Synthesis of cytochalasans using intramolecular Diels–Alder reactions: an alternative approach to cytochalasin D

Eric J. Thomas *† and John P. Watts

The Dyson Perrins Laboratory, South Parks Road, Oxford, UK OX1 3QY

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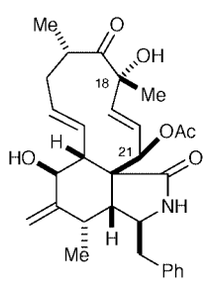
The macrocycle **25** which has the required functionality around the macrocyclic ring for incorporation into a synthesis of cytochalasin D **1** has been synthesized using an intramolecular Diels–Alder reaction to form the 11-membered ring. The Diels–Alder precursor **24** was prepared in a convergent fashion from the dienyl phosphonate **17**, the aldehyde **16** and the pyrrolidinone **21**, with phenylselenenylation and oxidative elimination being used to convert the pyrrolidinone **22** into the unstable pyrrolinone **24**. The Diels–Alder reaction of the pyrrolinone **24** under high dilution conditions gave the required *endo*-adduct **25** in a yield of 53% based on the phenylselenopyrrolidinone **23**. *N*-Debenzoylation gave the *NH*-lactam **26** but preliminary attempts to effect removal of the SEM-groups led to the formation of the methylenedioxy compound **27**.

The cytochalasans are a group of macrocyclic fungal metabolites which have attracted considerable attention from synthetic chemists because of their potent biological activity.[1,2] The preceding paper[3] reports details of the first synthesis of the [11]cytochalasan, cytochalasin D **1** using an intramolecular Diels–Alder reaction of a pyrrolinone to prepare the advanced intermediate **2**.[4] One aspect of this synthesis is the introduction



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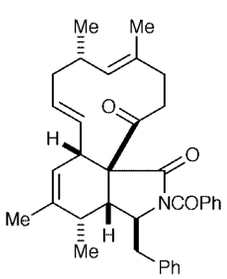

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of most of the functionality around the 11-membered ring including the stereogenic centres at C(18) and C(21) after the macrocyclisation step, using the conformational preferences of the macrocyclic ring to control stereochemistry. An advantage of this approach is that the Diels–Alder product **2**, which has the intact carbon skeleton of the [11]cytochalasans, is formed relatively early in the synthesis, only eleven linear steps being required to prepare it from methacrolein. However, a disadvantage is that the conversion of this intermediate into cytochalasin D is quite lengthy. We now report details of preliminary studies of an alternative approach to cytochalasin D **1** using an intramolecular Diels–Alder reaction, in which more functionality is introduced before the Diels–Alder step.[5]

Results and discussion

The synthesis of the alcohol **15** which corresponds to the C(14)–C(21) fragment of cytochalasin D is outlined in Scheme 1. The *anti*-2,4-dimethylhexa-1,5-dien-3-ol **3**, ee 84%, together with *ca.* 10% of its *syn*-diastereoisomer, is available from the reaction between methacrolein and (*E*)-but-2-enyldiisopinocampheylborane.[3] Sharpless epoxidation of this mixture using (+)-diethyl tartrate gave the hydroxyepoxide **4**, 57%, together with *ca.* 10% of a mixture of diastereoisomeric epoxides.[6] Interestingly the ee of the hydroxyepoxide **4** was found to correspond to 98% (Mosher's derivative), significantly better than that of the starting alcohol, perhaps because of the preferential formation of the epoxide **6**, a diastereoisomer of epoxide **4**, from the Sharpless epoxidation of the enantiomer of allylic alcohol **3**.

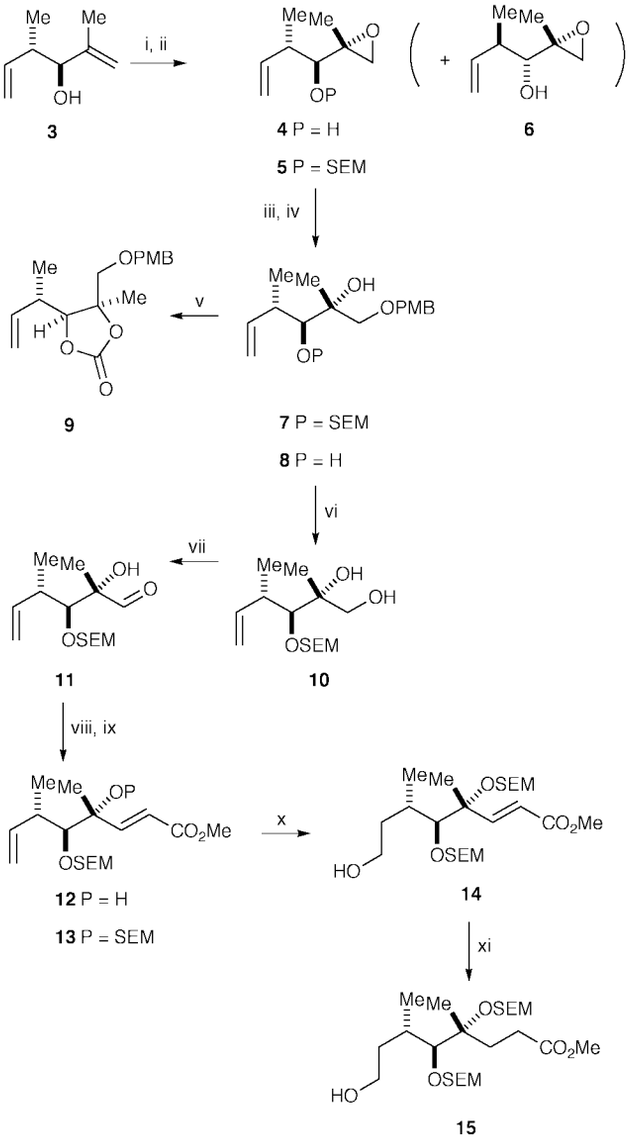
The hydroxyepoxide **4** was protected as its 2-trimethylsilylethoxymethyl (SEM) ether **5**[7] but attempts to open this epoxide using the lithium enolate of ethyl acetate[8] or lithiated 2-methyloxazolines[9] or metallated ethoxyacetylenes,[10] were unsuccessful. However, ring-opening of the epoxide was eventually achieved by heating a solution of the epoxide in *p*-methoxybenzyl alcohol containing powdered sodium hydroxide[11] at 80 °C for three days to give the *p*-methoxybenzyl ether **7** in reasonable yield (71%). The relative configurations of this ether at C(2) and C(4) were checked by deprotection of the 3-hydroxy group to give the diol **8** which was converted into the cyclic carbonate **9**. The configuration of this cyclic carbonate was confirmed by ^{1}H NMR, *e.g.* by the observation of significant NOE enhancements between the *cis*-disposed substituents about the 5-membered ring.

