# Cytochalasan Synthesis: Total Synthesis of Cytochalasin G

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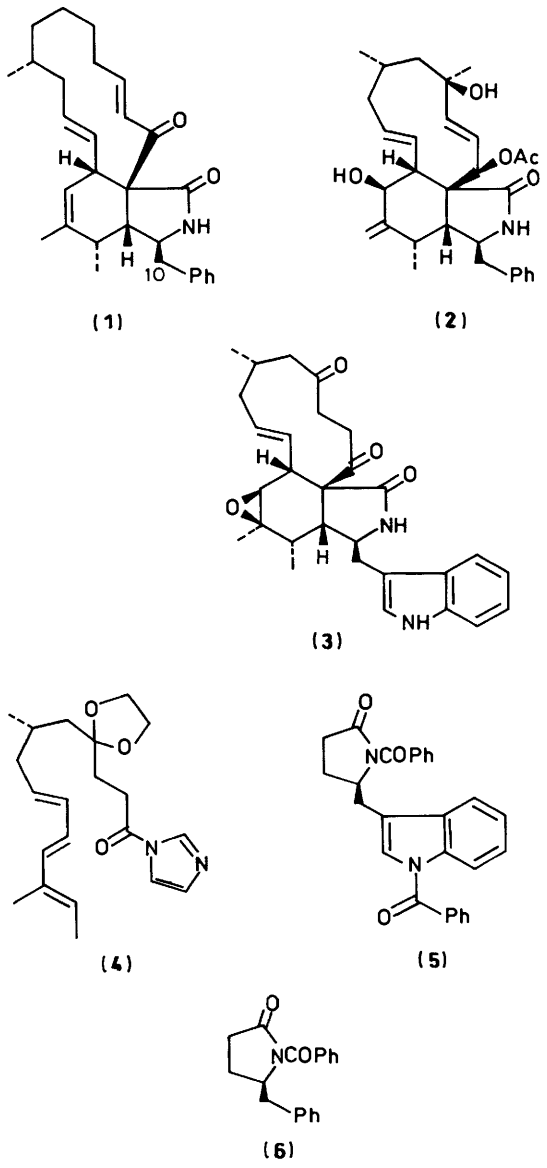
The optically active (5*R*)-5-indolylmethylpyrrolidin-2-one (**5**) has been prepared from *N*-benzyloxycarbonyltryptophan methyl ester (**7**), and incorporated into a total synthesis of cytochalasin G (**3**), using an intramolecular Diels–Alder reaction to assemble the cytochalasan skeleton.

The cytochalasans comprise a group of biologically active fungal metabolites of considerable interest at present.[1] An approach to the total synthesis of these compounds has been developed which makes use of an intramolecular Diels–Alder reaction to close the large-ring system simultaneously forming the hydrogenated isoindolone unit with a high degree of stereochemical control,[2] and has been applied to syntheses of proxiphomin (**1**)[3] and cytochalasin H (**2**).[4,5] Both of these cytochalasans are derived biosynthetically from phenylalanine as indicated by the presence of the phenyl substituent at C-10 (cytochalasan numbering[6]). We now report a total synthesis of cytochalasin G (**3**), a cytochalasan which has incorporated tryptophan during its biosynthesis.[7,8]




## Results and Discussion

Our strategy for cytochalasan synthesis has been outlined in previous papers.[2–5] As applied to cytochalasin G (**3**) the two key intermediates are the long chain imidazolyl trienone (**4**) and the 5-indolylmethylpyrrolidinone (**5**). An asymmetric synthesis of the imidazolyl trienone (**4**) is described in the previous paper in this series.[5] However for the preparation of compound (**5**), it was necessary to devise a new approach for the synthesis of optically active 5-substituted pyrrolidinones from amino acids, since the procedure used for the synthesis of (5*R*)-5-benzylpyrrolidinone (**6**) from phenylalanine required the use of strong acid,[9] and so was not compatible with the presence of an indole ring.

