (10 ml), and the mixture was warmed to room temperature and stirred for 1 h. After drying ($MgSO_4$), the mixture was filtered through Celite, and the filtrate concentrated under reduced pressure to leave the *title compound* (**8**) (12.7 g, 87.5%), as a pale yellow oil; $[\alpha]_D^{20}$ +6.23° (*c* 0.69 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 650, 3 450, and 1 250 cm^{-1}; δ_H 0.06 and 0.07 (each 3 H, s, SiMe), 0.87 (3 H, d, *J* 7.5 Hz, CH*Me*), 0.90 (9 H, s, CMe_3), 1.93 (1 H, m, C*H*Me), 3.03 (1 H, br s, OH), 3.50—3.66 (3 H, complex m, OCH_2 + OCH), and 3.73 (1 H, dd, *J* 10, 5 Hz, OCH); *m*/*z* (c.i.) 205 (M^+ + 1, 100%).

(4R,2E)-*Ethyl* 5-(*Dimethyl-t-butylsiloxy*)-2,4-*dimethylpent*-2-*enoate* (**11**).—Dimethyl sulphoxide (7.9 ml, 140 mmol) in dichloromethane (20 ml) was added to oxalyl chloride (7.32 ml, 84 mmol) in dichloromethane (30 ml) at −60 °C under argon, and the mixture stirred for 10 min. A solution of the propanol (**8**) (14.2 g, 70 mmol) in dichloromethane (30 ml) was added slowly, and the mixture stirred for 15 min at −60 °C before Et_3N (48.6 ml, 0.35 mol) was added. After a further 15 min at −60 °C, the mixture was warmed to room temperature, and stirred for 30 min. Saturated aqueous NH_4Cl (100 ml) was added, and the mixture extracted with ether (2 × 100 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave (2S)-3-(*dimethyl-t-butylsiloxy*)-2-*methylpropanal* (**9**) (13.5 g, 95%), as a pale yellow oil; $\nu_{max.}$($CHCl_3$) 2 870, 1 730, 1 260, and 1 100 cm^{-1}; δ_H 0.07 (6 H, s, 2 × SiMe), 0.90 (9 H, s, $SiCMe_3$), 1.08 (3 H, d, *J* 7.5 Hz, CH*Me*), 2.45 (1 H, m, C*H*Me), 3.70 (2 H, m, OCH_2), and 9.62 (1 H, d, *J* 1.5 Hz, CHO); *m*/*z* (e.i.) 201 (M^+ − 1, 10%), 175 (M^+ − 27, 78%), and 145 (M^+ − 57, 100%).

A solution of the propanal (**9**) (13.5 g, 66 mmol) in anhydrous benzene (80 ml) was added to a suspension of the (ethoxycarbonylethyl)triphenylphosphorane (**10**)[4] (31 g, 79 mmol) in benzene (100 ml), and the mixture heated to 70 °C for 5 h under an atmosphere of argon, before being concentrated under reduced pressure. The residue was triturated with light petroleum to precipitate out the triphenylphosphine oxide which was filtered off, and the filtrate was concentrated under reduced pressure to leave an oil which was purified by flash chromatography using ether–light petroleum as eluant (1:20) to give the *title compound* (**11**) (13.8 g, 71%), as a colourless liquid; $[\alpha]_D^{20}$ +2.06° (*c* 1.36 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 700, 1 645, 1 390, and 1 365 cm^{-1}; δ_H 0.06 and 0.07 (each 3 H, s, SiMe), 0.88 (9 H, s, $SiCMe_3$), 1.02 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.30 (3 H, t, *J* 7.5 Hz, OCH_2Me), 1.87 (3 H, d, *J* 1.5 Hz, =CMe), 2.70 (1 H, m, 4-H), 3.50 (2 H, d, *J* 7.5 Hz, OCH_2), 4.18 (2 H, m, OCH_2Me), and 5.56 (1 H, m, 3-H); *m/z* (c.i.) 304 (M^+ + 18, 100%), 287 (M^+ + 1, 68%), and 229 (M^+ − 57, 52%).

(4R,2E)-5-(*Dimethyl-t-butylsiloxy*)-2,4-*dimethylpent*-2-*en*-1-*ol* (**12**).—A solution of the pent-2-enoate (**11**) (13.8 g, 48.4 mmol) in ether (50 ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (1.84 g, 48.4 mmol) in anhydrous ether (200 ml) at 0 °C under an atmosphere of nitrogen, and the mixture stirred for 2 h. Saturated aqueous NH_4Cl (20 ml) was added cautiously with stirring, and the mixture filtered. After drying ($MgSO_4$), the filtrate was concentrated under reduced pressure, and the residue purified by flash chromatography using ether–light petroleum (1:3) as eluant to give the *title compound* (**12**) (10.4 g, 88%), as a colourless oil; $[\alpha]_D^{20}$ −11.1° (*c* 1.61 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 610, 3 440, and 1 260 cm^{-1}; δ_H 0.07 (6 H, s, 2 × SiMe), 0.87 (9 H, s, $SiCMe_3$), 0.95 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.51 (1 H, br s, OH), 1.69 (3 H, d, *J* 1.5 Hz, =CMe), 2.58 (1 H, m, 4-H), 3.37 (1 H, dd, *J* 12, 7 Hz, 5-*H*H), 3.45 (1 H, dd, *J* 12, 6 Hz, 5-H*H*), 3.97 (2 H, m, OCH_2), and 5.18 (1 H, m, 3-H); *m/z* (c.i.) 245 (M^+ + 1, 23%) and 227 (M^+ − 17, 83%).

Pyridine (50 μl) and Mosher's acid chloride (24 mg, 0.9 mmol) were added to a solution of the pentenol (**12**) (22 mg, 0.9 mmol) in carbon tetrachloride (0.1 ml), and the mixture stirred at room temperature for 12 h. The reaction mixture was then diluted with ether (20 ml), washed with ice-cold 0.1M aqueous HCl (20 ml) and saturated aqueous $NaHCO_3$ (20 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a pale yellow oil. Flash chromatography using ether–light petroleum (1:20) as eluant gave the *Mosher's ester* (**13**) (28 mg, 65%), as a colourless oil; $[\alpha]_D^{20}$ −34.7° (*c* 1.425 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 750 and 1 172 cm^{-1}; $\delta_H(C_6D_6)$ 0.01 and 0.02 (each 3 H, s, SiMe), 0.86 (3 H, d, *J* 7.5 Hz, CH*Me*), 0.95 (9 H, s, $SiCMe_3$), 1.47 (3 H, d, *J* 1.5 Hz, =CMe), 2.47 (1 H, m, 4-H), 3.30 (2 H, m, OCH_2), 3.43 (3 H, s, OMe), 4.50 (2 H, m, OCH_2), 5.18 (1 H, m, 3-H), 7.0—7.2 (3 H, m, ArH), and 7.8 (2 H, m, ArH); *m/z* (c.i.) 478 (M^+ + 18, 4%), 461 (M^+ + 1, 1%), and 227 (M^+ − 233, 100%). ^1H N.m.r. comparison of both the crude and chromatographed product with that prepared from the racemic pentenol established that the optical purity of pentenol (**12**) corresponded to an enantiomeric excess >92%.

(2R,4R)-5-(*Dimethyl-t-butylsiloxy*)-2,4-*dimethylpentane*-1,2-*diol* (**15**).—*m*-Chloroperoxybenzoic acid (5.7 g, 37.8 mmol) was added to a solution of the pentenol (**12**) (8.4 g, 34.4 mmol) in chloroform (100 ml) at −20 °C, and the mixture stirred for 2 h before being filtered. The filtate was washed with saturated aqueous $NaHCO_3$ (2 × 100 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave (2*S*,3*S*,4*S*)-5-(*dimethyl-t-butylsiloxy*)-2,4-*dimethyl*-2,3-*epoxypentan*-1-*ol* (**14**) (8.7 g, 96%) as a colourless oil used without purification; $[\alpha]_D^{20}$ −4.1° (*c* 0.39 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 580, 1 470, 1 460, 1 390, 1 255, and 1 100 cm^{-1}; δ_H 0.08 (6 H, s, 2 × SiMe), 0.92 (9 H, s, $SiCMe_3$), 1.00 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.33 (3 H, s, 2-Me), 1.58 (1 H, m, 4-H), 1.7 (1 H, br s, OH), 2.92 (1 H, d, *J* 10 Hz, 3-H), and 3.55—3.80 (4 H, m, 2 × CH_2O); *m/z* (c.i.) 261 (M^+ + 1, 100%).

A solution of the epoxide (**14**) (5 g, 19.2 mmol) in anhydrous THF (50 ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (1.46 g, 38.4 mmol) in anhydrous THF (50 ml) at 0 °C under an atmosphere of argon, and the mixture stirred for 2 h. Saturated aqueous NH_4Cl (10 ml) was cautiously added dropwise, the mixture was filtered, and the filtrate dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil. Flash chromatography on silica using ether–light petroleum (3:2) as eluant gave recovered epoxide (**14**) (0.9 g) followed by the *title compound* (**15**) (3.5 g, 69%) as an oil (Found: C, 59.7; H, 11.5. $C_{13}H_{30}O_3Si$ requires C, 59.5; H, 11.4%); $[\alpha]_D^{20}$ +1.59° (*c* 2.2 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 350, 1 390, and 1 260 cm^{-1}; δ_H 0.12 (6 H, s, 2 × SiMe), 0.91 (3 H, d, *J* 7.5 Hz, CH*Me*), 0.92 (9 H, s, $SiCMe_3$), 1.18 (3 H, s, 2-Me), 1.40 (1 H, dd, *J* 15, 2.5 Hz, 3-*H*H), 1.72 (1 H, dd, *J* 15 and 7.5 Hz, 3-H*H*), 2.00 (1 H, m, 4-H), 2.42 (1 H, br t, 1° OH), 3.30—3.47 (3 H, complex m, 1-CH_2 + 5-*H*H), 3.63 (1 H, dd, *J* 10, 5 Hz, 5-H*H*), and 4.60 (1 H, s, 3° OH); *m/z* (c.i.) 263 (M^+ + 1, 100%).