Oxidative removal of the *p*-methoxybenzyl group[12] from the ether **7** gave the diol **10** which was oxidized to the aldehyde **11**. Condensation with methoxycarbonylmethylene(triphenyl)-phosphorane gave the unsaturated ester **12** which was further protected as its bis-SEM derivative **13**. This was hydroborated regioselectively using 9-borabicyclo[3.3.1]nonane (9-BBN) to give the primary alcohol **14** and hydrogenation gave the saturated hydroxyester **15**.

Oxidation of this hydroxyester gave the aldehyde **16** which was condensed with the phosphonate **17**[3,13] under the usual conditions to give the (*E*,*E*,*E*)-trienyl ester **18** containing *ca.* 15% of its (*Z*,*E*,*E*)-isomer (^{1}H NMR), see Scheme 2. Saponification of this ester gave the acid **19** which was converted into the acyl imidazole **20**. This was used to acylate the *N*-benzoylpyrrolidinone **21**[14] to give an epimeric mixture of the 3-alkenoylpyrrolidinones **22**. Phenylselenation and oxidative elimination then gave the unstable pyrrol-2(5*H*)-one **24**. This was not isolated, rather it was heated in dilute solution in toluene to give the tricyclic Diels–Alder adduct **25**, which was isolated in a yield of 53% based on the phenylselenopyrrolidinone **23**, together with *ca.* 5% of a mixture of minor isomeric Diels–Alder adducts which were not fully characterized.

The structure of the major Diels–Alder adduct **25** was

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



Scheme 1 *Reagents and conditions*: i, (+)-diethyl tartrate, $Ti(OPr^i)_4$, 4 Å sieves, *tert*-butyl hydroperoxide, −20 °C, 60 h (57%); ii, diisopropylethylamine, 2-trimethylsilylethoxymethyl chloride (97%); iii, 4-methoxybenzyl alcohol, sodium hydroxide, 80 °C, 3 days (71%); iv, aqueous hydrogen fluoride, acetonitrile (63%); v, carbonyl-*N*,*N*′-diimidazole, benzene (76%); vi, DDQ, then sodium hydroxide, aqueous methanol (85%); vii, dimethylsulfoxide, oxalyl chloride, −50 °C then triethylamine (77%); viii, $Ph_3P{=}CH{\cdot}CO_2Me$, benzene 80 °C, 4 h (95%); ix, diisopropylethylamine, 2-trimethylsilylethoxymethyl chloride, dichloromethane, reflux, 48 h (92%); x, 9-BBN, THF, heat, 1.5 h then aqueous hydrogen peroxide, sodium hydroxide (76%); xi, 10% Pd/C, H_2, methanol (80%).

assigned on the basis of precedent[3,4] and was confirmed by extensive ^{1}H NMR studies. It corresponds to *endo*-addition of the triene onto the less hindered face of the pyrrol-2(5*H*)-one as has been observed in all other similar cases.[4] The 53% isolated yield of this Diels–Alder product is of note. However, problems were encountered in continuing with the synthesis. *N*-Deprotection gave the *NH*-lactam **26**, but attempts to introduce a phenylselenenyl group at C(20) using lithium amide bases and benzeneselenenyl chloride were unsuccessful. Moreover, treatment with aqueous hydrogen fluoride, in an attempt to remove the two SEM ethers, gave the cyclic acetal **27** rather than the required diol.

Summary and conclusions

This approach to a synthesis of cytochalasin D **1** complements that in the preceding paper in that more of the functionality about the 11-membered ring is introduced before the Diels–Alder step. This should mean that less chemistry is required after the Diels–Alder cyclisation. The satisfactory yield, 53%, of the bis-SEM protected Diels–Alder adduct **25** is of interest but this work was not continued because of the completion of the total synthesis of cytochalasin D **1** described in the preceding paper.[3]

Experimental †

For general experimental details see the preceding paper.[3]

(2*R*,3*S*,4*S*)-2,4-Dimethyl-1,2-epoxyhex-5-en-3-ol 4

(+)-Diethyl L-tartrate (12.2 cm^3, 71.4 mmol) was added to titanium(IV) isopropoxide (19.1 cm^3, 64.3 mmol) and sieves (4 Å; 6.5 g) in dichloromethane (200 cm^3) at −20 °C. After stirring for 5 min at −20 °C, the alcohol **3** (9 g, 71.4 mmol) in dichloromethane (50 cm^3) was added dropwise followed by *tert*-butyl hydroperoxide in toluene (3 M; 36 cm^3). The solution was stored at −20 °C for 60 h then poured into a solution of ferrous sulfate (35.6 g) and tartaric acid (14.5 g) in water (160 cm^3) at 0 °C and the mixture stirred for 30 min at ambient temperature before extracting with ether (2 × 200 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in ether (210 cm^3) and a cooled (0 °C) solution of sodium hydroxide (1 M; 120 cm^3) in brine added. The mixture was stirred at 0 °C for 1 h then extracted with ether (2 × 150 cm^3) and the ethereal extract dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (8:1) as eluant gave recovered starting material, 0.47 g (5%), followed by the *title compound* **4** (5.8 g, 57%), as a colourless oil; $[\alpha]_D^{20}$ +17 (*c* 1 in MeOH); ν_{max}/cm^{-1} 3475, 3090, 1644, 1245 and 910; δ_H 1.14 (3 H, d, *J* 7, 4-CH_3), 1.31 (3 H, s, 2-CH_3), 2.35 (1 H, br s, OH), 2.42 (1 H, m, 4-H), 2.55 and 2.85 (each 1 H, d, *J* 5, 1-H), 3.44 (1 H, d, *J* 4.5, 3-H), 5.04 (2 H, m, 6-H_2) and 5.78 (1 H, m, 5-H); *m*/*z* (EI) 142 (M^+, 67%), 112 (90) and 86 (100).