*N*-Benzyloxycarbonyltryptophan methyl ester (**7**)[10] was the starting material for the synthesis of the pyrrolidinone (**5**) (Scheme 1). Reduction using di-isobutylaluminium hydride gave the aldehyde (**8**)[11] which, without purification, was immediately condensed with the lithium salt of triethyl phosphonoacetate (**9**), to provide the unsaturated ester (**10**) [50% from the tryptophan ester (**7**)]. Simultaneous hydrogenation and hydrogenolysis under acidic conditions gave the saturated amino ester (**11**), which was cyclized to the pyrrolidinone (**12**) by stirring in solution in ethanol containing a catalytic amount of base. Bisbenzoylation using benzoyl chloride in the presence of triethylamine and 4-dimethylaminopyridine then gave the target pyrrolidinone (**5**) (77%). During this sequence care was taken to avoid racemization, and the 1-benzoyl pyrrolidinone (**5**) obtained was optically active $[\alpha]_D^{20}$ +51 ± 2° (*c* 0.87 in $CH_2Cl_2$), but its optical purity was not established.

Acylation of the 1-benzoylpyrrolidinone (**5**) by the long chain imidazolyl trienone (**4**)[5] was carried out under the conditions developed previously[2] using lithium hexamethyldisilazide as base, and gave the 3-(1-oxotrienyl)pyrrolidinone (**13**) as a mixture of epimers at C-3 which could not be separated from the excess of 1-benzoyl pyrrolidinone (**5**) (Scheme 2). However, using just sufficient base to deprotonate the more acidic 3-acylpyrrolidinone (**13**), the mixture was treated with base and benzeneselenenyl chloride to provide the 3-phenylselenopyrrolidinone (**14**) isolated pure, as a mixture of C-3 epimers, by flash chromatography. Oxidative elimination then generated the unstable 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**15**) which cyclized on heating in dilute solution in toluene at 86 °C for 5.5 h, to give a single Diels–Alder adduct after flash chromatography. This adduct was identified as the desired isomer (**16**) on

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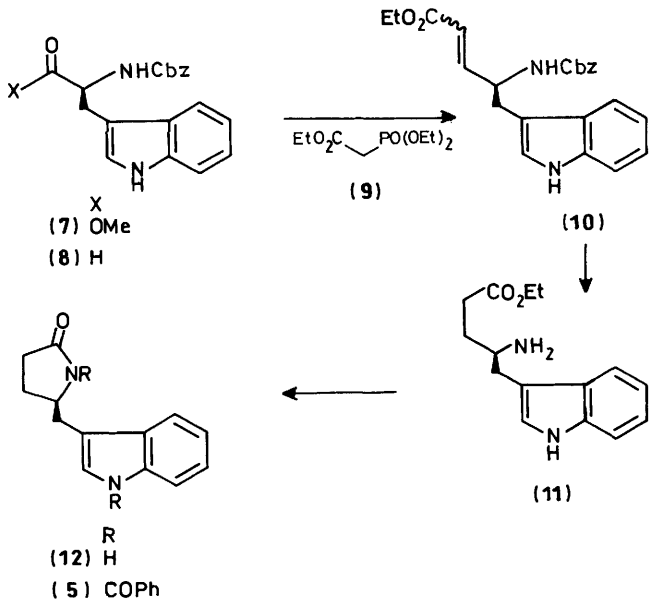



**Scheme 1.** Cbz = $PhCH_2OCO$

the basis of $^1H$ n.m.r. data, and by analogy with previous work.[2–5] Minor products (< 5%) were detected in the crude product mixtures from the Diels–Alder reaction, but were not isolated pure or identified.

The conversion of the Diels–Alder adduct (**16**) into cytochalasin G (**3**) required three steps, *N*-debenzoylation, epoxidation, and acetal hydrolysis. The order in which these steps were carried out was determined by the sensitivity of indoles to oxidation which required the epoxidation to be carried out on a 1-benzoyl indole. Thus acetal hydrolysis using dilute aqueous HCl was carried out first, and gave the diketone (**17**). Treatment of this with *m*-chloroperoxybenzoic acid gave a 39% yield of epoxide (**18**) together with indole oxidized products, and finally the two *N*-benzoyl groups were removed using sodium hydroxide in methanol to give cytochalasin G (**3**) identical within experimental error with an authentic sample of the natural product by $^1H$ n.m.r., $[\alpha]_D^{20}$, t.l.c., m.p., *etc.*

This work concludes the first synthesis of a non-phenylalanine derived cytochalasan, and confirms the usefulness of the intramolecular Diels–Alder reaction for natural product synthesis in this area.