(2R,4R)-5-(*Dimethyl-t-butylsiloxy*)-2,4-*dimethyl*-1,2-*epoxypentane* (**17**).—Pyridine (0.4 ml, 2 mmol) and toluene-*p*-sulphonyl chloride (268 mg, 1.3 mmol) were added to a solution of the pentanediol (**15**) (300 mg, 1.14 mmol) in dichloromethane (4 ml) at 0 °C, and the mixture stirred at 0 °C for 1 h, warmed to room temperature, and stirred for a further 12 h before being poured into water (50 ml) and extracted into ether (2 × 50 ml). The ether extracts were dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil which was purified by flash chromatography using ether–light petroleum (2:1) as eluant to give (2R,4R)-5-(*dimethyl-t-butylsiloxy*)-2,4-*dimethyl*-1-p-*tolylsulphonyloxypentan*-2-*ol* (**16**) (462 mg, 97%) as a colourless oil (Found: M^+, 417.3219. $C_{20}H_{35}O_5SSi$ requires *M*, 417.3221); $\nu_{max.}(CHCl_3)$ 3 430, 3 320, and 1 260 cm^{-1}, δ_H 0.08 (6 H, s, 2 × SiMe), 0.90 (3 H, d, *J* 7.5 Hz, CH*Me*), 0.91 (9 H, s, $SiCMe_3$), 1.16 (3 H, s, 2-Me), 1.56 (2 H, m, 3-CH_2), 2.00 (1 H, m, 4-H), 2.47 (3 H, s, ArMe), 3.27 (1 H, t, *J* 10 Hz, 5-*H*H), 3.79 (1 H, dd, *J* 10, 5 Hz, 5-H*H*), 3.78 and 3.80 (each 1 H, d, *J* 10 Hz, 1-H), 4.61 (1 H, s, OH), and 7.29 and 7.8 (each 2 H, d, *J* 10 Hz, ArH); *m/z* (c.i.) 417 (M^+ + 1, 10%).

A solution of the toluene-*p*-sulphonate (**16**) (1.54 g, 3.82 mmol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (1.83 g of a 50% dispersion in oil, washed with light petroleum, 38.2 mmol) in THF (10 ml) under argon, and the mixture stirred for 12 h before being cautiously added to ice-cold saturated aqueous NH_4Cl (50 ml), and extracted into ether (2 × 50 ml). The ether extracts were dried ($MgSO_4$), and concentrated under reduced pressure, to leave an oil which, after flash chromatography using ether–light petroleum (1:10) as eluant, gave the *title compound* (**17**) (0.74 g, 74%) as a colourless liquid (Found: C, 64.0; H, 11.35. $C_{13}H_{28}O_3Si$ requires C, 63.9; H, 11.5%); $[\alpha]_D^{20}$ −2.65° (*c* 0.85 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 010, 1 475, 1 468, 1 390, 1 260, 1 190, and 840 cm^{-1}; δ_H 0.06 (6 H, s, 2 × SiMe), 0.87 (9 H, s, $SiCMe_3$), 0.90 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.05 (1 H, dd, *J* 15, 10 Hz, 3-*H*H), 1.33 (3 H, s, 2-Me), 1.81 (1 H, m, 4-H), 1.92 (1 H, dd, *J* 15 and 5 Hz, 3-H*H*), 2.62 (2 H, s, 1-CH_2), and 3.38 and 3.46 (each 1 H, dd, *J* 11, 6 Hz, 5-H); *m/z* (c.i.) 245 (M^+ + 1, 43%).

(2R,4R)-5-(*Dimethyl-t-butylsiloxy*)-2-*hydroxy*-2,4-*dimethylpentanal* (**18**).—Dimethyl sulphide (4.02 ml, 37 mmol) was added to *N*-chlorosuccinimide (4.9 g, 36.4 mmol) in toluene (20 ml) at −20 °C under an atmosphere of argon, and the mixture stirred for 30 min.[5] The pentanediol (**15**) (4.8 g, 18.2 mmol) in ether (15 ml) was then added, and the mixture stirred for 2 h at

−20 °C, before the addition of triethylamine (7.6 ml, 54.6 mmol). After being stirred for 30 min, the reaction mixture was warmed to room temperature, and poured into saturated aqueous NH_4Cl (100 ml). Ether extraction and flash chromatography using ether–light petroleum (1:3) as eluant gave the *title compound* (**18**) (3.6 g, 75%) as a colourless oil (Found: M^+, 260.1357. $C_{13}H_{28}O_3$ requires M, 260.1361); $[\alpha]_D^{20}$ 9.2° (*c* 1.25 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 350, 3 030, 1 733, 1 260, 1 070, and 840 cm^{-1}; δ_H 0.08 (6 H, s, 2 × SiMe), 0.91 (3 H, d, *J* 7.5 Hz, C*Me*), 0.92 (9 H, s, $SiCMe_3$), 1.24 (3 H, s, 2-Me), 1.59 (1 H, dd, *J* 15, 5.5 Hz, 3-*H*H), 1.80 (1 H, m, 3-H*H*), 1.90 (1 H, m, 4-H), 3.27 (1 H, dd, *J* 11, 12 Hz, 5-H*H*), 3.50 (1 H, dd, *J* 12, 5 Hz, 5-H*H*), 4.50 (1 H, s, OH), and 9.56 (1 H, s, CHO); *m/z* 261 (M^+ + 1, 100%).

(4R,6R,2E)-*Methyl* 7-(*Dimethyl-t-butylsiloxy*)-4-*hydroxy*-4,6-*dimethylhept*-2-*enoate* (**20**).—A solution of the hydroxypentanal (**18**) (9.5 g, 36.3 mmol) in anhydrous benzene (50 ml) was added to a suspension of (methoxycarbonylmethylene)triphenylphosphorane (**19**) (16 g, 43.5 mmol) in anhydrous benzene (200 ml), and the mixture heated at 80 °C for 6 h under an atmosphere of argon. Concentration under reduced pressure gave a residue which was triturated with light petroleum and the precipitated triphenylphosphine oxide filtered off. The filtrate was concentrated under reduced pressure, and the residual oil purified by flash chromatography using ether–light petroleum (1:3) as eluant to give the *title compound* (**20**) (7.6 g, 63%), as a pale yellow viscous oil (Found: C, 60.9; H, 10.15. $C_{16}H_{32}O_4Si$ requires C, 60.75; H, 10.1%); $[\alpha]_D^{20}$ +26° (*c* 1.55 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 360, 1 720, 1 660, 1 440, 1 310, 1 290, 910, and 840 cm^{-1}; δ_H 0.08 (6 H, s, 2 × SiMe), 0.91 (3 H, d, *J* 7.5 Hz, CH*Me*), 0.92 (9 H, s, $SiCMe_3$), 1.22 (3 H, s, 4-Me), 1.60 (2 H, m, 5-CH_2), 2.00 (1 H, m, 6-H), 3.22 (1 H, t, *J* 10 Hz, 7-*H*H), 3.62 (1 H, dd, *J* 10, 4 Hz, 7-H*H*), 4.73 (3 H, s, OMe), 4.38 (1 H, s, OH), and 6.1 and 6.96 (each 1 H, d, *J* 15 Hz, vinylic H); *m/z* (c.i.) 317 (M^+ + 1, 100%).