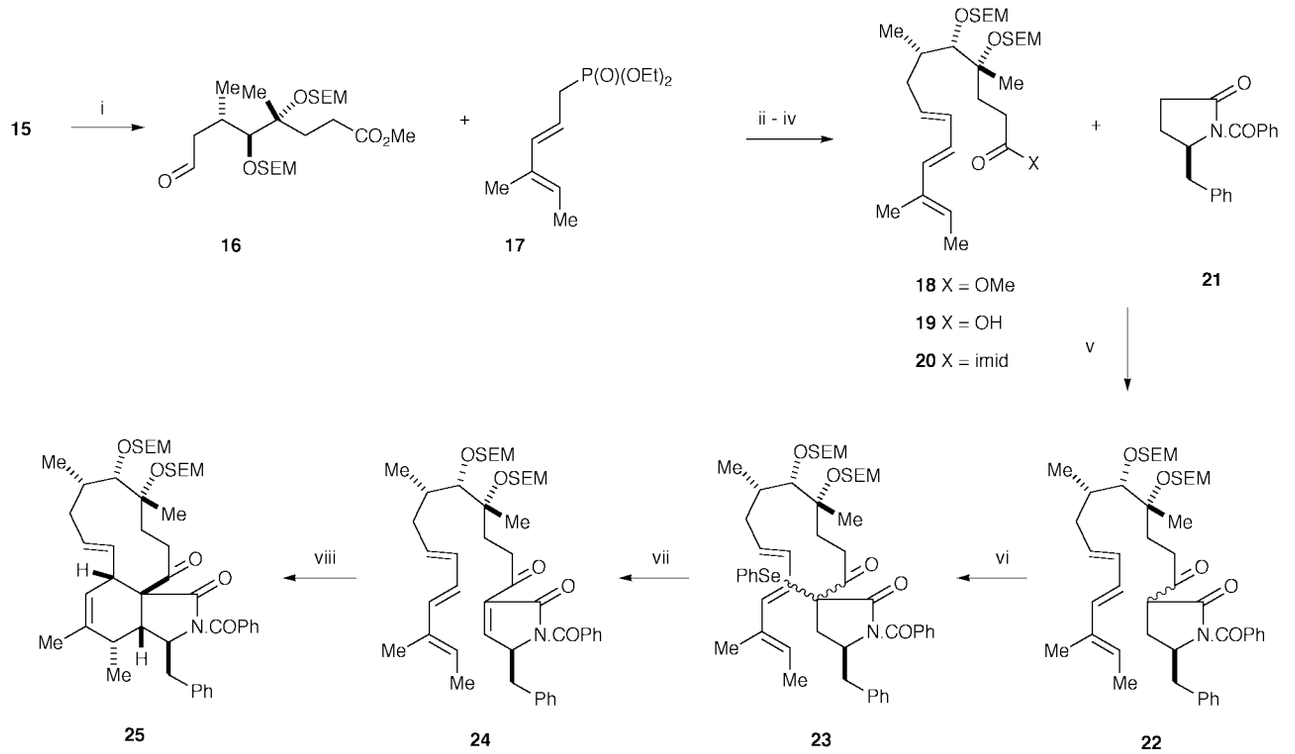
(2*R*,3*S*,4*S*)-2,4-Dimethyl-1,2-epoxy-3-(trimethylsilylethoxymethoxy)hex-5-ene 5

Diisopropylethylamine (14.5 cm^3, 83.5 mmol) was added to a solution of the alcohol **4** (4.74 g, 33.4 mmol) in CH_2Cl_2 (75 cm^3) followed by 2-trimethylsilylethoxymethyl chloride (8.6 cm^3, 50.1 mmol) and the solution stirred for 24 h then diluted with dichloromethane (300 cm^3). The solution was washed with saturated aqueous ammonium chloride (2 × 150 cm^3) and, after re-extracting the aqueous layers with dichloromethane (l00 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (15:l) as eluant gave the *title compound* **5** (8.66 g, 97%) as a colourless oil; $[\alpha]_D^{20}$ −18 (*c* 1 in MeOH); ν_{max}/cm^{-1} 3095, 1645, 1250, 1035, 940, 910, 880 and 840; δ_H 0.00 (9 H, s, 3 × SiMe), 0.95 (2 H, m, CH_2Si), 1.10 (3 H, d, *J* 7, 4-CH_3), 1.32 (3 H, s, 2-CH_3), 2.52 (1 H, m, 4-H), 2.52 and 2.78 (each 1 H, d, *J* 5, 1-H), 3.13 (1 H, d, *J* 5, 3-H), 3.62 (2 H, m, CH_2CH_2Si), 4.60 and 4.75 (each 1 H, d, *J* 8, OHC*H*O), 6.05 (2 H, m, 6-H_2) and 6.83 (1 H, m, 5-H); *m*/*z* (Cl) 287 (M^+ + 15, 2%), 273 (M^+ + 1, 0.5) and 215 (22).

(2*R*,3*S*,4*S*)-2,4-Dimethyl-1-(4-methoxybenzyloxy)-3-(trimethylsilylethoxymethoxy)hex-5-en-2-ol 7

p-Methoxybenzyl alcohol (187 cm^3, 1.5 mol) was added to the epoxide **5** (20.5 g, 75.4 mmol) and powdered sodium hydroxide

† In this discussion, the nomenclature devised for the cytochalasans is used for the Diels–Alder products and compounds derived from them (see refs. 3, 15).