## Experimental

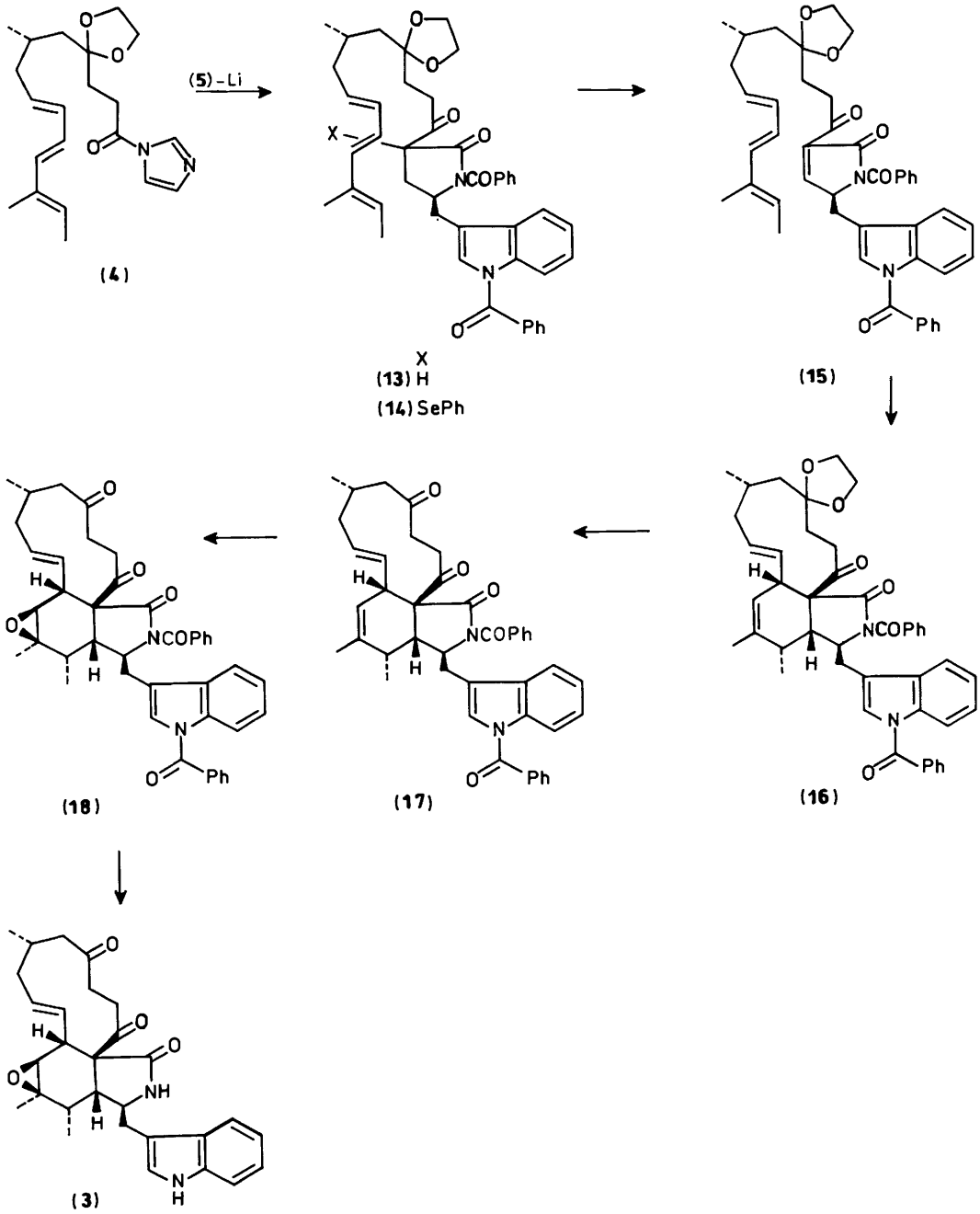
For general experimental details see the first paper in this series.[2] (2*S*)-2-(*N*-Benzyloxycarbonylamino)-3-indol-3′-yl-propanal (**8**)[11] was prepared by reduction of (2*S*)-methyl 2-(*N*-benzyloxycarbonylamino)-3-indol-3′-ylpropanoate (**7**)[10] using di-isobutylaluminium hydride at −60 °C. The crude aldehyde was not purified but was used immediately to minimize racemisation.

