Cytochalasan Synthesis: An Alternative Approach to Cytochalasin H

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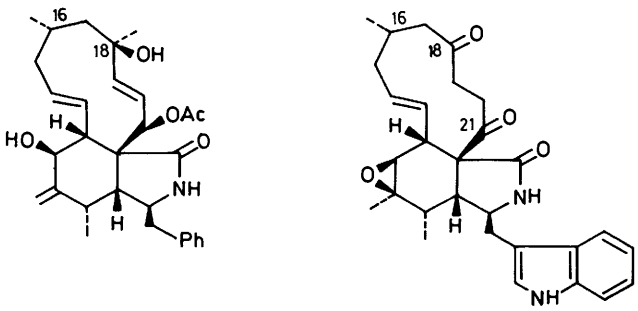
The oxo ester (**8**), from the thiazolium salt catalysed conjugate addition of (*S*)-citronellal to ethyl acrylate, has been used in a synthesis of the cytochalasa-1,18,21-trione (**3**). This reacts both regio- and stereo-selectively with methylmagnesium chloride to provide the cytochalasin H precursor (**4**).

The previous paper in this series describes a total synthesis of the naturally occurring [11]cytochalasan, cytochalasin H (**1**), which used an intramolecular Diels–Alder reaction of a long chain 3-(1-oxotrienyl)pyrrol-2(5*H*)-one to form both the 11-membered ring and the isoindolone fragment.[1] In this synthesis the chiral centres at C-16 and C-18 were introduced prior to cyclization using conventional acyclic stereochemical control. Recently it has been shown that it is possible to carry out stereoselective reactions on medium- and large-ring compounds with the conformational preferences of the rings controlling the stereochemistry.[2] Since this approach can lead to the shortening of a total synthesis, it was of interest to see whether this strategy could be applied to cytochalasan synthesis. The *X*-ray crystal structure of cytochalasin G (**2**)[3] shows that C-18 is more accessible than C-21, suggesting that it may be possible to react an organometallic reagent selectively with a cytochalasin G analogue at C-18. Moreover since one face of C-18 is shielded by the rest of the 11-membered ring, any attack on C-18 should be stereoselective and should give the cytochalasin H stereochemistry. To see whether this is so, it was decided to synthesize the phenylalanine analogue of cytochalasin G (**3**), and to examine its reactions with organometallic reagents in particular with methyl-lithium and methyl Grignard reagents, to see whether a short synthesis of the cytochalasin H precursor (**4**) could be developed.[4]



i, MeMgCl–THF gave compound (**4**) (84%). SEM = $CH_2OCH_2CH_2SiMe_3$

Results and Discussion

The chiral centre at C-16 was introduced *via* (*S*)-citronellal (**6**) which was added to ethyl acrylate using the thiazolium salt (**7**) as catalyst. This procedure for the *in situ* generation and conjugate addition of an acyl carbanion equivalent has been developed by Setter,[5] and in our hands gave a 58% yield of the oxo ester (**8**) which was isolated by distillation. Only a trace of the aldol dimer of citronellal was isolated if an excess of ethyl acrylate was used. Ketone protection and ozonolysis, with sodium borohydride reduction of the intermediate ozonide, then gave the hydroxy ester (**10**) (Scheme).

To shorten the chain length of the hydroxy ester (**10**) by one carbon, it was treated with tributylphosphine and *o*-nitrophenylselenocyanate, and the selenide (**11**) so obtained oxidized using alkaline hydrogen peroxide, to provide alkene (**12**). Ozonolysis then provided the aldehyde (**13**) which was condensed with the lithium salt of dienylphosphonate (**14**), using the conditions developed previously,[6] to give the (*E,E,E*)-trienyl ester (**15**), which in this case was found to contain a small amount, *ca.* 5%, of its (8*Z*)-isomer. Ester hydrolysis and treatment of the corresponding acid (**16**) with 1,1′-carbonyldi-imidazole gave the imidazolyl trienone (**17**) which was used to acylate the lithium salt of the 1-benzoylpyrrolidinone (**18**).[7] In this case the 3-(1-oxotrienyl) pyrrolidinone product (**19**) could not be separated from the excess of the pyrrolidinone (**18**), but treatment of this mixture with just enough base to deprotonate the more acidic 3-(1-oxotrienyl)pyrrolidinone followed by addition of benzeneselenenyl chloride, gave the 3-(1-oxotrienyl)-3-phenylselenopyrrolidinone (**20**) which was obtained pure as a mixture of C-3 epimers by flash chromatography over base washed silica.

Oxidative elimination of the phenylselenopyrrolidinone (**20**) using *m*-chloroperoxybenzoic acid–hydrogen peroxide at −50 to 0 °C gave a solution of the pyrrol-2(5*H*)-one (**21**) which was diluted with toluene and heated to 80 °C. Under these conditions Diels–Alder cyclization occurred and gave a 58% yield, based on selenide (**20**), of the desired *endo*-adduct after chromatography. The Diels–Alder adduct so obtained contained a small amount, less than 5%, of an isomer which could not be removed at this stage. However, hydrolysis of the 1-benzoyl substituent gave a good yield of the corresponding NH cytochalasan (**23**) (66%) which could be separated from a minor product, which accounted for 1—2% of the product mixture, and which was tentatively identified as the C-13–C-14