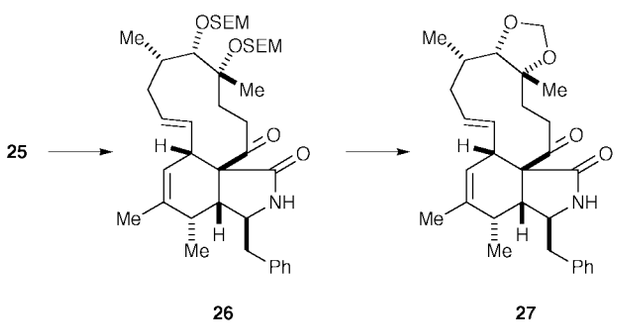
Scheme 2 *Reagents and conditions*: i, dimethyl sulfoxide, oxalyl chloride, −50 °C, then triethylamine (78%); ii, butyllithium, **17**, add **16**, −78 °C, then hexamethylphosphoramide, 3 h (79%); iii, sodium hydroxide, aqueous ethanol, 6 h; iv, carbonyl-*N*,*N*′-diimidazole, THF (94% from **18**); v, **21**, $LiN(SiMe_3)_2$, add **20** (92%); vi, $LiN(SiMe_3)_2$, benzeneselenenyl chloride, −78 °C (81%); vii, *m*-chloroperoxybenzoic acid, aqueous hydrogen peroxide, −50 °C, 15 min, then 0 °C, 10 min; viii, toluene, 80 °C, 16 h (53% from **23**).

(22.6 g, 565 mmol) and the solution heated at 80 °C for 3 days. After cooling to ambient temperature, water (400 cm^3) was added and the mixture extracted with dichloromethane (2 × 700 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Distillation using a Kugelröhr at 125 °C, 0.5 mmHg, removed the *p*-methoxybenzyl alcohol and chromatography of the residue using hexane–ether (2:1) as eluant gave the *title compound* **7** (21.8 g, 71%) as a colourless oil; $[\alpha]_D^{20}$ −14.4 (*c* 0.8 in MeOH); $[\alpha]_D^{20}$ −7.6 (*c* 0.83 in $CHCl_3$); ν_{max}/cm^{-1} 3500, 3070, 1620, 1520, 1245, 1030, 860 and 840; δ_H 0.00 (9 H, s, 3 × SiMe), 0.91 (2 H, m, CH_2Si), 1.10 (3 H, d, *J* 7, 4-CH_3), 1.14 (3 H, s, 2-CH_3), 2.62 (1 H, m, 4-H), 2.91 (1 H, br s, OH), 3.33 (1 H, d, *J* 10, 1-H), 3.39 (1 H, d, *J* 3, 3-H), 3.46 (1 H, d, *J* 10, 1-H), 3.65 (2 H, m, CH_2CH_2Si), 3.8 (3 H, s, OMe), 4.41 and 4.51 (each 1 H, d, *J* 12, OHC*H*Ar), 4.66 and 4.72 (each 1 H, d, *J* 7, OHC*H*O), 4.95 (2 H, m, 6-H_2), 5.94 (1 H, m, 5-H), and 6.86 and 7.23 (each 2 H, d, *J* 9, ArH); *m*/*z* (CI) 137 (21%) and 121 (100).

(2*R*,3*S*,4*S*)-2,4-Dimethyl-1-(4-methoxybenzyloxy)hex-5-ene-2,3-diol 8

Aqueous hydrogen fluoride (40%; l cm^3) in acetonitrile (11 cm^3) was added to the alcohol **7** (l00 mg, 0.24 mmol) and the solution stirred for 1 h then poured into dichloromethane (20 cm^3). The mixture was washed with water (12 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (4:1) as eluant gave the diol **8** (42 mg, 63%) as a colourless oil; ν_{max}/cm^{-1} 3450, 3090, 1620, 1595, 1520, 1300, 1245, 1170, 1080, 1040 and 830; δ_H 1.13 (3 H, d, *J* 7, 4-CH_3), 1.15 (3 H, s, 2-CH_3), 2.46 (1 H, m, 4-H), 2.75 (1 H, d, *J* 8, 3-OH), 3.05 (1 H, s, 2-OH), 3.37 and 3.63 (each 1 H, d, *J* 10, 1-H), 3.41 (1 H, m, 3-H), 3.80 (3 H, s, OMe), 4.42 (2 H, s, OCH_2Ar), 5.05 (2 H, m, 6-H_2), 5.83–6.00 (1 H, m, 5-H) and 6.88 and 7.23 (each 2 H, d, *J* 9, ArH).

1,1-Carbonyldiimidazole (81 mg, 0.5 mmol) was added to the



diol **8** (35 mg, 0.125 mmol) in benzene (2 cm^3) and the solution heated under reflux for 2 days. After cooling to ambient temperature, the mixture was washed with water (3 × 2 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (5:1) as eluant gave the carbonate **9** (29 mg 76%), as a colourless oil; ν_{max}/cm^{-1} 3095, 1800, 1620, 1580, 1520, 1310, 1255, 1185, 1100, 1040, 920 and 820; δ_H 1.03 (3 H, d, *J* 7, 4-CH_3), 1.48 (3 H, s, 2-CH_3), 2.79 (1 H, m, 4-H), 3.60 (2 H, s, 1-H_2), 3.83 (3 H, s, OMe), 4.05 (1 H, d, *J* 10, 3-H), 4.47 and 4.57 (each 1 H, d, *J* 12, OHC*H*Ar), 5.09 (2 H, m, 6-H_2), 5.83 (1 H, m, 5-H) and 6.90 and 7.25 (each 2 H, d, *J* 10, ArH); *m*/*z* (CI) 324 (M^+ + 18, 21%), 307 (M^+ + 1, 2) and 121 (100).

(2*R*,3*S*,4*S*)-2,4-Dimethyl-3-(trimethylsilylethoxymethoxy)hex-5-ene-1,2-diol 10

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (565 mg, 2.50 mmol) was added to the ether **7** (465 mg, 1,13 mmol) in dichloromethane (4.5 cm^3) and water (250 cm^3). After 20 min, the mixture was filtered, dichloromethane (20 cm^3) was added, and the mixture was washed with water (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (6:1) as eluant gave a mixture of 4-methoxybenzoate esters (458 mg,

97%); ν_{max}/cm^{-1} 3445, 3095, 1715, 1615, 1580, 1520, 1255, 1040, 870 and 835; δ_H 0.00 (9 H, s, 3 × SiMe), 0.92 (2 H, m, CH_2Si), 1.13 (2.1 H, d, *J* 7, 4-CH_3), 1.18 (0.9 H, d, *J* 7, 4-CH_3), 1.28 (2.1 H, s, 2-CH_3), 1.50 (0.9 H, s, 2-CH_3), 2.63 (1 H, m, 4-H), 2.78 (0.3 H, br s, OH), 3.43 (0.7 H, d, *J* l, 3-H), 3.58–4.17 (5.9 H, m, C$H_2$$CH_2Si$, 3-H, OMe, 1-$H_2$), 4.38 (1.4 H, s, 1-$H_2$), 4.68 (0.7 H, d, *J* 6, OHC*H*O), 4.78 and 4.88 (each 0.3 H, d, *J* 6, OHC*H*O), 4.92 (0.7 H, d, *J* 6, OHC*H*O), 5.06 (2 H, m, 6-H_2), 5.98 (1 H, m, 5-H), 6.90 (2 H, d, *J* 10, ArH), 7.97 (0.6 H, d, *J* 10, ArH) and 8.03 (1.4 H, d, *J* 10, ArH); *m*/*z* (FD) 425 ($M^+ + 1$).