Attempted Fluoride Induced Desilylation of Methyl Ester (**20**).—A solution of tetrabutylammonium fluoride in THF (1M, 0.2 ml) and potassium fluoride dihydrate (45 mg, 0.48 mmol) was added to a solution of the silylated methyl ester (**20**) (50 mg, 0.16 mmol) in anhydrous THF (0.3 ml), and the mixture stirred at room temperature for 4 h, before being diluted with ether (40 ml), washed with water (2 × 30 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was separated into two components by flash chromatography using ether–light petroleum (2:1) as eluant. The less polar fraction was identified as (1R,4R,6R)-4,6-*dimethyl*-2,7-*dioxabicyclo*-[4.3.0]*nonan*-8-*one* (**24**) (25 mg, 63%); $[\alpha]_D^{20}$ +40.1° (*c* 0.775 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 785, 1 288, 1 200, 1 160, 1 010, and 946 cm^{-1}; δ_H 0.88 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.20 (1 H, dd, *J* 15, 12 Hz, 5-H_{ax}), 1.29 (3 H, s, Me), 1.92 (1 H, m, 4-H), 2.25 (1 H, dt, *J* 15, 3.5 Hz, 5-H_{eq}), 2.45 (1 H, d, *J* 18 Hz, 9-H), 2.85 (1 H, dd, *J* 18, 4 Hz, 9-H), 2.93 (1 H, t, *J* 11 Hz, 3-H_{ax}), 3.75 (1 H, ddd, *J* 12, 5, 2 Hz, 3-H_{eq}), and 3.90 (1 H, d, *J* 4 Hz, 1-H); *m/z* (c.i.) 188 (M^+ + 18, 100%) and 171 (M^+ + 1, 48%). The more molar fraction was identified as (2S,3R,5R)-3-*hydroxy*-2-(*methoxycarbonylmethyl*)-3,5-*dimethyltetrahydropyran* (**25**) (7.2 mg, 19%); $[\alpha]_D^{20}$ +18.6° (*c* 0.36 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3.430, 1 720, 1 610, 1 420, and 1 280 cm^{-1}; δ_H 0.87 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.10 (3 H, s, Me), 1.30 (1 H, dd, *J* 15, 11 Hz, 4-H_{ax}), 1.70 (1 H, dd, *J* 12, 5 Hz, 4-H_{eq}), 2.03 (1 H, m, 5-*H*H), 2.50 (1 H, dd, *J* 14, 5 Hz, C-*H*H), 2.60 (1 H, br s, OH), 2.73 (1 H, dd, *J* 14, 10 Hz, C′-*H*H), 3.28 (1 H, dd, *J* 12, 10 Hz, 6-H), 3.59 (1 H, ddd, *J* 12, 6, 1 Hz, 6-H), 3.72 (3 H, s, OMe), and 4.00 (1 H, dd, *J* 10, 5 Hz, 2-H); *m/z* (c.i.) 218 (M^+ + 18, 64%) and 201 (M^+ + 1, 100%).

(4R,6R,2E)-*Methyl* 4,7-*Dihydroxy*-4,6-*dimethylhept*-2-*enoate* (**22**).—Dowex 50W-X8 (100 mg) was added to a solution of the silylated ether (**20**) (50 mg, 0.16 mmol) in methanol (0.4 ml), and the mixture was stirred at room temperature for 3 h. The resin was filtered off, the filtrate concentrated under reduced pressure, and the residue purified by flash chromatography using ether as eluant to provide the *title compound* (**22**) (33 mg, 98%), as a colourless oil (Found: M^+, 202.1679. $C_{10}H_{18}O_4$ requires M, 202.1681); $[\alpha]_D^{20}$ +26.1° (*c* 0.985 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 400, 1 725, 1 672, and 920 cm^{-1}; δ_H 0.91 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.30 (3 H, s, Me), 1.58 (2 H, m, 5-CH_2), 2.00 (1 H, m, 6-H), 3.31 (1 H, dd, *J* 12.5, 10 Hz, 7-*H*H), 3.60 (1 H, dd, *J* 12.5, 5 Hz, 7-H*H*), 4.72 (3 H, s, OMe), 4.12 (2 H, br s, 2 × OH), and 6.06 and 6.97 (each 1 H, d, *J* 15 Hz, vinylic H); *m/z* (c.i.) 220 (M^+ + 18, 50%) and 202 (M^+, 69%).

(4R,6R,2E)-*Methyl* 7-(*Dimethyl-t-butylsiloxy*)-4,6-*dimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*hept*-2-*enoate* (**21**).—Ethyl di-isopropylamine (2.84 ml, 15 mmol) and 2-trimethylsiloxymethyl chloride (1.15 ml, 6 mmol) were added to a solution of the methyl 4-hydroxyheptenoate (**20**) (1 g, 3.18 mmol) in dichloromethane (10 ml), and the solution heated under reflux under an atmosphere of argon for 2 h. After cooling, the reaction mixture was poured into light petroleum (50 ml), washed with saturated aqueous NH_4Cl (2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography using ether–light petroleum (1:6) as eluant to provide the *title compound* (**21**) (1.22 g, 86%) as a colourless oil (Found: C, 59.45; H, 10.4. $C_{22}H_{46}O_5Si_2$ requires C, 59.2; H, 10.3%); $[\alpha]_D^{20}$ +6.75° (*c* 0.74 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 720, 1 260, 1 028, and 842 cm^{-1}; δ_H 0.07 (15 H, s, 5 × SiMe), 0.82—1.00 (14 H, m, $SiCMe_3$, CH_2Si, and CH*Me*), 1.33 (3 H, s, Me), 1.41 (1 H, m, 5-*H*H), 1.73 (2 H, m, 5-H*H* and 6-H), 3.33 and 3.4 (each 1 H, dd, *J* 10, 5 Hz, 7-H), 3.63 (1 H, m, OCH_2), 3.75 (3 H, s, OMe), 4.70 and 4.72 (each 1 H, d, *J* 9 Hz, OHC*H*O), and 5.93 and 6.93 (each 1 H, d, *J* 15 Hz, vinylic H); *m/z* (c.i.) 447 (M^+ + 1, 0.3%).

(4R,6R,2E)-*Methyl* 7-*Hydroxy*-4,6-*dimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*hept*-2-*enoate* (**23**).—Dowex 50W X-8 (150 mg) was added to a solution of the silyl ether (**21**) (1.22 g, 2.74 mmol) in methanol (10 ml), and the mixture stirred at room temperature for 3 h. The resin was filtered off, and the filtrate concentrated under reduced pressure to leave an oil. Flash chromatography using ether–light petroleum (1:2) as eluant gave the *title compound* (**23**) (680 mg, 70%) as a colourless oil (Found: M^+, 332.2135. $C_{16}H_{32}O_5Si$ requires M, 332.2133); $\nu_{max.}$($CHCl_3$) 3 420, 3 020, 1 720, 1 660, 1 020, 868, and 842 cm^{-1}; δ_H 0.03 (9 H, s, 3 × SiMe), 0.93 (2 H, m, CH_2Si), 0.98 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.40 (1 H, m, 5-*H*H), 1.42 (3 H, s, 4-Me), 1.70 (1 H, dd, *J* 11, 5 Hz, 5-H*H*), 1.86 (1 H, m, 6-H), 2.62 (1 H, br s, OH), 3.58—3.73 (4 H, complex m, 2 × OCH_2), 3.76 (3 H, s, OMe), 4.70 (2 H, m, OCH_2O), and 5.93 and 6.93 (each 1 H, d, *J* 15 Hz, vinylic H); *m/z* (c.i.) 350 (M^+ + 18, 36%) and 333 (M^+ + 1, 2%).

(4S,6R)-*Methyl* 7-*Hydroxy*-4,6-*dimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*heptanoate* (**37**).—A solution of the unsaturated ester (**23**) (11.3 g, 35 mmol) in methanol (50 ml) was added to a suspension of 10% Pd–C (1 g) in methanol (100 ml) under an atmosphere of argon, and the mixture stirred for 4 h under an atmosphere of hydrogen. After the catalyst had been filtered through Celite, the filtrate was concentrated under reduced pressure to leave the *title compound* (**37**) (10.6 h, 95%) as an oil (Found: C, 57.4; H, 10.30. $C_{16}H_{34}O_5Si$ requires C, 57.5; H, 10.2%); $[\alpha]_D^{20}$ −3.13° (*c* 1.5 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 430, 1 735, 1 255, 1 020, 865, and 840 cm^{-1}; δ_H 0.03 (9 H, s, 3 × SiMe), 0.90 (2 H, t, *J* 9 Hz, CH_2Si), 0.93 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.23 (1 H, dd, *J* 14, 8 Hz, 5-*H*H), 1.30 (3 H, s, Me), 1.66—2.04 (4 H, complex m, 3-CH_2, 5-H*H*, and 6-H), 2.40 (2 H,

t, *J* 8 Hz, 2-CH_2), 3.05 (1 H, br s, OH), 3.33 (1 H, m, 7-*H*H), 3.55—3.65 (3 H, complex m, OCH_2 and 7-H*H*), 3.69 (3 H, s, OMe), and 4.72 and 4.73 (each 1 H, d, *J* 7 Hz, OHC*H*O); *m/z* (c.i.) 335 ($M^+ + 1$, 40%).

(4S,6R)-*Methyl* 4,6-*Dimethyl*-4-(2-*trimethylsilylethoxymethoxy*)-*oct*-7-*enoate* (**39**).—A solution of dimethyl sulphoxide (4.6 ml, 60.4 mmol) in dichloromethane (20 ml) was added to oxalyl chloride (3.16 ml, 36.4 mmol) in dichloromethane (30 ml) at −60 °C under argon, and the mixture stirred for 5 min. The hydroxy heptanoate (**37**) (10.5 g, 30.2 mmol) in dichloromethane (40 ml) was added slowly, followed, after 10 min, by triethylamine (21 ml, 150 mmol). After stirring at −60 °C for 15 min, the reaction mixture was warmed to room temperature, and stirred for a further 15 min before the addition of saturated aqueous NH_4Cl (50 ml). The mixture was poured into light petroleum, and the organic phase separated, washed with saturated aqueous NH_4Cl (2 × 200 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave (4S,6R)-*methyl* 6-*formyl*-4-*methyl*-4-(2-*trimethylsilylethoxymethoxy*)*heptanoate* (**38**) (9.98 g, 95%) as a pale yellow oil; $[\alpha]_D^{20}$ −6.5° (*c* 0.84 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730, 1 260, and 1 030 cm^{-1}; δ_H 0.04 (9 H, s, 3 × SiMe), 0.89 (2 H, m, CH_2Si), 1.09 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.22 (3 H, s, 4-Me), 1.33 (1 H, dd, *J* 11, 3 Hz, 5-*H*H), 1.89 (2 H, m, 3-CH_2), 2.11 (1 H, dd, *J* 12, 8 Hz, 5-H*H*), 2.41 (2 H, t, *J* 8 Hz, 2-CH_2), 2.55 (1 H, m, 6-H), 3.57 (2 H, m, OCH_2), 3.69 (3 H, s, OMe), 4.65 (2 H, m, OCH_2O), and 9.46 (1 H, d, *J* 2 Hz, CHO); *m/z* (c.i.) 350 ($M^+ + 18$, 2%) and 331 ($M^+ + 1$, 1%).