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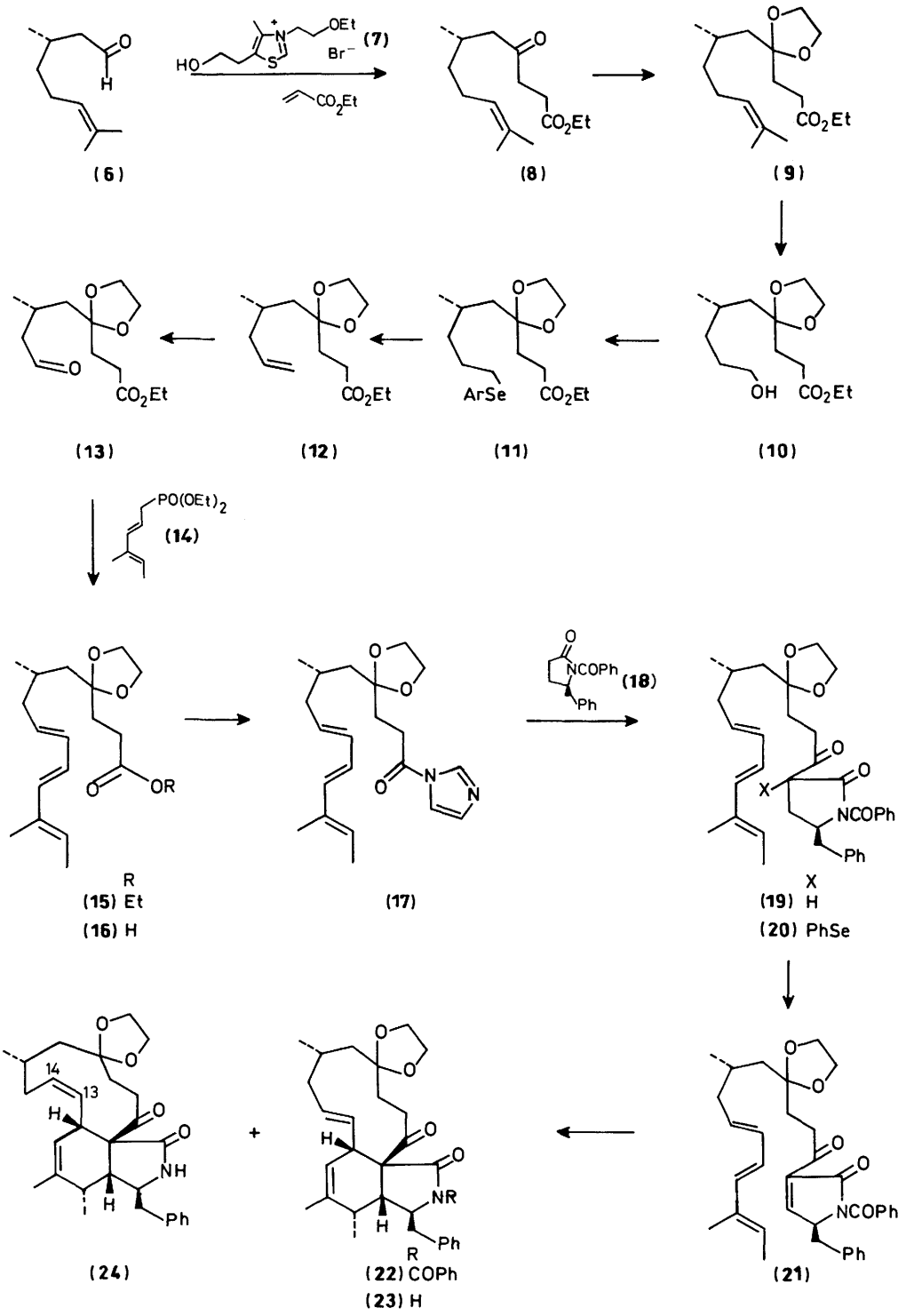

Scheme.

Z-isomer (**24**) on the basis of strong n.O.e. enhancements between 13- and 14-H. The structure and stereochemistry of the major Diels–Alder product (**22**) and its NH derivative were assigned by analogy with previous results, and were consistent with ^{1}H n.m.r. data. Hydrolysis of the ketal protecting group then gave the required trione (**3**).

Initial studies into the reactions of organometallic reagents with the trione (**3**) were carried out using solutions of methyllithium. These were found to be highly stereoselective and gave essentially a single product identified as the desired alcohol (**4**), but only in modest yield. Better results were obtained using methylmagnesium chloride in tetrahydrofuran which gave the tertiary alcohol (**4**) stereoselectively in 84% isolated yield after chromatography.

The structure of the Grignard adduct was initially assigned on the basis of spectroscopic data, and was confirmed by comparison with a sample prepared by deprotection of the 18-(2-trimethylsilylethoxymethoxy) (SEM) ether (**5**) which had

been prepared previously, and which had been converted into cytochalasin H (**1**), identical with a sample of the natural product.[1]

This work formally constitutes a second synthesis of cytochalasin H (**1**) since SEM-protection of the Grignard adduct (**4**) would provide the ether (**5**) an intermediate in the cytochalasin H synthesis.[1] Of interest, however, is the selective reaction between the dioxo pyrrolidinone (**3**) and methylmagnesium chloride which demonstrates the potential of medium-ring conformational control for cytochalasan synthesis.

Experimental

For general experimental details see the first paper in this series. (*S*)-Citronellal (**6**) was prepared by oxidation of (*S*)-citronellol using dimethyl sulphoxide–oxalyl chloride and had $[\alpha]_D^{20}$ −10.9° (*c* 0.8 in $CHCl_3$) [lit.,[8] (*R*)-enantiomer + 12.12°].