Sodium hydroxide (216 mg, 5.4 mmol) in water (5 cm^3) was added to the mixture of 4-methoxybenzoate esters (458 mg, 1.08 mmol) in methanol (10 cm^3) and the mixture stirred for 30 min. Water (5 cm^3) was added and the aqueous layer extracted with dichloromethane (2 × 25 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (5:1) as eluant gave the *title compound* **10** (276 mg, 88%) as a colourless oil; $[\alpha]_D^{20}$ +10 (*c* 1 in MeOH); ν_{max}/cm^{-1} 3400, 3085, 1635, 1370, 1245, 1020, 860 and 830; δ_H 0.00 (9 H, s, 3 × SiMe), 0.98 (2 H, m, CH_2Si), 1.1 (3 H, s, 2-CH_3), 1.12 (3 H, d, *J* 7, 4-CH_3), 2.63 (1 H, m, 4-H), 2.82 (1 H, dd, *J* 10, 3, 1-OH), 3.36 (1 H, dd, *J* 11, 10, 1-H), 3.40 (1 H, d, *J* 2.5, 3-H), 3.58 (1 H, m, HC*H*CH_2Si), 3.62 (1 H, s, 2-OH), 3.78 (2 H, m, 1-H, HC*H*-CH_2Si), 4.65 and 4.85 (each 1 H, d, *J* 7, OHC*H*O), 5.04 (2 H, m, 6-H_2) and 5.88 (1 H, m, 5-H); *m*/*z* (CI) 308 ($M^+ + 18$, 10%) and 291 ($M^+ + 1$, 19).

(2*S*,3*S*,4*S*)-2,4-Dimethyl-2-hydroxy-3-(trimethylsilylethoxymethoxy)hex-5-enal 11

Dimethyl sulfoxide (3.4 cm^3, 47 mmol) in dichloromethane (10 cm^3) was added dropwise to oxalyl chloride (1.9 cm^3, 22 mmol) at −50 °C. After stirring for 10 min, the diol **10** (5.7g, 19.7 mmol) in dichloromethane (6 cm^3) was added and the suspension stirred for 10 min. Triethylamine (14 cm^3, 0.1 mol) was added and the mixture stirred a further 10 min at −60 °C before being allowed to warm to ambient temperature. Saturated aqueous ammonium chloride (20 cm^3) was added and the mixture extracted with ether (2 × 65 cm^3). The organic extracts were washed with water (2 × 80 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (5:1) as eluant gave the *title compound* **11** (4.34 g, 77%) as a colourless oil; $[\alpha]_D^{20}$ +6 (*c* 1.3 in MeOH); ν_{max}/cm^{-1} 3410, 3090, 1725, 1640, 1025, 860, 835; δ_H 0.00 (9 H, s, 3 × SiMe), 1.01 (2 H, m, CH_2Si), 1.12 (3 H, d, *J* 7, 4-CH_3), 1.32 (3 H, s, 2-CH_3), 2.65 (1 H, m, 4-H), 3.50 (1 H, d, *J* l, 3-H), 3.55 and 3.75 (each 1 H, m, HC*H*CH_2Si), 4.64 and 4.88 (each 1 H, d, *J* 7, OHC*H*O), 5.12 (2 H, m, 6-H_2), 5.87 (1 H, m, 5-H) and 9.70 (1 H, s, 1-H); *m*/*z* (CI) 306 ($M^+ + 18$, 0.3%), 157 (21) and 140 (20).

Methyl (4*R*,5*S*,6*S*)-4,6-dimethyl-4-hydroxy-5-(trimethylsilylethoxymethoxy)octa-2,7-dienoate 12

Methoxycarbonylmethylene(triphenyl)phosphorane (7.6 g, 22.8 mmol) was added to the aldehyde **11** (5.45 g, 18.9 mmol) in benzene (200 cm^3) and the solution heated at 80 °C for 16 h before concentrating under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (8:1) as eluant gave the *title compound* **12** (6.15g, 95%) as a colourless oil; $[\alpha]_D^{20}$ +17.7 (*c* 0.35 in MeOH); ν_{max}/cm^{-1} 3430, 3095, 1745, 1668, 1030, 870 and 845; δ_H 0.00 (9 H, s, 3 × SiMe), 0.96 (2 H, m, CH_2Si), 1.08 (3 H, d, *J* 7, 6-CH_3), 1.28 (3 H, s, 4-CH_3), 2.58 (1 H, m, 6-H), 3.35 (1 H, d, *J* l, 5-H), 3.53 (1 H, m, HC*H*-CH_2Si), 3.72 (3 H, s, OMe), 3.78 (1 H, m, HC*H*CH_2Si), 4.42 (1 H, s, OH), 4.63 and 4.87 (each 1 H, d, *J* 10, OHC*H*O), 5.07 (2 H, m, 8-CH_2), 5.9 (1 H, m, 7-H), 6.07 (1 H, d, *J* 16, 2-H) and 7.22 (1 H, d, *J* 16, 3-H); *m*/*z* (CI) 362 ($M^+ + 18$, 4%) and 317 (80).