Butyl-lithium (22 ml of a 1.6M solution in hexane, 36.3 mmol) was added to a suspension of methyl triphenylphosphonium bromide (13 g, 36.3 mmol) in anhydrous THF (100 ml) at 0 °C under argon, and the mixture stirred for 3 h. The aldehyde (**38**) (10.05 g, 30.3 mmol) in THF (50 ml) was added and the mixture stirred for 2 h at 0 °C, before being poured into saturated aqueous NH_4Cl (300 ml). Ether extraction and flash chromatography using ether–light petroleum (1:7) as eluant gave the *title compound* (**39**) (7.4 g, 74%) as a colourless oil (Found: M^+, 330.2128. $C_{17}H_{34}O_4Si$ requires *M*, 330.2125); $[\alpha]_D^{20}$ −9.1° (*c* 0.605 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 040, 1 730, and 1 255 cm^{-1}; δ_H 0.05 (9 H, s, 3 × SiMe) 0.95 (2 H, m, CH_2Si), 1.06 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.25 (3 H, s, 4-Me), 1.52 (1 H, dd, *J* 15, 5 Hz, 5-*H*H), 1.65 (1 H, dd, *J* 15, 7.5 Hz, 5-H*H*), 1.92 (2 H, m, 3-CH_2), 2.33 (1 H, m, 6-H), 2.42 (2 H, t, *J* 8 Hz, 2-CH_2), 3.65 (2 H, m, OCH_2), 3.72 (3 H, s, OMe), 4.73 (2 H, s, OCH_2O), 4.95 (2 H, m, 8-CH_2), and 5.79 (1 H, m, 7-H); *m/z* (c.i.) 331 ($M^+ + 1$, 0.5%).

(4S,6S)-*Methyl* 8-*Hydroxy*-4,6-*dimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*octanoate* (**40**).—9-Bicycloboranonane in THF (67 ml, 30 mmol) was added to a solution of the octenoate (**39**) (7.4 g, 22.4 mmol) in THF (100 ml) under argon, and the mixture heated under reflux for 4 h. After cooling to 0 °C, aqueous NaOH (1M; 34 ml) and 30% hydrogen peroxide (7 ml, 66 mmol) were added, and the mixture stirred for 30 min and poured into ether (200 ml). The ether extract was washed with water (2 × 200 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was flash chromatographed using ether–light petroleum (2:1) as eluant to give the *title compound* (**40**) (5.8 g, 78%) as a colourless viscous oil (Found: M^+, 348.2130. $C_{17}H_{36}O_5Si$ requires *M*, 348.2128); $[\alpha]_D^{20}$ +25.2° (*c* 1.195 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 500, 1 740, 1 028, and 916 cm^{-1}; δ_H 0.04 (9 H, s, 3 × SiMe), 0.88 (2 H, m, CH_2Si), 1.00 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.21 (1 H, m, HC*H*), 1.27 (3 H, s, 4-Me), 1.52 (2 H, m, CH_2), 1.69 (1 H, dd, *J* 10, 5 Hz, HC*H*), 1.79—1.98 (3 H, complex m, CH_2 + 6-H), 2.23 (1 H, br s, OH), 2.38 (2 H, t, *J* 8 Hz, 2-CH_2), 3.68 (3 H, m, 2 × CH_2O), 3.69 (4 H, s, OMe), and 4.71 (2 H, m, OCH_2O); *m/z* (c.i.) 349 ($M^+ + 1$, 2%).

(4S,6S,8E,10E,12E)-*Methyl* 4,6,12-*Trimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*tetradeca*-8,10,12-*trienoate* (**42**).—Dimethyl sulphoxide (2 ml, 27.8 mmol) in dichloromethane (20 ml) was added to a solution of oxalyl chloride (1.57 ml, 16 mmol) in dichloromethane (30 ml) at −60 °C under argon. The hydroxy octanoate (**40**) (4.8 g, 13.9 mmol) in dichloromethane (20 ml) was added slowly, and the mixture stirred for 10 min before the addition of triethylamine (10 ml, 50 mmol). The reaction mixture was then stirred for 15 min at −60 °C, and at room temperature for 15 min. Saturated aqueous NH_4Cl (20 ml) was added, and the mixture poured into light petroleum (200 ml). The organic phase was separated, washed with saturated aqueous NH_4Cl (2 × 200 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil. Flash chromatography using ether–light petroleum (1:2) as eluant gave (4S,6R)-*methyl* 7-*formyl*-4,6-*dimethyl*-4-(2-*trimethylsilylethoxymethoxy*)-*heptanoate* (**41**) (4.1 g, 85%) as a colourless oil; $[\alpha]_D^{20}$ +13.2° (*c* 1.20 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730 and 1 030 cm^{-1}; δ_H 0.04 (9 H, s, 3 × SiMe), 0.91 (2 H, m, CH_2Si), 1.03 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.25 (3 H, s, 4-Me), 1.27 (1 H, dd, *J* 14, 5 Hz, 5-H*H*), 1.56 (1 H, dd, *J* 15, 5 Hz, 5-H*H*), 1.89 (2 H, m, 3-CH_2), 2.24—2.44 (4 H, complex m, 2-CH_2, 6-H, and 7-*H*H), 2.61 (1 H, m, 7-H*H*), 3.61 (2 H, m, OCH_2), 3.68 (3 H, s, OMe), 4.68 and 4.69 (each 1 H, d, *J* 10 Hz, OHC*H*O), and 9.74 (1 H, t, *J* 2 Hz, CHO); *m/z* (c.i.) 363 ($M^+ + 17$, 3%) and 346 ($M^+ + 1$, 2%).

Butyl-lithium in hexane (7.8 ml, 1.6M, 13.3 mmol) was added to a solution of the dienylphosphonate (**32**) (3 g, 13.2 mmol) in THF (20 ml) at −78 °C under argon, and the mixture stirred for 1 h. A pre-cooled solution of the aldehyde (**41**) (4.1 g, 11.9 mmol) was added slowly *via* cannula, and the mixture stirred for 2 h at −78 °C. Hexamethylphosphoric triamide (3.2 ml, 18 mmol) was added, and the mixture warmed to room temperature and stirred for 3 h before being poured into saturated aqueous NH_4Cl (100 ml). Ether extraction and flash chromatography using ether–light petroleum (1:6) as eluant over base-washed silica gave the *title compound* (**42**) (4.25 g, 87%) as a colourless oil (Found: M^+, 424.3316. $C_{24}H_{44}O_4Si$ requires *M*, 424.3315); $[\alpha]_D^{20}$ −20.4° (*c* 0.68 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 020, 1 735, 1 255, 1 030, and 995 cm^{-1}; δ_H 0.03 (9 H, s, 3 × SiMe), 0.88 (2 H, m, CH_2Si), 0.95 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.23 (3 H, s, 4-Me), 1.28 (2 H, m, 5-*H*H and 6-H), 1.56 (1 H, dd, *J* 15, 5 Hz, 5-H*H*), 1.75 (6 H, m, 12 + 14-Me), 1.85—2.0 (3 H, m, 3-CH_2 and 7-*H*H), 2.05 (1 H, m, 7-H*H*), 2.39 (2 H, t, *J* 8 Hz, 2-CH_2), 3.63 (2 H, m, OCH_2), 3.69 (3 H, s, OMe), 4.67 and 4.69 (each 1 H, d, *J* 9 Hz, OHC*H*O), 5.58 (2 H, m, vinylic H), and 6.10 (3 H, m, vinylic *H*); *m/z* (c.i.) 425 ($M^+ + 1$, 3%) and 309 ($M^+ - 115$, 100%).

(4S,6S,8E,10E,12E)-1-(*Imidazol*-1′-*yl*)-4,6,12-*trimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*tetradeca*-8,10,12-*trien*-1-*one* (**44**).—A solution of the triene ester (**42**) (4.25 g, 10.1 mmol) in methanol (10 ml) was added slowly to sodium hydroxide (1.61 g, 40 mmol) in methanol (40 ml) containing water (1.6 ml), and the mixture stirred at room temperature for 3 h before being poured into water (50 ml). Tartaric acid (15 g, 0.1 mol) in water (50 ml) was added, and the mixture rapidly extracted with ether (4 × 100 ml) to leave (4S,6S,8E,10E,12E)-4,6,12-*trimethyl*-4-(2-*trimethylsilylethoxymethoxy*)*tetradeca*-8,10,12-*trienoic acid* (**43**) (4.0 g, 98%) as a yellow gum after concentration under reduced pressure; $[\alpha]_D^{20}$ −21.6° (*c* 0.93 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 200—3 560, 1 700, and 1 260 cm^{-1}; δ_H 0.05 (9 H, s, 3 × SiMe), 0.95 (5 H, m, CH_2Si and CH*Me*), 1.25 (3 H, s, 4-Me), 1.33 (1 H, m, 5-*H*H), 1.60 (1 H, dd, *J* 15, 5 Hz, 5-H*H*), 1.75 (6 H, m, 2 × Me), 1.78—1.93 (3 H, complex m, 3-CH_2 and 6-H), 1.93—2.23 (2 H, m, 7-CH_2), 2.47 (2 H, t, *J* 10 Hz, 2-CH_2), 3.65 (2 H, m, OCH_2), 4.71 and 4.73 (each 1 H, d, *J* 9 Hz, OHC*H*O), 5.60 (2 H, m, vinylic H), and 6.11 (3 H, m, vinylic H); *m/z* (c.i.) 428 ($M^+ + 18$, 4%) and 411 ($M^+ + 1$, 2%).