(6S)-*Ethyl* 6,10-*Dimethyl*-4-*oxoundec*-9-*enoate* (**8**).—A solution of (*S*)-citronellal (**6**) (22.5 g, 146 mmol) and ethyl acrylate (32 ml, 292 mmol) in dioxane (150 ml) was added slowly over 8 h using a syringe pump to a suspension of the thiazolium salt (**7**) (5.2 g, 17.5 mmol), triethylamine (12.2 ml, 88 mmol), and ethyl acrylate (32 ml, 292 mmol) in dioxane (200 ml) at 80 °C under an atmosphere of nitrogen. The mixture was then heated at 80 °C for 48 h and concentrated under reduced pressure to leave a residue which was dissolved in chloroform (400 ml). The chloroform solution was washed with 10% aqueous H_2SO_4 (100 ml), saturated aqueous $NaHCO_3$ (200 ml), and water (200 ml). After re-extracting the aqueous phase with chloroform (50 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil. Distillation through a Vigreux column gave the *title compound* (**8**) (21.55 g, 58%) as an oil. A sample was further purified by flash chromatography using ether–light petroleum (1:10) as eluant (Found: M^+, 154.1881. $C_{15}H_{26}O_3$ requires *M*, 154.1882); $[\alpha]_D^{20}$ −5.92° (*c* 1.44 in $CHCl_3$); $\nu_{max.}$(film) 1 720, 1 380, 1 232, and 1 180 cm^{-1}; δ_H 0.87 (3 H, d, *J* 6 Hz, CH*Me*), 1.1—1.43 (2 H, m, 7-CH_2), 1.21 (3 H, t, *J* 7.5 Hz, CH_2*Me*), 1.55 and 1.63 (each 3 H, s, vinylic Me), 1.84—2.03 (3 H, m, 6-H and 8-CH_2), 2.21 (1 H, dd, *J* 16, 8 Hz, 5-*H*H), 2.40 (1 H, dd, *J* 16, 6 Hz, 5-H*H*), 2.52 (2 H, t, *J* 6.5 Hz, 2-CH_2), 2.65 (2 H, m, 3-CH_2), 4.07 (2 H, q, *J* 7.5 Hz, C*H*$_2$Me), and 5.04 (1 H, m, vinylic H); *m*/*z* (e.i.) 254 (M^+, 6%).

(6S)-*Ethyl* 4,4-*Ethylenedioxy*-6,10-*dimethylundec*-9-*enoate* (**9**).—A solution of the ketone (**8**) (40.31 g, 0.16 mol), ethylene glycol (29.52 g, 0.48 mol), and toluene-*p*-sulphonic acid (trace) in benzene (500 ml) was heated for 16 h under reflux using a Dean-Stark trap to remove water. After cooling to room temperature, the solution was washed with saturated aqueous $NaHCO_3$ (100 ml) and water (100 ml). The combined aqueous phases were extracted with ethyl acetate (2 × 75 ml), and the combined organic extracts washed with brine (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Distillation of the residue gave the *title compound* (**9**) (33.1 g, 70%); b.p. 128—130 °C (0.3 mmHg) (Found: M^+, 298.2144. $C_{17}H_{30}O_4$ requires *M*, 298.2144); $\nu_{max.}$(film) 1 737, 1 450, 1 375, 1 180, 1 130, 1 080, and 1 040 cm^{-1}; δ_H 0.93 (3 H, d, *J* 6 Hz, CH*Me*), 1.09—1.43 (3 H, m, 6-H and 7-CH_2), 1.23 (3 H, t, *J* 7.5 Hz, CH_2*Me*), 1.38 (1 H, dd, *J* 16, 8 Hz, 5-*H*H), 1.58 and 1.69 (each 3 H, s, vinylic H), 1.56—1.69 (1 H, m, 5-H*H*), 1.88—2.03 (4 H, m, 3- and 8-CH_2), 2.33 (2 H, t, *J* 7 Hz, 2-CH_2), 3.89 (4 H, m, OCH_2CH_2O), 4.09 (2 H, q, *J* 7.5 Hz, C*H*$_2$Me), and 5.05 (1 H, m, vinylic H); *m*/*z* (e.i.) 298 (M^+, 0.5%).

(6S)-*Ethyl* 4,4-*Ethylenedioxy*-9-*hydroxy*-6-*methylnonanoate* (**10**).—A solution of the alkene (**9**) (25.08 g, 0.13 mol) in methanol–dichloromethane (1:1, 400 ml) was cooled to −70 °C and treated with ozone until a blue colour persisted (about 2 h). Sodium borohydride (6.4 g, 0.17 mol) was added, the reaction mixture stirred at −70 °C for 1 h, and then additional sodium borohydride (6.4 g, 0.17 mol) added. The reaction mixture was slowly allowed to attain room temperature, and stirred for 2 h. After concentration under reduced pressure, the residue was dissolved in ether (500 ml), and the resulting solution washed with saturated aqueous NH_4Cl (100 ml), water (100 ml), and brine (100 ml), then dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography using ethyl acetate–light petroleum (1:2) as eluant gave the *title compound* (**10**) (13.14 g, 57%) as an oil; $[\alpha]_D^{20}$ + 0.66° (*c* 1.82 in MeOH); $\nu_{max.}$(film) 3 450br, 1 740, 1 180, 1 135, and 1 040 cm^{-1}; δ_H 0.93 (3 H, d, *J* 6 Hz, CH*Me*), 1.13—1.63 (7 H, m, 5-CH_2, 6-H, 7-CH_2, and 8-CH_2), 1.22 (3 H, t, *J* 7.5 Hz, CH_2*Me*), 1.95 (2 H, t, *J* 5 Hz, 3-CH_2), 2.05 (1 H, br s, OH), 2.31 (2 H, t, *J* 5 Hz, 2-CH_2), 3.57 (2 H, t, *J* 7 Hz, 9-CH_2), 3.88 (4 H, s, OCH_2CH_2O), and 4.07 (2 H, q, *J* 7.5 Hz, C*H*$_2$Me); *m*/*z* (c.i.) 213 (M^+ − 61, 100%).