(4S)-*Ethyl* 4-(N-*Benzyloxycarbonylamino*)-5-*indol*-3′-*ylpent*-2-*enoate* (**10**).—Triethyl phosphonoacetate (8.18 g, 36.5 mmol) was added to a solution of lithium di-isopropylamide (LDA) (36.69 mmol) in THF–hexane (75 ml, 2:1) at −40 °C under an atmosphere of argon, and the resultant mixture stirred at this temperature for 1 h. A solution of the freshly prepared aldehyde (**8**)[11] (3.94 g, 12.24 mmol) in THF (50 ml) was added and the mixture stirred for a further 1 h. After warming to 0 °C, the reaction mixture was poured into ice–water, acidified (3M HCl), and extracted with ethyl acetate (3 × 70 ml). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ethyl acetate–light petroleum (2:3) as eluant gave the *title compound* (**10**) (2.98 g, 50%), as an oil, a mixture of *E*- and *Z*-isomers; $\nu_{max.}$(film) 3 480, 3 430, and 1 715 $cm^{-1}$; $\delta_H$ 1.29 (3 H, two overlapping t, $CH_2Me$), 2.9—3.1 (2 H, m, 5-$CH_2$), 4.15 (2 H, two overlapping q, $CH_2Me$), 4.85—5.20 (3 H, m, 4-H and $CH_2Ph$), 5.57 (0.5 H, br s, NH), 5.88 (1 H, m, 2-H of both isomers), 6.21 (0.5 H, br s, NH), 6.93—7.42 (10 H, m, 3-H and ArH), 7.57 and 7.72 (each 0.5 H, d, *J* 7 Hz, 4′-H), and 8.10 (1 H, br s, NH); *m/z* (c.i.) 393 ($M^+$ + 1, 57%).

(5R)-1-*Benzoyl*-5-(1-*benzoylindol*-3-*ylmethyl*)*pyrrolidin*-2-*one* (**5**).—A mixture of the pentenoate (**10**) (4.69 g, 11.96 mmol), 10% Pd–C (800 mg), and acetic acid (8 drops), in ethanol (200 ml) was stirred under an atmosphere of hydrogen at room temperature for 48 h. The mixture was then filtered through Celite, and the filtrate concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and extracted with 3M aqueous HCl. The aqueous extracts were combined, basified (2M NaOH), and re-extracted with ethyl acetate. These organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue identified as the saturated amino ester (**11**). This was dissolved in ethanol (70 ml), a trace of sodium hydride added, and the solution stirred at room temperature for 16 h. Concentration under reduced pressure gave (5R)-5-(*indol*-3′-*ylmethyl*)-*pyrrolidin*-2-*one* (**12**) (2.06 g, 80%), as a white solid, m.p. 182—184 °C; $[\alpha]_D^{20}$ +28.3° (*c* 0.95 in MeOH); $\nu_{max.}$ 3 490, 3 440, and 1 695 $cm^{-1}$; $\delta_H(CD_3OD)$ 1.79—1.95 (1 H, m, 4-*H*H), 2.07—2.25 (3 H, m, 3-$CH_2$ and 4-H*H*), 2.88 (1 H, dd, *J* 14, 6 Hz, HC*H*Ar), 3.02 (1 H, dd, *J* 14, 5 Hz, *H*CHAr), 4.02 (1 H, m, 5-H), 6.97—7.15 (3 H, m, ArH), 7.32 (1 H, d, *J* 7.5 Hz, 7′-H), and 7.53 (1 H, d, *J* 7.5 Hz, 4′-H); *m/z* (c.i.) 215 ($M^+$ + 1, 100%).