1,1′-Carbonyldi-imidazole (2.4 g, 15 mmol) was added to a solution of the triene acid (**43**) (4.0 g, 9.9 mmol) in THF (30 ml) under an atmosphere of argon, and the mixture stirred for 12 h.

The solution was then poured into ether (200 ml), and the ether extract washed with ice-cold water (2 × 200 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave the *title compound* (**44**) (4.13 g, 95%) as a pale yellow oil (Found: M^+, 460.4699. $C_{26}H_{44}N_2O_3Si$ requires M, 460.4701); $[\alpha]_D^{20}$ − 22.9° (*c* 0.81 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 745, 1 258, 1 030, and 916 cm^{-1}; δ_H 0.02 (9 H, s, 3 × SiMe), 0.87 (2 H, m, CH_2Si), 0.96 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.28 (3 H, s, 4-Me), 1.30 (1 H, dd, *J* 10, 7.5 Hz, 5-*H*H), 1.65 (1 H, dd, *J* 10, 5 Hz, 5-H*H*), 1.75 (6 H, m, 12- and 14-Me), 1.81—2.20 (5 H, complex m, 3-CH_2, 7-CH_2, and 6-H), 2.97 (2 H, m, 2-CH_2), 3.60 (2 H, m, OCH_2), 4.71 and 4.73 (each 1 H, d, *J* 9 Hz, OHC*H*O), 5.6 (2 H, m, vinylic H), 6.11 (3 H, m, vinylic H), 7.10 (1 H, d, *J* 2 Hz, 4′-H), 7.50 (1 H, s, 5′-H), and 8.22 (1 H, s, 2′-H).

(5R,4′S,6′S,8′E,10′E,12′E)-1-*Benzoyl*-5-*benzyl*-3-[4′,6′,12′-*trimethyl*-4′-(2-*trimethylsilylethoxymethoxy*)-1′-*oxotetradeca*-8′,10′,12′-*trienyl*]*pyrrolidin*-2-*one* (**46**).—A pre-cooled solution of lithium hexamethyldisilazide (22.75 mol) in THF–hexane (30 ml) was added to a solution of the 1-benzoylpyrrolidinone (**45**) (6.1 g, 22.75 mmol) in THF (20 ml) at −78 °C under an atmosphere of argon, and the mixture stirred for 1 h before being transferred using a cannula into a solution of the imidazolyl trienone (**44**) (4.13 g, 9.1 mmol) in THF (40 ml) at −78 °C under argon. After 7 h, saturated aqueous NH_4Cl was added, and the mixture allowed to warm to room temperature. Ether extraction and flash chromatography over base washed silica gave the *title compound* (**46**) (5.3 g, 87%) as an oil, a mixture of epimers at C-3 (Found: M^+, 671.5865. $C_{41}H_{57}NO_5Si$ requires M, 671.5861); $[\alpha]_D^{20}$ +31.5° (*c* 1.45 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 020, 1 740, 1 720, 1 685, 1 610, 1 290, 1 030, and 995 cm^{-1}; δ_H 0.04 (9 H, s, 3 × SiMe), 0.83—1.00 (5 H, d + overlapping m, CH*Me* and CH_2Si), 1.15 and 1.20 (each 1.5 H, s, 4′-Me), 1.15—1.35 (2 H, complex m, 5′-CH_2), 1.75 (6 H, m, 2 × Me), 1.45—2.23 (5 H, complex m, 3′-CH_2, 6′-H, and 7′-CH_2), 2.38—3.02 (4 H, complex m, 4- and 2′-CH_2), 3.27 (1 H, dd, *J* 12, 5 Hz, HC*H*), 3.56 (3 H, m, HC*H* and OCH_2), 3.73 (1 H, dd, *J* 10, 8 Hz, 3-H), 4.50—4.83 (3 H, overlapping m, OCH_2O and 5-H), 5.48—5.70 (2 H, m, vinylic H), 5.97—6.16 (3 H, m, vinylic H), and 7.20—7.68 (10 H, m, ArH); *m*/*z* (c.i.) 689 (M^+ + 18, 1%) and 672 (M^+ + 1, 0.7%).

(16S,18S)-2-*Benzoyl*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(7),13^{1}-*diene*-1,21-*dione* (**49**).—A pre-cooled solution of lithium hexamethyldisilazide (11.85 mmol) in THF–hexane (15 ml) was added to a solution of the 3-(1-oxotrienyl) pyrrolidinone (**46**) (5.3 g, 7.9 mmol) in THF (50 ml) at −78 °C under an atmosphere of argon. After stirring for 1 h, a pre-cooled solution of benzeneselenenyl chloride (2.77 g, 11.85 mmol) in THF (30 ml) was added, and the mixture stirred for 2 h. Saturated aqueous NH_4Cl (10 ml) was added, and the reaction mixture allowed to warm to room temperature. Ether extraction and flash chromatography on base washed silica using ether–light petroleum (3:1) as eluant gave (5S,4′S,6′S,8′E,10′E,12′E)-1-*benzoyl*-5-*benzyl*-3-*phenylseleno*-3-[4′,6′,12′-*trimethyl*-4′-(2-*trimethylsilylethoxymethoxy*)-1′-*oxotetradeca*-8′,10′,12′-*trienyl*]-*pyrrolidin*-2-*one* (**47**) (6.2 g, 95%) as a viscous oil, a mixture of epimers at C-3; $[\alpha]_D^{20}$ +96.5° (*c* 1.175 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730, 1 688, 1 600, 1 380, 1 350, 1 280, 1 020, and 908 cm^{-1}; δ_H 0.05 (9 H, s, 3 × SiMe), 0.83—1.00 (5 H, complex m, 6′-Me and CH_2Si), 1.0—1.3 (2 H, m, 5′-CH_2), 1.22 (3 H, s, 4′-Me), 1.74 (6 H, m, 2 × Me), 1.83—2.27 (5 H, m, complex m, 3′-CH_2, 6′-H, and 7′-CH_2), 2.47 (1 H, dd, *J* 15, 7 Hz, HC*H*), 2.60 (1 H, dd, *J* 14, 5 Hz, HC*H*), 2.68—2.95 (2 H, m, CH_2), 3.27 (2 H, m, CH_2), 3.55 (2 H, m, OCH_2), 4.34 (0.25 H, m, 5-H), 4.54 (0.75 H, m, 5-H), 4.66 (2 H, s, OCH_2O), 5.43—5.68 (2 H, m, vinylic H), 5.92—6.12 (3 H, m, vinylic H), and 7.04—7.65 (15 H, m, ArH); *m*/*z* (c.i.) 671 (M^+ − 157, 65%).

m-Chloroperoxybenzoic acid (1.42 g, 8.4 mmol) in $CDCl_3$ (50 ml) was added to a solution of the selenide (**47**) (6.2 g, 7.5 mmol) in $CDCl_3$ (300 ml) at −50 °C followed immediately by a solution of 30% hydrogen peroxide (6 ml) in water (18 ml). The mixture was stirred at −50 °C for 15 min, warmed to 0 °C, and stirred for a further 15 min, before being washed with ice-cold saturated aqueous $NaHCO_3$ (200 ml), brine (200 ml), and water (200 ml). After drying (Na_2SO_4), a small portion of the solution was examined by ^1H n.m.r. which showed the presence of the *pyrrol*-2(5H)-*one* (**48**); δ_H 5.33 (1 H, m, 5-H) and 7.96 (1 H, d, *J* 1 Hz, 4-H). The remainder of the solution was diluted with anhydrous toluene (6 l), and heated at 100 °C for 5 h under an atmosphere of argon. Concentration under reduced pressure and flash chromatography using ether–light petroleum (1:3) as eluant gave the *title compound* (**49**) (1.86 g, 37%) as an amorphous white powder (Found: C, 73.35; H, 8.2; N, 2.25%; M^+, 669.3851. $C_{41}H_{55}NO_5Si$ requires C, 73.3; H, 8.2; N, 2.1%; M, 669.3849); $[\alpha]_D^{20}$ −38.1° (*c* 0.65 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730, 1 705, 1 685, 1 600, 1 380, 1 290, 1 140, 1 100, 1 055, 1 018, and 980 cm^{-1}; δ_H(C_6D_6) 0.08 (9 H, s, 3 × SiMe), 0.43 (3 H, s, 18-Me), 0.63 (3 H, d, *J* 7.5 Hz, 11-Me), 0.98—1.10 (5 H, m, 16-Me and CH_2Si), 1.11—1.65 (4 H, m, 17- and 19-CH_2), 1.42 (3 H, s, 12-Me), 1.74 (1 H, m, 16-H), 1.85—2.25 (4 H, complex m, 5-H, 15-CH_2, 20-H), 2.85 (2 H, dd and overlapping m, HC*H*Ph and 8-H), 3.15 (1 H, dd, *J* 13, 3 Hz, *H*CHPh), 3.19 (1 H, dd, *J* 6, 2 Hz, 4-H), 3.45 (1 H, ddd, *J* 18, 10, 1 Hz, 20-H), 3.67 and 3.82 (each 1 H, dt, *J* 9, 7.5 Hz, OCH_2), 4.43 (1 H, m, 3-H), 4.75 and 4.79 (each 1 H, d, *J* 7 Hz, OHC*H*O), 5.25 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.47 (1 H br s, 7-H), 6.13 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.01—7.22 (10 H, m, ArH); *m*/*z* (c.i.) 699 (M^+, 2%).