(6S)-*Ethyl* 4,4-*Ethylenedioxy*-6-*methyl*-9-(o-*nitrophenylseleno*)*nonanoate* (**11**).—Tributylphosphine (3.2 ml, 12.9 mmol was added dropwise over a period of 10 min to the alcohol (**10**) (3.04 g, 11.1 mmol) and *o*-nitrophenylselenocyanate (3.0 g, 13.2 mmol) in THF (35 ml). After stirring for 65 h, concentration under reduced pressure gave an oil which was purified by flash chromatography using ethyl acetate–light petroleum (1:4) as eluant to provide the *title compound* (**11**) (4.12 g, 81%) as an oil (Found: M^+, 459.1155. $C_{20}H_{29}NO_6{}^{80}Se$ requires *M*, 459.1160); $[\alpha]_D^{20}$ −1.98° (*c* 1.01 in MeOH); $\nu_{max.}$(film) 1 740, 1 600, 1 580, 1 525, 1 344, 1 318, and 1 050 cm^{-1}; δ_H 0.95 (3 H, d, *J* 6 Hz, CH*Me*), 1.25 (3 H, t, *J* 7.5 Hz, CH_2*Me*), 1.23—1.86 (7, H, m, 5-CH_2, 6-H, 7-CH_2, and 8-CH_2), 1.97 (2 H, m, 3-CH_2), 2.34 (2 H, t, *J* 7.5 Hz, 2-CH_2), 2.90 (2 H, t, *J* 7.5 Hz, 9-CH_2), 3.92 (4 H, br s, OCH_2CH_2O), 4.11 (2 H, q, *J* 7.5 Hz, C*H*$_2$Me), 7.28 (1 H, m, ArH), 7.5 (2 H, m, ArH), and 8.26 (1 H, m, ArH); *m*/*z* (e.i.) 459 (M^+, 1%).

(6S)-*Ethyl* 4,4-*Ethylenedioxy*-6-*methylnon*-8-*enoate* (**12**).—Alkaline hydrogen peroxide (15 ml of a solution prepared by adding 2.0 ml of 1M aqueous NaOH to 15.0 ml of 100 volume hydrogen peroxide) was added dropwise to a solution of the selenide (5.0 g, 10.9 mmol) in THF (38 ml) at 0 °C. The mixture was stirred for 5 min at 0 °C, and at room temperature for 16 h, before being diluted with ether (275 ml), and washed with brine (170 ml) and water (170 ml). The aqueous layers were re-extracted with ether (70 ml), and the combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure to leave an oil. Flash chromatography using ether–light petroleum as eluant gave the *title compound* (**12**) (2.43 g, 87%) as a pale yellow oil; $\nu_{max.}$(film) 1 740, 1 650, 1 180, and 1 040 cm^{-1}; δ_H 0.96 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.25 (3 H, t, *J* 7.1 Hz, CH_2*Me*), 1.42 (1 H, dd, *J* 14, 7 Hz, 5-*H*H), 1.62—1.73 (2 H, m, 5-H*H* and 6-H), 1.91—2.13 (4 H, m, 3- and 7-CH_2), 2.35 (2 H, m, 2-CH_2), 3.93 (4 H, br s, OCH_2CH_2O), 4.12 (2 H, q, *J* 7.1 Hz, C*H*$_2$Me), 4.97—5.03 (2 H, m, 9-CH_2), and 5.69—5.83 (1 H, m, 8-H); *m*/*z* (c.i.) 257 (M^+ + 1, 100%).

(6S,8E,10E,12E)-*Ethyl* 4,4-*Ethylenedioxy*-6,12-*dimethyltetradeca*-8,10,12-*trienoate* (**15**).—Ozone was bubbled through a mixture of alkene (**12**) (2.59 g, 10.1 mmol) and methanol (100 ml) at −72 °C for 35 min by which time the solution remained blue. Oxygen was then bubbled through for 10 min before dimethyl sulphide (10.2 ml, 139 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, and was stirred for 2 h. Concentration under reduced pressure gave a residue which was dissolved in ether, and the ether extract was washed with water (2 × 80 ml). After re-extracting