Methyl (4*R*,5*S*,6*S*)-4,5-bis(trimethylsilylethoxymethoxy)-4,6-dimethylocta-2,7-dienoate 13

Diisopropylethylamine (4 cm^3, 22.8 mol) was added to the alcohol **12** (1.57 g, 4.56 mmol) in dichloromethane (20 cm^3) followed by 2-trimethylsilylethoxymethyl chloride (1.6 cm^3, 9.13 mmol) and the solution heated under reflux for 48 h. The solution was then poured into light petroleum (100 cm^3) and washed with aqueous saturated ammonium chloride (2 × 100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using hexane–ethyl acetate (3:1) as eluant gave the *title compound* **13** (2 g, 92%), as a pale yellow oil; $[\alpha]_D^{20}$ −11 (*c* 0.3 in MeOH); ν_{max}/cm^{-1} 3085, 1725, 1650, 1260, 1020, 860 and 835; δ_H 0.00 (18 H, s, 6 × SiMe), 0.93 (4 H, m, CH_2Si), 1.12 (3 H, d, *J* 7, 6-CH_3), 1.38 (3 H, s, 4-CH_3), 2.65 (1 H, m, 6-H), 3.42 (1 H, d, *J* 2, 5-H), 3.50–3.77 (4 H, m, 2 × C$H_2$$CH_2Si$), 3.70 (3 H, s, OMe), 4.69 (4 H, m, 2 × OCH_2O), 4.95 (2 H, m, 8-H_2), 5.92 (1 H, d, *J* 16, 2-H), 5.93 (1 H, m, 7-H) and 6.95 (1 H, d, *J* 16, 3-H); *m*/*z* (CI) 547 (85%), 492 ($M^+ + 18$, 33), 463 (27), 447 (22) and 417 (36).

Methyl (4*R*,5*S*,6*S*)-4,5-bis(trimethylsilylethoxymethoxy)-4,6-dimethyl-8-hydroxyoct-2-enoate 14

9-Borabicyclo[3.3.1]nonane in THF (0.5 M; 5.1 cm^3) was added to the diene **13** (l g, 2.1 mmol) over 10 min and the mixture heated under reflux for 1.5 h. The mixture was then cooled to ambient temperature and water (5 cm^3) added dropwise. After stirring for 10 min, the solution was cooled to 0 °C and sodium hydroxide (3 M; 5.25 cm^3) and aqueous hydrogen peroxide (100 vol; 5.25 cm^3) were added dropwise. The mixture was stirred for 1 h at ambient temperature then water (25 cm^3) was added and the aqueous phase extracted with dichloromethane (2 × 50 cm^3). The organic extracts were washed with brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether–hexane (2:1) as eluant gave the *title compound* **14** (790 mg, 76%), as a colourless oil; ν_{max}/cm^{-1} 3460, 1736, 1665, 1310, 1280, 1250, 1035, 870 and 845; δ_H 0.00 (18 H, s, 6 × SiMe), 0.92 (4 H, m, 2 × CH_2Si), 1.04 (3 H, d, *J* 7, 6-CH_3), 1.41 (3 H, s, 4-CH_3), 1.4–2.1 (4 H, m, 6-H, 7-H_2, OH), 3.37 (1 H, d, *J* 2, 5-H), 3.48–3.79 (6 H, m, 8-H_2, 2 × C$H_2$$CH_2Si$), 3.73 (3 H, s, OMe), 4.67 and 4.7 (each 1 H, d, OHC*H*O), 4.7 (2 H, s, OCH_2O), 5.94 (1 H, d, *J* 16, 2-H) and 6.97 (1 H, d, *J* 16, 3-H); *m*/*z* (CI) 332 (23%), 317 (79), 287 (36) and 274 (34).

Methyl (4*R*,5*S*,6*S*)-4,5-bis(trimethylsilylethoxymethoxy)-4,6-dimethyl-8-hydroxyoctanoate 15

A solution of the alkene **14** (753 mg, 1.53 mmol) in methanol (4 cm^3) was added to a suspension of palladium on charcoal (10%; 64 mg) in methanol (3 cm^3) and the mixture stirred under an atmosphere of hydrogen at 1 atm for 2 h. The reaction was then filtered through Celite and concentrated under reduced pressure. Chromatography of the residue using hexane–ether (1:2) as eluant gave the *title compound* **15** (608 mg, 80%) as a colourless oil; ν_{max}/cm^{-1} 3450, 1740, 1250, 1040, 860 and 840; δ_H 0.00 (18 H, s, 6 × SiMe), 0.91 (4 H, m, 2 × CH_2Si), 1.05 (3 H, d, *J* 7, 6-CH_3), 1.22 (3 H, s, 4-CH_3), 1.38 (1 H, m, 6-H), 1.75 (1 H, br s, OH), 1.75–2.15 (4 H, m, 7-H_2, 3-H_2), 2.39 and 2.46 (each 1 H, dt, *J* 13, 6, 2-H), 3.27 (1 H, d, *J* 7, 5-H), 3.53–3.80 (6 H, m, 2 × C$H_2$$CH_2Si$, 8-$H_2$), 3.64 (3 H, s, OMe) and 4.7 (4 H, m, 2 × OCH_2O); *m*/*z* (CI) 513 ($M^+ + 19$, 0.25%) and 319 (40).

Methyl (4*R*,5*S*,6*S*)-4,5-bis(trimethylsilylethoxymethoxy)-4,6-dimethyl-7-formylheptanoate 16

Following the procedure outlined for the synthesis of the aldehyde **11**, the alcohol **15** (2.7 g, 5.5 mmol) gave, after chromatography using hexane–ether (2:1) as eluant and Kugelröhr distillation (210 °C, 0.5 mmHg), the *title compound* **16** (2.1 g, 78%) as a colourless oil; ν_{max}/cm^{-1} 1745, 1740, 1250,

1040, 865 and 840; δ_H 0.00 (18 H, s, 6 × SiMe), 0.9 (4 H, m, 2 × CH_2SiMe), 1.10 (3 H, d, *J* 7, 6-CH_3), 1.23 (3 H, s, 4-CH_3), 1.7–2.8 (7 H, overlapping m, 2-H_2, 3-H_2, 6-H, 7-H_2), 3.23 (1 H, d, *J* 2, 5-H), 3.6 (4 H, m, 2 × CH_2CH_2Si), 3.65 (3 H, s, OMe), 4.7 (4 H, m, 2 × OCH_2O), 9.73 (1 H, t, *J* 1.5, CHO); *m*/*z* (CI) 510 (M^+ + 18, 5%), 345 (19%) and 287 (100).