Benzoyl chloride (4.66 g, 33.17 mmol) was added to a stirred solution of the pyrrolidinone (**12**) (1.42 g, 6.64 mmol), 4-dimethylaminopyridine (0.81 g, 6.64 mmol), and triethylamine (3.35 g, 33.71 mmol) in dichloromethane (130 ml) at room temperature. The resulting yellow solution was stirred for 16 h, then washed with aqueous HCl (3M, 50 ml), saturated aqueous $NaHCO_3$ (50 ml), and brine (50 ml), and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue using ethyl acetate–light petroleum (1:2) as eluant gave the *title compound* (**5**) (2.17 g, 77%) as a white crystalline solid, m.p. 163—164 °C (from ethyl acetate–light petroleum) (Found: C, 76.7; H, 5.3; N, 6.5. $C_{27}H_{22}N_2O_3$ requires C, 76.75; H, 5.25; N, 6.6%); $[\alpha]_D^{20}$ +51.04° (*c* 0.87 in $CH_2Cl_2$); $\nu_{max.}(CHCl_3)$ 1 745, 1 680, 1 600, 1 452, 1 355, and 1 304 $cm^{-1}$; $\delta_H$ 1.87—2.0 and 2.05—2.23 (each 1 H, m, 4-H), 2.48—2.63 (2 H, m, 3-$CH_2$), 2.90 (1 H, dd, *J* 14, 8 Hz, HC*H*Ar), 3.47 (1 H, dd, *J* 14, 3 Hz, *H*CHAr), 4.80 (1 H, m, 5-H), 7.17—7.9 (14 H, m, ArH), and 8.38 (1 H, d, *J* 7 Hz, ArH); *m/z* (c.i.) 440 ($M^+$ + 18, 100%) and 423 ($M^+$ + 1, 39%).

(3RS,5S,6′S,8′E,10′E,12′E)-1-*Benzoyl*-5-(1-*benzoylindol*-3-*ylmethyl*)-3-(4′,4′-*ethylenedioxy*-6′,12′-*dimethyl*-1′-*oxotetradeca*-8′,10′,12′-*trienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**14**).—A solution of the 1-benzoyl pyrrolidin-2-one (**5**) (1.11 g, 2.63 mmol) in THF (20 ml) was cooled to −70 °C, added to a solution of lithium hexamethyldisilazide (2.6 mmol) in THF–hexane (14 ml) at −70 °C under an atmosphere of argon, and the resulting mixture stirred for 45 min, before being added to a pre-cooled solution of imidazolyl trienone (**4**)[5] (470 mg, 1.31 mmol) in THF (10 ml). After stirring for 5 h at −70 °C, the reaction mixture was warmed to 0 °C and stirred for a further 30 min. Saturated aqueous $NH_4Cl$ (40 ml) was added, and the mixture extracted with ether (3 × 40 ml). The ethereal extracts were combined, washed with brine (40 ml), dried ($K_2CO_3$;




Scheme 2.

$MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ether–light petroleum (1:1) as eluant on base washed silica, gave a mixture of recovered pyrrolidinone (**5**) together with the 3-acyl pyrrolidinone (**13**). A solution of this mixture of pyrrolidinones (1.1 g) in THF (9 ml) cooled to −70 °C was added to a solution of lithium hexamethyldisilazide (0.98 mmol) in THF–hexane (2.5 ml) at −70 °C under argon, and the mixture stirred for 1 h before the addition of a pre-cooled (−70 °C) solution of benzeneselenenyl chloride (186 mg, 0.97 mmol) in THF (4 ml). After stirring the reaction mixture for 3 h at −70 °C, saturated aqueous $NH_4Cl$ (15 ml) was added, and the mixture warmed to room temperature and extracted with ether (3 × 20 ml). The organic extracts were combined, washed with brine (20 ml), dried ($K_2CO_3$; $MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on base washed silica using ether–light petroleum (1:2) as eluant gave the *title compound* (**14**) [650 mg, 57% from imidazolyl trienone (**4**)], as an oil; $\nu_{max.}(CHCl_3)$ 1 730, 1 680, 1 600, 1 450, 1 355, 1 275, 1 145, 985, and 870 $cm^{-1}$; $\delta_H$ 0.89 and 0.95 (each 1.5 H, d, *J* 7 Hz, CH*Me*), 1.2—2.25 (14 H, complex m, 3 × $CH_2$, 6′-H, HC*H* and 2 × Me), 2.46 (0.5 H, dd, *J* 15, 7 Hz, HC*H* of one isomer), 2.6—3.5 (4.5 H, complex m, 2′-$CH_2$, $CH_2Ph$, and HC*H*), 3.6—3.95 (4 H, m, $OCH_2CH_2O$), 4.55 (0.45 H, m, 5-H), 4.66 (0.55 H, m, 5-H), 5.35—5.75 (2 H, m, vinylic H), 5.95—6.0 (3 H, m, vinylic H), 7.1—7.8 (14 H, complex m, ArH), and 8.40 and 8.42 (each 0.5 H, d, *J* 8 Hz, ArH).