the aqueous layers with ether (10 ml), the organic phases were combined, dried ($MgSO_4$), and concentrated under reduced pressure to leave a pale yellow oil, which was purified by flash chromatography using ethyl acetate–light petroleum (2:7) as eluant to give the aldehyde (**13**). Distillation using a Kugelrohr then gave (6S)-*ethyl* 4,4-*ethylenedioxy*-7-*formyl*-6-*methylheptanoate* (**13**) (1.48 g, 66%) as a colourless oil, b.p. 140 °C (0.15 mmHg); $[\alpha]_D^{20}$ +0.83° (*c* 1.08 in $CHCl_3$); $\nu_{max.}$(film) 2 730, 1 730, 1 185, 1 140, and 1 035 cm^{-1}; δ_H 1.0 (3 H, d, *J* 6 Hz, CH*Me*), 1.24 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.57 (1 H, dd, *J* 12, 5 Hz, 5-*H*H), 1.62 (1 H, dd, *J* 12, 6 Hz, 5-H*H*), 1.90—2.06 (2 H, m), 2.21—2.37 (4 H, m), 2.51—2.62 (1 H, m, 7-H), 3.90 (4 H, s, OCH_2CH_2O), 4.09 (2 H, q, *J* 7 Hz, CH_2Me), and 9.70 (1 H, t, *J* 0.5 Hz, CHO); *m/z* (c.i.) 259 (M^+ + 1, 100%).

A solution of butyl-lithium in hexane (1.6M, 1.14 ml) was added to the phosphonate (**14**)[9] (450 mg, 1.94 mmol) in THF (8 ml) at −60 °C under an atmosphere of nitrogen, and the mixture stirred for 30 min at −60 °C and for 1 h at −30 °C. After cooling to −72 °C, the orange–brown solution was added *via* a cannula to the aldehyde (**13**) (454 mg, 1.75 mmol) in THF (6 ml) also at 72 °C, and the mixture stirred at −70 °C for 1 h. The mixture was then allowed to warm to room temperature, hexamethylphosphoric triamide (1.52 ml, 8.76 mmol) was added, and the mixture was stirred for 3 h. After diluting with ether (25 ml), the mixture was poured into saturated aqueous NH_4Cl (7 ml), and the aqueous layer extracted with ether (3 × 10 ml). The combined organic extracts were washed with water (3 × 4 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the residue on base washed silica using ether–light petroleum (1:7) as eluant gave the *title compound* (**15**) (480 mg, 81%) as an oil containing *ca.* 5% of a *Z*-isomer (Found: M^+, 336.2296. $C_{20}H_{32}O_4$ requires *M*, 336.2300); $[\alpha]_D^{20}$ −10.8° (*c* 1.88 in $CHCl_3$); $\nu_{max.}$(film) 1 740 and 990 cm^{-1}; δ_H 0.95 (3 H, d, *J* 6 Hz, CH*Me*), 1.23 (3 H, t, *J* 7.5 Hz CH_2*Me*), 1.4 (1 H, dd, *J* 15, 7 Hz, 5-*H*H), 1.61—1.84 (8, H, m, 5-H*H*, 6-H, 12-, and 14-Me), 1.90—2.02 (3 H, m, 3-CH_2 and 7-*H*H), 2.06—2.18 (1 H, m, 7-H*H*), 2.35 (2 H, m, 2-CH_2), 3.91 (4 H, narrow m, OCH_2CH_2O), 4.10 (2 H, q, *J* 7.5 Hz, CH_2Me), 5.48—5.66 (2 H, m, vinylic H), and 6.00—6.21 (3 H, m, vinylic H); *m/z* (e.i.) 336 (M^+, 8%).

(6S,8E,10E,12E)-4,4-*Ethylenedioxy*-1-(*imidazol*-1-*yl*)-6,12-*dimethyltetradeca*-8,10,12-*trien*-1-*one* (**17**).—Sodium hydroxide (2.0 g, 49.8 mmol) in water (3.25 ml) was added to a solution of the ester (**15**) (4.18 g, 12.4 mmol) in ethanol (45 ml), and the mixture stirred for 4 h at room temperature. An ice-cold solution of tartaric acid (18.6 g, 124 mmol) in water (180 ml) was added, and the aqueous phase rapidly extracted with ether (4 × 150 ml). The combined ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Azeotropic drying with benzene then gave the *acid* (**16**) (4.05 g) used without further purification; $\nu_{max.}$(film) 2 500—3 500, 1 715, and 990 cm^{-1}; δ_H 0.95 (2 H, d, *J* 6 Hz, CH*Me*), 1.32 (1 H, dd, *J* 12, 7 Hz, 5-H), 1.53—1.74 (8 H, m, 5-H, 6-H, 12-, and 14-Me), 1.95—2.02 (3 H, m, 3-CH_2 and 7-*H*H), 2.05—2.12 (1 H, m, 7-H*H*), 2.32 (2 H, t, *J* 7.5 Hz, 2-CH_2), 3.83 (4 H, narrow m, OCH_2CH_2O), 5.39—5.60 (2 H, m, vinylic H), and 5.90—6.11 (3 H, m, vinylic H); *m/z* (e.i.) 308 (M^+, 4%).