Methyl (4*R*,5*S*,6*S*,8*E*,10*E*,12*E*)-4,5-bis(trimethylsilylethoxymethoxy)-4,6,12-trimethyltetradeca-8,10,12-trienoate 18

Butyllithium in hexanes (1.6 M; 2.8 cm³) was added dropwise to the phosphonate **17** (1.1 g, 4.73 mmol) in THF (20 cm³) at −60 °C and the solution stirred at −60 °C for 30 min. The mixture was then allowed to warm to −30 °C and was stirred at this temperature for 30 min before being cooled to −78 °C and added to a solution of the aldehyde **16** (2.1 g, 4.27 mmol) in THF (15 cm³) at −78 °C. After stirring for 1 h, the cooling bath was removed and the mixture allowed to warm to ambient temperature. Hexamethylphosphoramide (3.7 cm³, 21 mmol) was added and the mixture stirred for 3 h. Ether (60 cm³) was added and the mixture poured into saturated aqueous ammonium chloride (17 cm³) then extracted with ether (3 × 25 cm³). The organic extracts were washed with water (3 × 10 cm³), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on base washed silica using light petroleum (bp 30–40 °C)–ether (6:1) as eluant gave the *title compound* **18** (1.65 g, 79%) as a colourless oil, a mixture of 8*E*:8*Z* isomers (8:1); ν_{max}/cm^{-1} 1740, 1250, 1040, 870 and 845; δ_H 0.00 (18 H, s, 6 × SiMe), 0.91 (4 H, m, 2 × CH_2Si), 1.02 (3 H, d, *J* 7, 6-CH_3), 1.22 (3 H, s, 4-CH_3), 1.72–2.10 (10 H, m, 12-CH_3, 14-H_3, 3-H_2, 6-H, 7-H), 2.29–2.56 (3 H, m, 2-H_2, 7-H), 3.29 (1 H, d, *J* 2, 5-H), 3.62 (4 H, m, 2 × C$H_2$$CH_2$Si), 3.63 (3 H, s, OMe), 4.73 (4 H, m, 2 × OCH_2O), 5.39 (0.1 H, m, 9$_Z$-H), 5.6 (1.9 H, m, 9$_E$-H, 13-H) and 6.0–6.2 (3 H, m, 8-H, 10-H, 11-H); *m*/*z* (CI) 508 (M^+ + 18, 38%), 453 (26), 425 (25) and 395 (28).

Sodium hydroxide (0.68 g, 17 mmol) in water (1.1 cm³) was added to the ester **18** (2.08 g, 4.2 mmol) in ethanol 15 cm³ and the mixture stirred for 4 h at room temperature. An ice-cold solution of tartaric acid (6.3 g, 42 mmol) in water (60 cm³) was added and the aqueous phase extracted with ether (4 × 50 cm³). The ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the acid **19** (2.1 g) as a pale yellow oil, used without further purification; δ_H 0.00 (18 H, s, 6 × $SiMe_3$), 0.93 (4 H, m, 2 × CH_2Si), 1.05 (3 H, d, *J* 7, 6-CH_3), 1.25 (3 H, s, 4-CH_3), 1.73–2.12 (10 H, m, 12-CH_3, 14-H_3, 3-H_2, 6-H, 7-H), 2.42–2.60 (3 H, m, 2-H_2, 7-H), 3.3 (1 H, d, *J* 2, 5-H), 3.65 (4 H, m, 2 × C$H_2$$CH_2$Si), 4.74 (4 H, m, 2 × OCH_2O), 5.44 (0.1 H, m, 9$_Z$-H), 5.65 (1.9 H, m, 9$_E$-H, 13-H) and 5.93–6.22 (3 H, m, vinylic H).

Carbonyl 1,1′-diimidazole (0.71 g, 4.4 mmol) was added to a solution of the acid **19** (2.1 g, 3.65 mmol) in THF (25 cm³) and the mixture stirred at room temperature for 6 h before being diluted with ether (40 cm³). The ethereal solution was washed with ice-cold water (30 cm³) and brine (25 cm³), dried (Na_2SO_4) and concentrated under reduced pressure to give the acyl imidazole **20** (2.1 g, 94%), as a viscous colourless oil used without further purification; δ_H 0.00 (18 H, s, 3 × SiMe), 0.91 (4 H, m, 2 × CH_2Si), 1.08 (3 H, d, *J* 7, 6-CH_3), 1.28 (3 H, s, 4-CH_3), 1.73–2.23 (10 H, m, 12-CH_3, 14-H_3, 3-H_2, 6-H, 7-H), 2.47 (1 H, m, 7-H), 3.00 and 3.15 (each 1 H, m, 2-H), 3.38 (1 H, d, *J* l, 5-H), 3.63 (4 H, m, 2 × C$H_2$$CH_2$Si), 4.75 (4 H, m, 2 × OCH_2O), 5.44 (0.1 H, m, 9$_Z$-H), 5.55–5.78 (1.9 H, m, 9$_E$-H, 13-H), 6.02–6.2 (3 H, m, vinylic H) and 7.09, 7.53 and 8.23 (each 1 H, s, imid-H).