(16S)-2-*Benzoyl*-10-(1-*benzoylindol*-3-*yl*)-18,18-*ethylenedioxy*-16-*methyl*[11]*cytochalasa*-6(7),13[1]-*diene*-1,21-*dione*

(**16**).—A solution of hydrogen peroxide (30%; 0.87 ml, 7.5 mmol) in water (2.7 ml) was added to a solution of the selenide (**4**) (650 mg, 0.75 mmol) in chloroform (50 ml) at −50 °C under argon, followed immediately by a solution of *m*-chloroperoxybenzoic acid (78 mg, 0.83 mmol) in chloroform (12 ml). The mixture was stirred for 25 min at −50 °C, and at 0 °C for 15 min. Chloroform (50 ml) was added, and the organic layer washed with cold saturated aqueous $NaHCO_3$ (2 × 30 ml), cold water (30 ml), and brine (30 ml). After brief (2 min) drying ($Na_2SO_4$), the filtered solution was added to anhydrous argon-purged toluene (650 ml) at 86 °C. The resulting solution was heated under an atmosphere of argon at 86 °C for 5.5 h, then cooled to room temperature, and concentrated under reduced pressure. Flash chromatography of the residue using ether–light petroleum (1:2) as eluant gave the *title compound* (**16**) [165 mg, 31% based on selenide (**14**)] as a pale yellow solid, m.p. 113—114 °C (Found: C, 76.1; H, 6.85; N, 3.8. $C_{45}H_{44}N_2O_6$ requires C, 76.05; H, 6.55; N, 3.95%); $[\alpha]_D^{20}$ −2.08° (*c* 1.5 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 735, 1 680, 1 600, 1 452, 1 382, 1 365, 1 295, 1 265, 1 180, 1 155, 1 070, and 985 $cm^{-1}$; $\delta_H$ 0.96 and 1.03 (each 3 H, d, *J* 7 Hz, CH*Me*), 1.13—2.0 (7 H, complex m), 1.75 (3 H, br s, 12-Me), 1.98 (1 H, m, 15-H), 2.46 (1 H, m, 5-H), 2.75 (2 H, m, 8-H and HC*H*Ar), 3.08 (1 H, d, *J* 5 Hz, 4-H), 3.28 (1 H, dd, *J* 14, 13 Hz, *H*CHAr), 3.47 (1 H, m, 20-H), 3.78 (4 H, m, $OCH_2CH_2O$), 4.49 (1 H, m, 3-H), 5.27 (1 H, ddd, *J* 15, 11, 4 Hz, 14-H), 5.53 (1 H, narrow m, 7-H), 6.02 (1 H, dd, *J* 15, 9 Hz, 13-H), 7.1—7.82 (14 H, m, ArH), and 8.40 (1 H, d, *J* 6.5 Hz, ArH); *m*/*z* (c.i.) 728 ($M^+$ + 18, 10%) and 711 ($M^+$ + 1, 8%).

(16S)-2-*Benzoyl*-10-(N-*benzoylindol*-3-*yl*)-16-*methyl*[11]-*cytochalasa*-6(7),13$^1$-*diene*-1,18,21-*trione* (**17**).—Aqueous HCl (5%, 3 ml) was added to a solution of the Diels–Alder adduct (**16**) (114 mg, 0.16 mmol) in THF (4 ml), and the resulting solution stirred at room temperature for 24 h. The reaction mixture was then neutralized by the addition of saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 5 ml). The organic extracts were combined, washed with brine (5 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ether–light petroleum (1:2) as eluant gave the *title compound* (**17**) (76 mg, 71%) as a white crystalline solid, m.p. 121—122 °C (Found: C, 77.4; H, 6.6; N, 4.0. $C_{43}H_{40}N_2O_5$ requires C, 77.4; H, 6.4; N, 4.2%); $[\alpha]_D^{20}$ +15.32° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 735, 1 685, and 1 605 $cm^{-1}$; $\delta_H$ 0.90 and 1.00 (each 3 H, d, *J* 6.5 Hz, CH*Me*), 1.58 (1 H, m), 1.74 (3 H, br s, 12-Me), 1.8 (1 H, m), 2.15—2.5 (6 H, complex m), 2.55—2.72 (2 H, m), 2.8—2.98 (2 H, m), 3.17 (1 H, dd, *J* 15, 2 Hz), 3.35 (1 H, m, 20-H), 4.43 (1 H, m, 3-H), 5.03 (1 H, ddd, *J* 15, 11, 3 Hz, 14-H), 5.45 (1 H, narrow m, 7-H), 5.94 (1 H, ddd, *J* 15, 10, 1 Hz, 13-H), 7.07—7.78 (14 H, m, ArH), and 8.37 (1 H, d, *J* 6.5 Hz, ArH); *m*/*z* (e.i.) 666 ($M^+$, 10%).