1,1′-Carbonyldi-imidazole (2.41 g, 14.9 mmol) was added to a solution of the acid (**16**) (3.82 g, 12.4 mmol) in THF (80 ml), and the mixture stirred for 16 h at room temperature before being diluted with ether (160 ml). The organic solution was washed with ice-cold water (120 ml) and brine (90 ml). After re-extracting the aqueous layers with ether (100 ml), the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Azeotropic drying with benzene then gave the *title compound* (**17**) (4.45 g, 98%) as an oil (Found: M^+, 358.2258. $C_{21}H_{30}O_3N_2$ requires *M*, 358.2256); $[\alpha]_D^{20}$ −8.2° (*c* 1.27 in $CHCl_3$); $\nu_{max.}$(film) 3 020, 1 740, 1 470, 1 318, 1 235, 1 060, and 988 cm^{-1}; δ_H 0.97 (3 H, d, *J* 6 Hz, CH*Me*), 1.37—1.45 (1 H, m, 5-*H*H), 1.62—1.82 (8 H, m, 5-H*H*, 6-H, 12-, and 14-Me), 1.87—2.17 (2 H, m, 7-CH_2), 2.17 (2 H, t, *J* 7.5 Hz, 3-CH_2), 2.88 (2 H, t, *J* 7.5 Hz, 2-CH_2), 3.8—3.98 (4 H, m, OCH_2CH_2O), 5.47—5.68 (2 H, m, vinylic H), 6.00—6.18 (3 H, m, vinylic H), and 7.05, 7.45, and 8.15 (each 1 H, br s, imidazolyl H); *m/z* (e.i.) 358 (M^+, 5%).

(5S,6′S,8′E,10′E,12′E)-1-*Benzoyl*-5-*benzyl*-3-(4′,4′-*ethylenedioxy*-6′,12′-*dimethyl*-1′-*oxotetradeca*-8′,10′,12′-*trienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**20**).—A solution of the 1-benzoyl-5-benzylpyrrolidin-2-one (**18**)[6] (6.9 g, 24.6 mmol) in THF (50 ml) pre-cooled to −72 °C was added *via* a cannula to a solution of lithium hexamethyldisilazide (24 mmol) in THF (50 ml) at −72 °C under an atmosphere of nitrogen. After stirring for 45 min a pre-cooled solution of the imidazolyl trienone (**17**) (4.2 g, 11.7 mmol) in THF (80 ml) was added, and the mixture stirred at −72 °C for 6 h, and at room temperature for 1 h. Saturated aqueous NH_4Cl (40 ml) was added, and the mixture extracted with ether (3 × 100 ml). The ethereal extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to leave an oil. Flash chromatography over base washed silica using ether–light petroleum (1:2) as eluant gave an inseparable mixture of the C-3 epimers of 3-(1-oxotrienyl) pyrrolidinone (**19**) and the starting pyrrolidinone (**18**) as an oil [7.45 g, (**19**):(**18**) = 1.9:1]; $\nu_{max.}$(film) 1 745, 1 718, 1 675, 1 604, 1 585, 1 300, and 990 cm^{-1}; δ_H 4.52—4.67 [0.3 H, m, 5-H of pyrrolidinone (**18**)] and 4.70—4.82 [0.7 H, m, 5-H of pyrrolidinone (**19**)]; *m/z* (c.i.) 570 (M^+ + 1, 28%).

A solution of the mixture of pyrrolidinones (**18**) and (**19**) (7.45 g) prepared above in THF (80 ml), pre-cooled to −72 °C, was added to a solution of lithium hexamethyldisilazide (11.0 mmol) in THF (50 ml) at −72 °C under an atmosphere of nitrogen and the mixture stirred for 1 h. A pre-cooled solution of benzeneselenenyl chloride (2.2 g, 11.6 mmol) in THF (50 ml) was added, and the mixture stirred for 4 h at −72 °C. Saturated aqueous NH_4Cl was added, and the mixture allowed to warm to room temperature when water (30 ml) was added. The aqueous layer was extracted with ether (3 × 200 ml), and the ether extracts combined, washed with brine (150 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the residue over base washed silica using ether–light petroleum (1:4) as eluant gave the *title compound* (**20**) [6.6 g, 78% based on imidazolyl trienone (**17**)] as an oil, a mixture of epimers at C-3; $\nu_{max.}$($CHCl_3$) 3 030, 3 010, 1 730, 1 690, 1 600, 1 580, 1 348, 1 278, and 990 cm^{-1}; δ_H 0.88 and 0.96 (each 1.5 H, d, *J* 6 Hz, CH*Me*), 1.13—2.18 (14 H, m, 3 × CH_2, *H*CH, 6′-H, and 2 × Me), 2.44 (0.5 H, dd, *J* 15, 7.5 Hz, HC*H*), 2.72—3.30 (4.5 H, m, 2′-CH_2, CH_2Ph, and HC*H*), 3.65—3.97 (4 H, m, OCH_2CH_2O), 4.38—4.51 (0.45 H, m, 5-H), 4.51—4.62 (0.55 H, m, 5-H), 5.37—5.77 (2 H, m, vinylic H), 5.98—6.47 (3 H, m, vinylic H), and 7.05—7.68 (15 H, m, ArH); *m/z* (f.d.) 726 (M^+ + 1).