(16S,18S)-16,18-*Dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(7),13^{1}-*diene*-1,21-*dione* (**50**).—A solution of sodium hydroxide (100 mg, 1.6 mmol) in water (0.1 ml) was added to a solution of the 2-benzoyl cytochalasan (**49**) (300 mg, 0.44 mmol) in methanol (5 ml) at 0 °C, and the solution stirred for 2 h at 0 °C. The mixture was poured into ether (100 ml), and the ethereal solution washed with water (100 ml), saturated aqueous $NaHCO_3$ (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a pale yellow solid. Flash chromatography using ether–light petroleum (1:2) as eluant gave the *title compound* (**50**) (248 mg, 98%) as an amorphous solid (Found: C, 72.45; H, 9.3; N, 2.3%; M^+, 565.3587. $C_{34}H_{51}NO_4Si$ requires C, 72.2; H, 9.0; N, 2.5%; M, 565.3587); $[\alpha]_D^{20}$ −13.4° (*c* 0.45 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 1 700, 1 600, 1 380, 1 300, 1 140, 1 100, 1 055, 1 018, and 980 cm^{-1}; δ_H 0.05 (9 H, s, 3 × SiMe), 0.95 (2 H, t, *J* 10 Hz, CH_2Si), 1.00 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.13 (3 H, s, 18-Me), 1.17 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.32 (2 H, m, 17-CH_2), 1.61—1.87 (5 H, complex m, 15-H, 16-H, 19-CH_2, 20-*H*H), 1.73 (3 H, s, 12-Me), 2.05 (1 H, m, 15-H), 2.45 (2 H, m, 5-*H* and HC*H*Ph), 2.62 (1 H, m, 8-H), 2.77 (1 H, dd, *J* 15, 5 Hz, *H*CHPh), 3.00 (1 H, dd, *J* 5, 2.5 Hz, 4-H), 3.25 (1 H, m, 3-H), 3.53—3.79 (3 H, m, OCH_2 and 20-H*H*), 4.72 and 4.79 (each 1 H, d, *J* 9 Hz, OHC*H*O), 5.3 (1 H, ddd, *J* 15, 10, 5, Hz, 14-H), 5.35 (1 H, s, NH), 5.50 (1 H, br s, 7-H), 6.17 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.08—7.32 (5 H, m, ArH); *m*/*z* (e.i.) 565 (M^+, 2%).

(6R,7S,16S,18S)-6,7-*Epoxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalas*-13^{1}-*ene*-1,21-*dione* (**51**).—The cytochalasadiene (**50**) (300 mg, 0.53 mmol) in dichloromethane (7 ml) was cooled to −20 °C, and *m*-chloroperoxybenzoic acid (91.6 mg, 0.58 mmol) in dichloromethane was added. After stirring for 1 h at −20 °C, the mixture was warmed to 0 °C and stirred for 12 h before being poured into ether (150 ml). The ether extract was washed with aqueous $NaHCO_3$ (2 × 150 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a white solid. Flash chromato-

graphy using ether as eluant gave unchanged diene (**50**) (70 mg) followed by the *title compound* (**51**) (198 mg, 65%) (Found: M^+, 581.4308. $C_{34}H_{51}NO_5Si$ requires M, 581.4306); $[\alpha]_D^{20}$ −98.05° (*c* 0.36 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 425, 1 700, 1 605, 1 380, 1 255, 1 060, 1 025, and 987 cm^{-1}; δ_H 0.07 (9 H, s, 3 × SiMe), 0.95 (2 H, t, *J* 9 Hz, CH_2Si), 0.99 and 1.01 (each 3 H, d, *J* 7.5 Hz, 11- and 16-Me), 1.22 (3 H, s, 18-Me), 1.33 (2 H, m, 17-CH_2), 1.57 (3 H, s, 12-Me), 1.62—1.83 (5 H, m, 5-H, 15-*H*H, 16-H, and 19-CH_2), 2.05 (1 H, dd, *J* 12, 5 Hz, 15-H*H*), 2.14 (1 H, dd, *J* 8, 5 Hz, 8-H), 2.50 and 2.57 (each 1 H, dd, *J* 13, 6 Hz, HC*H*Ph), 2.92 (1 H, d, *J* 6 Hz, 4-H), 3.02 (1 H, d, *J* 8 Hz, 7-H), 3.43—3.77 (4 H, m, 3-H, OCH_2, and 20-H), 4.72 and 4.79 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.30 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.80 (1 H, s, NH), 6.15 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.08—7.31 (5 H, m, ArH); *m/z* (e.i.) 581 (M^+, 2%).

Rearrangement of Epoxide (**51**).—Aluminium isopropoxide (69 mg, 0.33 mmol) was added to a solution of the epoxide (**51**) (66 mg, 0.113 mmol) in *o*-xylene (4 ml), and the mixture heated to 125 °C for 8 h under an atmosphere of argon. After cooling, the mixture was poured into ether (50 ml), and the ethereal solution washed with saturated aqueous $NaHCO_3$ (3 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography using ether as eluant gave two fractions. The less polar compound was identified as (7S,16S,18S)-7-*hydroxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-5(6),13'-*diene*-1,21-*dione* (**53**) (14 mg, 22%) (Found: C, 69.9; H, 8.85; N, 2.15. $C_{35}H_{51}NO_5Si$ requires C, 70.2; H, 8.8; N, 2.4%); $[\alpha]_D^{20}$ −50.9° (*c* 0.2 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 440, 1 710, and 1 035 cm^{-1}; δ_H 0.02 (9 H, s, 3 × SiMe), 0.83 (2 H, m, CH_2Si), 1.00 (3 H, d, *J* 7.5 Hz, 16-Me), 1.15 (3 H, s, 18-Me), 1.55 and 1.67 (each 3 H, s, 11- and 12-Me), 1.00—2.2 (10 H, m), 2.55 (2 H, d, *J* 10 Hz, CH_2Ph), 3.33—3.75 (5 H, m, 3-H, 20-H, OH, and OCH_2), 4.08 (1 H, m, 7-H), 4.73 and 4.78 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.43 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.53 (1 H, s, NH), 6.17 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.08—7.30 (5 H, m, ArH); *m/z* (c.i.) 582 (M^+ + 1, 65%). The more polar compound was identified as (7S,16S,18S)-7-*hydroxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(12),13'-*diene*-1,21-*dione* (**52**) (34 mg, 51%) (Found: C, 70.2; H, 9.4; N, 2.1%); $[\alpha]_D^{20}$ −26.5° (*c* 0.2 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 1 700, 1 250, 1 060, 1 025, and 912 cm^{-1}; δ_H 0.05 (9 H, s, 3 × SiMe), 0.93 (2 H, m, CH_2Si), 1.00 (6 H, overlapping d, *J* 7.5 Hz, 11- and 16-Me), 1.12 (3 H, s, 18-Me), 1.2—1.9 (8 H, m), 2.07 (1 H, m, 15-H), 2.47 (2 H, m, 5-H and HC*H*Ph), 2.67 (1 H, dd, *J* 14, 5 Hz, *H*CHPh), 2.83 (1 H, m, 8-H), 3.07 (1 H, dd, *J* 6, 2.5 Hz, 4-H), 3.32 (1 H, m, 3-H), 3.50 (1 H, m, 20-H), 3.65 (2 H, m, OCH_2), 4.12 (1 H, d, *J* 10 Hz, 7-H), 4.71 and 4.79 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.09 (1 H, s, 12-H), 5.28 (1 H, s, 12-H), 5.47 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.49 (1 H, s, NH), 6.03 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.02—7.32 (5 H, m, ArH); *m/z* (c.i.) 582 (M^+ + 1, 65%).