(6R,7S,16S)-2-*Benzoyl*-10-(1-*benzoylindol*-3-*yl*)-6,7-*epoxy*-16-*methyl*[11]*cytochalas*-13$^1$-*ene*-1,18,21-*trione* (**18**).—A solution of *m*-chloroperoxybenzoic acid (13.4 mg, 66 μmol) in dichloromethane (0.4 ml) was added to a solution of cytochalasadiene (**17**) (40 mg, 60 μmol) in dichloromethane (0.8 ml), and the mixture stirred for 16 h. Concentration under reduced pressure, and flash chromatography of the residue using ether–light petroleum (1:1) as eluant gave the *title compound* (**18**) (16 mg, 39%) as a white crystalline solid, m.p. 107—109 °C, $\nu_{max.}$($CHCl_3$) 1 735 and 1 685 $cm^{-1}$; $\delta_H$ 0.83 and 0.93 (each 3 H, d, *J* 6.5 Hz, CH*Me*), 1.20 (3 H, s, 12-Me), 1.58 (1 H, m), 1.75—2.05 (3 H, m), 2.15—2.5 (7 H, m), 2.75 (1 H, dd, *J* 14, 8 Hz, HC*H*Ar), 2.82 (1 H, d, *J* 7 Hz, 7-H), 2.85 (1 H, m, 20-H), 3.16 (1 H, dd, *J* 14, 2.5 Hz, *H*CHAr), 4.82 (1 H, m, 3-H), 5.10 (1 H, ddd, *J* 15, 12, 4 Hz, 14-H), 5.99 (1 H, ddd, *J* 15, 10, 1 Hz, 13-H), 7.08 (1 H, s, ArH), 7.28—7.83 (13 H, m, ArH), and 8.35 (1 H, dd, *J* 6.5, 1 Hz, ArH).

*Cytochalasin G* (**3**).—A solution of NaOH (4.4 mg, 0.11 mmol) in water (60 μl) was added to a solution of the epoxide (**18**) (14 mg, 20.5 μmol) in methanol (0.8 ml), and the resulting solution stirred for 16 h. After removal of methanol, the residue was taken up in ethyl acetate and water. The mixture was then extracted into ethyl acetate (3 × 2 ml), and the organic extracts washed with brine (2 ml) and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography using ethyl acetate–pentane (3:1) as eluant gave *cytochalasin G* (**3**) (6 mg, 62%), as a white solid, m.p. 251—253 °C (from methanol) (lit.,[7] 255—257 °C); $[\alpha]_D^{20}$ −90° (*c* 0.3 in methanol) [lit.,[7] −99° (*c* 0.35 in methanol)]; $\delta_H$ 0.95 and 1.08 (each 3 H, d, *J* 7 Hz, CH*Me*), 1.21 (3 H, s, 12-Me), 1.63—1.78 (2 H, m), 1.82—1.95 (2 H, m), 2.12 (1 H, dd, *J* 10, 6 Hz), 2.2—2.55 (4 H, m), 2.55—2.7 (2 H, m), 2.83 (1 H, d, *J* 7 Hz, 7-H), 2.83—2.94 (2 H, m), 3.45 (1 H, ddd, *J* 18, 10, 2 Hz, 20-H), 3.78 (1 H, m, 3-H), 5.02 (1 H, ddd, *J* 15, 12, 3 Hz, 14-H), 5.8 (1 H br s, NH), 6.17 (1 H, ddd, *J* 15, 10, 1 Hz, 13-H), 6.98 (1 H, d, *J* 1 Hz, ArH), 7.12—7.25 (2 H, m, ArH), 7.38 and 7.5 (each 1 H, dd, *J* 7, 1 Hz, ArH), and 8.2 (1 H, br s, NH).

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