(16S)-2-*Benzoyl*-18,18-*ethylenedioxy*-16-*methyl*-10-*phenyl*-[11]*cytochalasa*-6(7),13[1]-*diene*-1,21-*dione* (**22**).—A solution of hydrogen peroxide (100 vol, 2.9 ml, 25.6 mmol) in water (8.5 ml) was added to a solution of the selenide (**20**) (1.82 g, 2.51 mmol) in $CHCl_3$ (80 ml) under an atmosphere of argon at −50 °C. A solution of *m*-chloroperoxybenzoic acid (485 mg, 2.51 mmol) in $CHCl_3$ (55 ml) was then added, and the mixture stirred at −50 °C for 15 min and at 0 °C for 10 min before being washed with saturated aqueous $NaHCO_3$ (2 × 30 ml), brine (35 ml), and water (35 ml) to provide a solution of the tetraene (**21**); δ_H 5.3 (1 H, m, 5-H) and 7.92 (1 H, d, *J* 2 Hz, 4-H). After drying (Na_2SO_4), the chloroform solution of the tetraene (**21**) was added to degassed toluene (1.7 l) at 80 °C under an atmosphere

of nitrogen, and the mixture heated at 80 °C for 16 h. Concentration under reduced pressure gave an oil which was purified by flash chromatography using ether–chloroform–light petroleum (1:0.5:4) as eluant to give the *title compound* (**22**) (0.83 g, 58%) containing *ca.* 2% of a minor component; $[\alpha]_D^{20}$ −18.6° (*c* 0.87 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 728, 1 703, 1 670, 1 290, 1 130, and 1 072 cm^{-1}; δ_H 0.83 and 0.91 (each 3 H, d, *J* 7 Hz, CH*Me*), 1.1 (1 H, m, 17-H), 1.35 (1 H, m, 16-H), 1.75 (3 H, br s, 12-Me), 1.50—1.93 (5 H, complex m), 2.02 (1 H, m, 15-H), 2.32 (1 H, m, 5-H), 2.51 (1 H, dd, *J* 13, 9 Hz, HC*H*Ph), 2.63 (1 H, m, 8-H), 3.04 (1 H, dd, *J* 7, 2 Hz, 4-H), 3.07 (1 H, dd, *J* 13, 5 Hz, *H*CHPh), 3.39 (1 H, ddd, *J* 18, 9, 1.5 Hz, 20-H), 3.72—3.88 (4 H, m, OCH_2CH_2O), 4.22 (1 H, m, 3-H), 5.19 (1 H, ddd, *J* 16, 10, 5 Hz, 14-H), 5.42 (1 H, narrow m, 7-H), 5.93 (1 H, ddd, *J* 16, 10, 2 Hz, 13-H), and 7.0—7.5 (10 H, m, ArH); *m/z* (c.i.) 568 (M^+ + 1, 52%).

2-*Debenzoylation of the Diels–Alder Adducts.*—A solution of the Diels–Alder product (**22**) (2.20 g, 3.88 mmol) in methanol (30 ml) was added to a solution of sodium hydroxide (3.1 g, 77.6 mmol) in methanol (45 ml) containing water (3.5 ml), and the mixture stirred for 2½ h before being poured into water (250 ml) and extracted into ether (3 × 250 ml). The combined ether extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil. Flash chromatography using ethyl acetate–light petroleum (1:2) as eluant gave two components. The less polar component was tentatively identified as (16S)-18,18-*ethylenedioxy*-16-*methyl*-10-*phenyl*[11]*cytochalasa*-6(7),13^c-*diene*-1,21-*dione* (**24**) (9 mg, 5%), an oil (Found: M^+, 463.2725. $C_{29}H_{37}NO_4$ requires *M*, 463.2722); $\nu_{max.}(CHCl_3)$ 3 410, 1 695, and 695 cm^{-1}; δ_H 1.03 (3 H, d, *J* 7 Hz, 16-Me), 1.35 (3 H, d, *J* 7 Hz, 11-Me), 1.55—1.95 (4 H, m), 1.80 (3 H, br s, 12-Me), 2.00 (1 H, dd, *J* 15, 13 Hz, 15-H), 2.12—2.25 (2 H, m), 2.40—2.55 (2 H, m), 2.45 (1 H, dd, *J* 14, 9 Hz, HC*H*Ph), 3.05 (1 H, dd, *J* 14, 4 Hz, *H*CHPh), 3.15—3.27 (2 H, m, 3- and 8-H), 3.30 (1 H, dd, *J* 6, 5 Hz, 4-H), 3.68—3.82 (1 H, m, 20-H), 3.83—3.98 (4 H, m, OCH_2CH_2O), 5.28 (1 H, br s, 7-H), 5.38 (1 H, br s, NH), 5.63 (1 H, ddd, *J* 12, 10, 5 Hz, 14-H), 5.97 (1 H, ddd, *J* 12, 10, 1 Hz, 13-H), and 7.10—7.35 (5 H, m, ArH); *m/z* (c.i.) 464 (M^+ + 1, 100%). The more polar component was identified as (16S)-18,18-*ethylenedioxy*-16-*methyl*-10-*phenyl*[11]*cytochalasa*-6(7),13^t-*diene*-1,21-*dione* (**23**) (1.51 g, 84%), an amorphous solid, m.p. 184—185 °C (Found: C, 75.1; H, 8.05; N, 2.85. $C_{29}H_{37}NO_3$ requires C, 75.15; H, 8.05; N, 3.0%); $\nu_{max.}(CHCl_3)$ 3 420, 1 695, 1 300, and 980 cm^{-1}; δ_H 1.03 and 1.15 (each 3 H, d, *J* 7.5 Hz, CH*Me*), 1.2—1.95 (6 H, m), 1.72 (3 H, br s, 12-Me), 2.04 (2 H, m), 2.42 (1 H, dd, *J* 14, 8 Hz, HC*H*Ph), 2.38—2.47 (1 H, m, 5-H), 2.53—2.72 (1 H, m, 8-H), 2.70 (1 H, dd, *J* 14, 5 Hz, *H*CHPh), 2.93 (1 H, dd, *J* 6.5, 3 Hz, 4-H), 3.27 (1 H, m, 3-H), 3.78—4.00 (5 H, m, 20-H and OCH_2CH_2O), 5.28 (1 H, ddd, *J* 16, 11, 5 Hz, 14-H), 5.48 (1 H, br s, 7-H), 5.55 (1 H, br s, NH), 6.21 (1 H, dd, *J* 16, 10 Hz, 13-H), and 7.07—7.35 (5 H, m, ArH); *m/z* (c.i.) 464 (M^+ + 1, 100%).