(16S,18R)-16,18-*Dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(7),13',19'-*triene*-1,21-*dione* (**56**).—A solution of lithium di-isopropylamide (0.89 mmol) in THF–hexane (2 ml) was added to a solution of the cytochalasadienedione (**50**) (50 mg, 0.08 mmol) in THF (2 ml) at −78 °C under argon, and the mixture stirred for 1 h at −78 °C. Trimethylsilyl chloride (0.11 ml, 0.9 mmol) was added, and the mixture stirred for 2 h, before solid NH_4Cl (100 mg) was added, and the reaction mixture allowed to warm to room temperature. Concentration under reduced pressure left a residue which was triturated with light petroleum. The washings were filtered, and concentrated under reduced pressure to leave the *enol ether* (**54**) (62 mg, 98%) as a waxy solid; δ_H 0.05—0.32 (27 H, m, 9 × SiMe), 0.53 (3 H, d, *J* 7.5 Hz, 11-Me), 0.95 (2 H, m, CH_2Si), 1.05 (3 H, d, *J* 7.5 Hz, 16-Me), 1.29 (3 H, s, 18-Me), 1.2—1.8 (3 H, m, 16-H and 17-CH_2), 1.67 (3 H, s, 12-Me), 1.9—2.1 (3 H, m, 15-CH_2 and 19-*H*H), 2.17 (1 H, m, 5-H), 2.33 (1 H, d, *J* 7.5 Hz, 4-H), 2.47—2.60 (2 H, m, HC*H*Ph and 19-H*H*), 2.90 (1 H, dd, *J* 12, 4 Hz, *H*CHPh), 3.00 (1 H, m, 8-H), 3.33 (1 H, dd, *J* 10, 4 Hz, 3-H), 3.57 and 3.75 (each 1 H, m, OHC*H*), 4.60 (1 H, m, 20-H), 4.72 and 4.88 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.22 (1 H, ddd, *J* 15, 10, 4 Hz, 14-H), 5.53 (1 H, br s, 7-H), 5.83 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.15—7.31 (5 H, m, ArH).

Benzeneselenenyl chloride (100 mg, 0.45 mmol) in THF (1 ml) was added to a solution of the silyl enol ether (**54**) (131 mg, 0.18 mmol) in THF (2 ml) at 0 °C under an atmosphere of argon. An anhydrous solution of tetrabutylammonium fluoride in THF (0.6 mmol) was then added, and the solution stirred at 0 °C for 2 h before being poured into ether (50 ml). The ethereal extract was washed with saturated aqueous NH_4Cl (50 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil. Flash chromatography using ether–light petroleum (1:1) as eluant gave (16S,18R)-16,18-*dimethyl*-10-*phenyl*-20-*phenylseleno*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(7),13'-*diene*-1,21-*dione* (**55**) (101 mg, 78%); $[\alpha]_D^{20}$ −111.8° (*c* 0.51 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 430, 1 690, 1 025, and 911 cm^{-1}; δ_H 0.03 (9 H, s, 3 × SiMe), 0.87 (2 H, m, CH_2Si), 1.00 (3 H, d, *J* 7.5 Hz, 11-Me), 1.31 (3 H, d, *J* 7.5 Hz, 16-Me), 1.47 (3 H, s, 18-Me), 1.57 (3 H, s, 12-Me), 1.1—2.05 (7 H, m), 2.63 (1 H, m, 5-H), 2.75—3.1 (4 H, overlapping m, 8-H, 4-H, and CH_2Ph), 3.23 (1 H, m, 3-H), 3.55 (2 H, m, OCH_2), 4.62 and 4.68 (each 1 H, d, *J* 8 Hz, OHC*H*O), 4.85 (1 H, d, *J* 10 Hz, 20-H), 5.27 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.45 (1 H, s, NH), 5.53 (1 H br s, 7-H), 6.01 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.15—7.53 (10 H, m, ArH); *m/z* (c.i.) 722 (M^+ + 1, 0.5%).

Pyridine (0.2 ml) and 30% hydrogen peroxide (0.5 ml) in water (0.5 ml) were added to a solution of the selenide (**55**) (101 mg, 0.14 mmol) in dichloromethane (2 ml), and the mixture stirred at room temperature for 12 h before being poured into ether (50 ml). The ethereal solution was washed with saturated aqueous NH_4Cl (2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil. Flash chromatography using ether–light petroleum (2:1) as eluant gave the *title compound* (**56**) (48 mg, 68%) (Found: M^+, 563.3699. $C_{34}H_{49}NO_4Si$ requires M, 563.3701); $[\alpha]_D^{20}$ −101.2° (*c* 0.25 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 430, 1 695, 1 620, and 1 025 cm^{-1}; δ_H 0.08 (9 H, s, 3 × SiMe), 0.97 (2 H, t, *J* 8 Hz, CH_2Si), 1.03 (3 H, d, *J* 5 Hz, 16-Me), 1.20 (3 H, d, *J* 7.5 Hz, 11-Me), 1.40 (3 H, s, 18-Me), 1.77 (3 H, s, 12-Me), 1.6—1.95 (4 H, m), 2.01 (1 H, m, 15-H), 2.47 (2 H, m, HC*H*Ph and 5-H), 2.60 (1 H, m, 8-H), 2.80 (1 H, dd, *J* 12.5, 5 Hz, *H*CHPh), 3.20 (2 H, m, 3- and 4-H), 3.69 (2 H, m, OCH_2), 4.79 and 4.84 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.08 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.46 (1 H, s, NH), 5.49 (1 H br s, 7-H), 5.87 (1 H, dd, *J* 15, 10 Hz, 13-H), 6.89 (1 H, d, *J* 17 Hz, 20-H), 7.05 (1 H, d, *J* 17 Hz, 19-H), and 7.20—7.32 (5 H, m, ArH); *m/z* (c.i.) 564 (M^+ + 1, 42%).

(16S,18S,21R)-21-*Hydroxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(7),13',19'-*trien*-1-*one* (**57**).—Sodium borohydride (200 mg) was added to a solution of the trienedione (**56**) (262 mg, 0.47 mmol) in ethanol (5 ml) at 0 °C, and the mixture stirred for 3 h before being poured into ice-cold water. Ether extraction and flash chromatography using ether–light petroleum (2:1) as eluant gave the *title compound* (**57**) (180 mg, 72%) as a white amorphous powder (Found: M^+, 565.3710. $C_{34}H_{51}NO_4Si$ requires M, 565.3707); $[\alpha]_D^{20}$ −162° (*c* 0.35 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 3 010, 1 690, 1 600, 1 110, and 1 025 cm^{-1}; δ_H 0.06 (9 H, s, 3 × SiMe), 0.95 (2 H, m, CH_2Si), 1.00 (3 H, d, *J* 6 Hz, 16-Me), 1.27 (3 H, d, *J* 7.5 Hz, 11-Me), 1.31 (3 H, s, 18-Me), 1.6—1.85 (4 H, m), 1.73 (3 H, s, 12-Me), 2.00 (2 H, m, 5-H and 15-*H*H), 2.53 (1 H, dd, *J* 15, 5 Hz, HC*H*Ph), 2.62 (2 H, m, 4-H and 15-H*H*), 2.97 (1 H, dd, *J* 12.5, 5 Hz, *H*CHPh), 3.23 (2 H, m,

3- and 8-H), 3.70 (2 H, m, OCH_2), 4.29 (1 H, br s, 21-H), 4.71 and 4.74 (each 1 H, d, *J* 7 Hz, OHC*H*O), 5.21 (1 H, ddd, *J* 15, 10, 5, Hz, 14-H), 5.30 (1 H, br s, 7-H), 5.43 (1 H, s, NH), 5.82 (1 H, dd, *J* 15, 10 Hz, 13-H), 5.86 (1 H, d, *J* 15, Hz, 19-H), 6.03 (1 H, dd, *J* 15, 2.5 Hz, 20-H), and 7.13—7.32 (5 H, m, ArH); *m/z* (c.i.) 566 (M^+ + 1, 40%).

(16S,18R,21R)-21-*Acetoxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(7),13^t,19^t-*trien*-1-*one* (**58**).—Pyridine (0.55 ml, 7 mmol), 4-dimethylaminopyridine (43 mg, 0.35 mmol), and acetic anhydride (0.36 ml, 3.5 mmol) were added to a solution of the allylic alcohol (**57**) (195 mg, 0.35 mmol) in dichloromethane (4 ml), and the mixture stirred at room temperature for 2 h before being poured into ice-cold saturated aqueous $NaHCO_3$. Ether extraction and flash chromatography using ether–light petroleum (2:1) as eluant gave the *title compound* (**58**) (195 mg, 94%) as a white powder (Found: M^+, 607.4017. $C_{36}H_{53}NO_5Si$ requires *M*, 607.4015); $[\alpha]_D^{20}$ −141.9° (*c* 0.105 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 3 010, 1 740, 1 690, 1 380, 1 240, 1 050, 1 020, and 970 cm^{-1}; δ_H 0.05 (9 H, s, 3 × SiMe), 0.93 (2 H, m, CH_2Si), 1.02 (3 H, d, *J* 7.5 Hz, 11-Me), 1.15 (3 H, d, *J* 7.5 Hz, 16-Me), 1.32 (3 H, s, 18-Me), 1.66—1.83 (7 H, s and overlapping m, 12-Me, 15-*H*H, 16-H, and 17-CH_2), 1.99 (1 H, m, 15-H*H*), 2.20 (1 H, t, *J* 5 Hz, 4-H), 2.25 (3 H, s, Ac), 2.49 (1 H, m, 5-H), 3.43 (1 H, dd, *J* 15, 10 Hz, HC*H*Ph), 2.92 (1 H, dd, *J* 12.5, 5 Hz, *H*CHPh), 3.17 (1 H, m, 3-H), 3.27 (1 H, m, 8-H), 3.63 (2 H, m, OCH_2), 4.63 and 4.65 (each 1 H, d, *J* 7 Hz, OHC*H*O), 5.27 (1 H, m, 14-H), 5.39 (1 H, br s, 7-H), 5.40 (1 H, s, NH), 5.61 (1 H, t, *J* 2.5 Hz, 21-H), 5.71 (1 H, dd, *J* 17, 2.5 Hz, 19-H), 5.80 (1 H, dd, *J* 15, 10 Hz, 13-H), 5.83 (1 H, dd, *J* 17, 2.5 Hz, 20-H), and 7.13—7.32 (5 H, m, ArH); *m/z* (c.i.) 608 (M^+ + 1, 20%).