(16S)-16-*Methyl*-10-*phenyl*[11]*cytochalasa*-6(7),13^t-*diene*-1,18,21-*trione* (**3**).—Dilute aqueous HCl (5%, 1.85 ml) was added to the ketal (**23**) (390 mg, 0.84 mmol) in THF (12 ml), and the mixture stirred for 20 h at room temperature. Concentration under reduced pressure and flash chromatography using ether–benzene–light petroleum (8:4:3) as eluant gave the *title compound* (**3**) (280 mg, 80%), as a white solid, m.p. 199—200 °C (Found: M^+, 419.2462. $C_{27}H_{33}NO_3$ requires *M*, 419.2460); $[\alpha]_D^{20}$ −62.5° (*c* 0.25 in MeOH); $\nu_{max.}(CHCl_3)$ 3 420, 1 715, 1 700sh, 1 290, 1 130, and 1 075 cm^{-1}; δ_H 0.98 and 1.19 (each 3 H, d, *J* 7 Hz, CH*Me*), 1.68—1.78 (1 H, m), 1.74 (3 H, br s, 12-Me), 1.90 (1 H, d, *J* 16.3 Hz, 17-H), 2.02 (1 H, ddd, *J* 18, 8, 2.5 Hz), 2.20 (1 H, m, 15-H), 2.4—2.6 (5 H, m), 2.61—2.66 (1 H, m, 8-H), 2.71—2.79 (2 H, m), 2.85 (1 H, dd, *J* 6, 3 Hz, 4-H), 3.31 (1 H, m, 3-H), 3.66 (1 H, ddd, *J* 18, 12, 2 Hz, 20-H), 5.06 (1 H, ddd, *J* 15, 11, 3 Hz, 14-H), 5.40 (1 H, br s, 7-H), 5.55 (1 H, br s, NH), 6.17 (1 H, ddd, *J* 15, 10, 2 Hz, 13-H), and 7.15—7.35 (5 H, m, ArH); *m/z* (e.i.) 419 (M^+, 20%).

(16S,18S)-18-*Hydroxy*-16,18-*dimethyl*-10-*phenyl*[11]*cytochalasa*-6(7),13^t-*diene*-1,21-*dione* (**4**).—A solution of methylmagnesium chloride in THF (3M, 0.73 ml) was added dropwise to a solution of the trione (**3**) (204 mg, 0.49 mmol) in THF (7.5 ml) at 0 °C, and the mixture stirred for 5 min at 0 °C and for 3 h at room temperature. Saturated aqueous NH_4Cl (40 ml) was then added, and the aqueous phase extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ether–benzene–light petroleum (2.5:1:1) as eluant gave the *title compound* (**4**) (178 mg, 84%) as a white solid, m.p. 192—193 °C (Found: C, 77.4; H, 8.50; N, 3.2. $C_{28}H_{37}NO_3$ requires C, 77.2; H, 8.6; N, 3.2%); $[\alpha]_D^{20}$ −127.6° (*c* 0.985 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 600, 3 420, 3 200—3 700, 1 695, 1 454, 1 378, 1 302, 1 136, 1 105, and 980 cm^{-1}; δ_H 1.04 (3 H, d, *J* 7 Hz, CH*Me*), 1.10 (3 H, s, 18-Me), 1.18 (3 H, d, *J* 7 Hz, CH*Me*), 1.2 (1 H, m), 1.5—1.85 (7 H, m), 1.75 (3 H, br s, 12-*Me*), 2.02—2.10 (1 H, m, 15-H), 2.44 (1 H, dd, *J* 13.5, 8 Hz, 10-H), 2.41—2.48 (1 H, m, 5-H), 2.61 (1 H, m, 8-H), 2.75 (1 H, dd, *J* 13.5, 5 Hz, 10-H), 2.97 (1 H, dd, *J* 6, 3 Hz, 4-H), 3.28 (1 H, m, 3-H), 3.63 (1 H, m, 20-H), 5.30 (1 H, ddd, *J* 15, 11, 4 Hz, 14-H), 5.49 (2 H, br s, NH and 7-H), 6.15 (1 H, ddd, *J* 15, 10, 1.5 Hz, 13-H), and 7.15—7.30 (5 H, m, ArH); *m/z* (c.i.) 436 (M^+ + 1, 39%) and 418 (M^+ − 17, 100%).

Acknowledgements

We thank the S.E.R.C. and I.C.I. Pharmaceuticals Division for support (to J. P. W.) under the CASE Scheme. We also thank I.C.I. Pharmaceuticals for generous gifts of chemicals, Dr. A. E. Derome and Mrs. McGuinness for n.m.r. spectra, Dr. R. T. Aplin for mass spectra, and Dr. D. J. Tapolczay for helpful discussions. R. S. was on leave from Dr. Karl Thomae GmbH, Chemisch-pharmazeutische Fabrik, Biberach an der Riss, West Germany.

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Received 15*th June* 1988; *Paper* 8/02407C