Epoxidation of Allylic Acetate (**58**).—A solution of *m*-chloroperoxybenzoic acid (44 mg, 0.26 mmol) in dichloromethane (1 ml) was added to a solution of the allylic acetate (**58**) (140 mg, 0.23 mmol) in dichloromethane (6 ml) at −20 °C, and the mixture stirred at −20 °C for 1 h, and at 0 °C for 12 h before being poured into ether (50 ml). The ether extract was washed with saturated aqueous $NaHCO_3$ (2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue which was separated into unchanged starting material (40 mg) and two products by flash chromatography using ether–light petroleum (2:1) then ether as eluant. The less polar product was identified as (13R,14R,16S,18R,21R)-21-*acetoxy*-13,14-*epoxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)-[11]*cytochalasa*-6(7),19^t-*dien*-1-*one* (**59**) (51 mg, 37%), an amorphous solid (Found: C, 69.5; H, 8.6; N, 2.3. $C_{36}H_{53}NO_6Si$ requires C, 69.3; H, 8.5; N, 2.2%); $[\alpha]_D^{20}$ −74° (*c* 0.315 in $CHCl_3$); $\delta_H(C_6D_6)$ 0.000 (9 H, s, 3 × SiMe), 0.67 (3 H, d, *J* 7.5 Hz, 11-Me), 0.97 (2 H, t, *J* 7.5 Hz, CH_2Si), 1.05 (3 H, d, *J* 7.5 Hz, 16-Me), 1.0—1.4 (2 H, m, 17-CH_2), 1.32 (3 H, s, 18-Me), 1.52 (3 H, s, 12-Me), 1.65 (1 H, dd, *J* 15, 5 Hz, 15-*H*H), 1.70 (1 H, dd, *J* 15, 4 Hz, 15-H*H*), 1.87 (3 H, s, Ac), 2.03—2.15 (2 H, m, 5- and 16-H), 2.20 (1 H, t, *J* 5 Hz, 4-H), 2.23—2.32 (2 H, m, HC*H*Ph and 8-H), 2.51 (1 H, dd, *J* 12.5, 5 Hz, *H*CHPh), 2.89 (2 H, m, 3- and 14-H), 3.61 and 3.79 (each 1 H, m, OHC*H*), 4.19 (1 H, dd, *J* 7.5, 2 Hz, 13-H), 4.67 and 4.73 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.45 (1 H, s, NH), 5.87 (1 H, narrow m, 21-H), 6.12 (1 H, br s, 7-H), 6.29 (1 H, dd, *J* 17, 2 Hz, 19-H), 6.54 (1 H, dd, *J* 17, 4 Hz, 20-H), and 6.81—7.20 (5 H, m, ArH); *m/z* (c.i.) 624 (M^+ + 1, 83%). The more polar product was identified as (6R,7S,16S,18R,21R)-21-*acetoxy*-6,7-*epoxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-13^t,19^t-*dien*-1-*one* (**60**) (26 mg, 19%), an amorphous solid (Found: C, 69.4; H, 8.65; N, 2.15%); $[\alpha]_D^{20}$ −58° (*c* 0.55 in $CHCl_3$); $\nu_{max.}$ 3 440, 1 750, 1 710, 1 240, and 1 030 cm^{-1}; $\delta_H(C_6D_6)$ −0.03 (9 H, s, 3 × SiMe), 0.50 (3 H, d, *J* 7.5 Hz, 11-Me), 0.95 (2 H, t, *J* 10 Hz, CH_2Si), 1.00 (3 H, s, 12-Me), 1.12 (3 H, d, *J* 7.5 Hz, 16-Me), 1.22—1.40 (2 H, m), 1.49 (3 H, s, 18-Me), 1.77—1.90 (3 H, m), 1.85 (3 H, s, Ac), 2.04 (1 H, dt, *J* 15, 5 Hz, 5-H), 2.19 (1 H, dd, *J* 5, 2 Hz, 4-H), 2.47 (2 H, m, CH_2Ph), 2.89—2.95 (2 H, m, 7- and 8-H), 3.15 (1 H, m, 3-H), 3.70 (2 H, m, OCH_2), 4.69 and 4.72 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.38 (1 H, s, NH), 5.49 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.98 (1 H, s, 21-H), 6.02 (1 H, dd, *J* 15, 2 Hz, 19-H), 6.17 (1 H, dd, *J* 15, 2.5 Hz, 20-H), 6.30 (1 H, dd, *J* 15, 10 Hz, 13-H), and 6.93—7.20 (5 H, m, ArH); *m/z* (c.i.) 624 (M^+ + 1, 3%).

Cytochalasin H (**2**).—Aluminium isopropoxide (16 mg, 0.1 mmol) was added to a solution of the epoxide (**60**) (24 mg, 0.038 mmol) in *o*-xylene (0.3 ml), and the mixture heated to 125 °C under an atmosphere of argon for 5 h before being cooled, diluted with ether (10 ml), washed with saturated aqueous $NaHCO_3$ (2 × 10 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ether–light petroleum (8:1) as eluant gave (7S,16S,18R,21R)-21-*acetoxy*-7-*hydroxy*-16,18-*dimethyl*-10-*phenyl*-18-(2-*trimethylsilylethoxymethoxy*)[11]*cytochalasa*-6(12),13^t,19^t-*trien*-1-*one* (**61**) 17 mg, 67%), an amorphous solid; $[\alpha]_D^{20}$ −23° (*c* 0.45 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 3 010, 1 740, 1 700, 1 610, 1 265, 1 100, and 1 020 cm^{-1}; δ_H 0.11 (9 H, s, 3 × SiMe), 0.93 (2 H, m, CH_2Si), 1.02 (6 H, overlapping d, 11- and 16-Me), 1.33 (3 H, s, 18-Me), 1.60—2.10 (6 H, m), 2.16 (1 H, t, *J* 7.5 Hz, 4-H), 2.27 (3 H, s, Ac), 2.67 (1 H, dd, *J* 15, 10 Hz, HC*H*Ph), 2.80 (1 H, m), 2.87 (1 H, dd, *J* 12.5, 5 Hz, *H*CHPh), 2.97 (1 H, t, *J* 10 Hz, 8-H), 3.27 (1 H, m, 3-H), 3.63 (2 H, m, OCH_2), 3.83 (1 H, d, *J* 10 Hz, 7-H), 4.63 and 4.65 (each 1 H, d, *J* 8 Hz, OHC*H*O), 5.13 (1 H, s, 12-*H*H), 5.31 (1 H, s, 12-H*H*), 5.54 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.50 (1 H, s, 21-H), 5.53 (1 H, s, NH), 5.70—5.85 (3 H, m, 13-, 19-, and 20-H), and 7.13—7.32 (5 H, m, ArH).

A 5% aqueous solution of HF (0.1 ml) was added to a solution of the SEM ether (**61**) (17 mg, 0.027 mmol) in acetonitrile (0.3 ml), and the mixture stirred at room temperature for 3 h before being poured into dichloromethane (15 ml). The dichloromethane extract was washed with water (15 ml), saturated aqueous $NaHCO_3$ (15 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a solid. Flash chromatography using ether as eluant gave *cytochalasin H* (**2**) (5.3 mg, 40%), m.p. 260—265 °C (lit.,[11] 258—263 °C; commercial sample[10] 258—263 °C); $[\alpha]_D^{20}$ −14.5° (*c* 0.265 in $CHCl_3$) [lit.,[11] −9.0° (*c* 0.5 in $CHCl_3$); commercial sample[10] −13.3° (*c* 0.075 in $CHCl_3$)]; $\nu_{max.}$($CHCl_3$) 3 430, 3 020, 1 745, 1 700, 1 380, 1 240, 1 020, and 973 cm^{-1}; δ_H 1.02 and 1.07 (each 3 H, d, *J* 7.5 Hz, 11- and 16-Me), 1.32 (3 H, s, 18-Me), 1.55 (1 H, s, OH), 1.58 (1 H, m), 1.75—1.95 (3 H, m), 2.03 (2 H, m), 2.15 (1 H, t, *J* 5 Hz, 4-H), 2.27 (3 H, s, Ac), 2.65 (1 H, dd, *J* 15, 10 Hz, HC*H*Ph), 2.80 (1 H, m, 5-H), 2.89 (1 H, dd, *J* 12.5, 5 Hz, HC*H*Ph), 2.97 (1 H, t, *J* 10 Hz, 8-H), 3.28 (1 H, m, 3-H), 3.85 (1 H, d, *J* 10 Hz, 7-H), 5.13 (1 H, s, 12-*H*H), 5.32 (1 H, s, 12-H*H*), 5.41 (1 H, m, 14-H), 5.47 (1 H, s, NH), 5.55 (1 H, dd, *J* 17, 2.5 Hz, 19-H), 5.59 (1 H, s, 21-H), 5.75 (1 H, dd, *J* 15, 10 Hz, 13-H), 5.89 (1 H, dd, *J* 17, 2.5 Hz, 20-H), and 7.12—7.30 (5 H, m, ArH); *m/z* (c.i.) 494 (M^+ + 1, 60%).

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