(5*S*)-l-Benzoyl-3-[(4*R*,5*S*,6*S*,8*E*,10*E*,12*E*)-4,5-bis(trimethylsilylethoxymethoxy)-1- oxo-4,6,12-trimethyltetradeca-8,10,12-trienyl]-5-phenylmethyl-3-phenylselenopyrrolidin-2-one 23

A cooled solution of the pyrrolidinone **21** (2 g, 7.1 mmol) in THF (20 cm³) was added to a solution of lithium hexamethyldisilazide (6.93 mmol) in THF (20 cm³) at −78 °C *via* a cannula and the mixture stirred for 45 min. The imidazole **20** (2.05 g, 3.38 mmol) in THF (25 cm³) was added and the mixture stirred for 2 h at −78 °C then for 1 h at ambient temperature. Saturated aqueous ammonium chloride (15 cm³) was added and the mixture extracted with ether (3 × 75 cm³). The ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on base washed silica using light petroleum–ether (4:1) as eluant gave the pyrrolidinone **22** (2.55 g, 92%) as a pale yellow oil; δ_H 0.00–0.10 (18 H, m, 6 × SiMe), 0.80–1.13 (10 H, m, 4′-CH_3, 6′-CH_3, 2 × CH_2Si), 1.7–3.0 (15 H, overlapping m), 3.2–3.8 (8 H, m, 5′-H, CH_2Ph, 3-H, 2 × C$H_2$$CH_2$Si), 4.65–4.85 (5 H, m, 2 × OCH_2O, 5-H), 5.43 (0.15 H, m, 9′$_Z$-H), 5.50–5.78 (1.85 H, m, 9′$_E$-H, 13′-H), 6.00–6.25 (3 H, m, vinylic H) and 7.25–7.70 (10 H, ArH); *m*/*z* (DCI-ZAB) 835 (M^+ + 18), 818 (M^+ + 1); followed by recovered lactam **21** (0.75 g).

A cooled solution of the pyrrolidinone **22** (2.55 g, 3.12 mmol) in THF (20 cm³) was added to lithium hexamethyldisilazide (3.12 mmol) in THF (20 cm³) at −72 °C *via* a cannula and the mixture stirred at this temperature for 30 min before adding benzeneselenenyl chloride (0.66 g, 3.43 mmol) in THF (l0 cm³). The mixture was stirred for 2.5 h at −72 °C then saturated aqueous ammonium chloride (20 cm³) was added and the mixture allowed to warm to room temperature. Water (15 cm³) was added, the mixture was extracted with ether (3 × 75 cm³) and the ethereal extracts were washed with brine (50 cm³), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on base washed silica using light petroleum–ether (5:1) as eluant gave the pyrrolidinone **23** (2.45 g, 81%) as a 2:1 mixture of diastereoisomers; δ_H 0.00 and 0.05 (each 9 H, s, 3 × $SiMe_3$), 0.85–1.05 (7 H, m, 2 × CH_2Si, 6′-CH_3), 1.25 (2 H, s, 4′-CH_3), 1.28 (1 H, s, 4′-CH_3), 1.70–2.10 (10 H, m, 12′-CH_3, 14′-H_3, 6′-H, 7′-H, 3′-H_2), 2.40–2.95 (5 H, m, HC*H*Ph, 4-H, 2′-H_2, 7′-H), 3.18–3.40 (3 H, m, 5′-H, HC*H*Ph, 4-H), 3.65 (4 H, m, 2 × C$H_2$$CH_2$Si), 4.45–4.82 (5 H, m, 5-H, 2 × OCH_2O), 5.37–5.83 (2 H, m, 9′-H, 13′-H), 6.00–6.30 (3 H, m, 8′-H, 10′-H, 11′-H) and 7.05–7.66 (15 H, m, ArH); *m*/*z* (CI) 564 (3%) and 418 (13).

(16*S*,17*S*,18*R*)-2-Benzoyl-17,18-bis(trimethylsilylethoxymethoxy)-16,18-dimethyl-10-phenyl[11]cytochalasa-6(7),13-diene-1,21-dione 25

A solution of hydrogen peroxide (100 vol; 2.85 cm³) in water (1.1 cm³) was added to a solution of the selenide **23** (2.45 g, 2.52 mmol) in chloroform (175 cm³) at −50 °C. A solution of *m*-chloroperoxybenzoic acid (510 mg, 2.52 mmol) in chloroform (90 cm³) was added, and the mixture stirred at −50 °C for 15 min then at 0 °C for 10 min before being washed with saturated aqueous sodium bicarbonate (2 × 50 cm³), water (50 cm³) and brine (50 cm³) to provide a solution of the pyrrolinone **24**; δ_H 7.94 (1 H, d, *J* 2, 4-H). After drying (Na_2SO_4), the solution of the pyrrolinone **24** was added to degassed toluene (900 cm³) and the solution heated at 80 °C for 16 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ether (8:1) as eluant gave the *title compound* **25** (1.09 g, 53%) as a colourless oil; ν_{max}/cm^{-1} ($CHCl_3$) 1735, 1695, 1684, 1600, 1290, 1250, 1055, 1020, 862 and 840; δ_H 0.00 and 0.05 (each 9 H, s, 3 × SiMe), 0.92 (7 H, m, 2 × CH_2Si, 16-CH_3), 1.05 (3 H, d, *J* 6, 5-CH_3), 1.15 (3 H, s, 18-CH_3), 1.55–1.97 (5 H, m, 15-H, 16-H, 19-H_2, 20-H), 1.73 (3 H, s, 6-CH_3), 2.35–2.53 (2 H, m, 5-H, 15-H), 2.65 (1 H, m, 8-H), 2.73 (1 H, dd, *J* 14, 9, 10-H), 3.05 (1 H, d, *J* 14, 10-H), 3.15 (1 H, m, 4-H), 3.35 (1 H, m, 17-H), 3.40–3.85 (4 H, m, 2 × C$H_2$$CH_2$Si), 4.32 (1 H, m, 3-H), 4.37 (1 H, m, 20-H), 4.57–4.87 (4 H, m, 2 × OCH_2O), 5.20 (1 H, m, 14-H), 5.65 (1 H, br s, 7-H), 6.12 (1 H, dd, *J* 13, l0, 13-H) and 7.13–7.57 (10 H, m, ArH); *m*/*z* (FAB) 833 (M^+ + 18); a second fraction (118 mg, 5%) contained a mixture of minor diastereoisomers.

(16*S*,17*S*,18*R*)-17,18-Bis(trimethylsilylethoxymethoxy)-16,18-dimethyl-10-phenyl[11]cytochalasa-6(7),13-diene-1,21-dione 26

A solution of the Diels–Alder product **25** (1.06 g, 1.3 mmol) in methanol (10 cm^3) was added to a solution of sodium hydroxide (1.04 g, 26 mmol) in methanol (15 cm^3) containing water (1.2 cm^3) and the mixture stirred for 2.5 h before being poured into water (100 cm^3) and extracted into ether (3 × 100 cm^3). The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3:2) as eluant gave the *title compound* **26** (817 mg, 89%) as a white powder; $[\alpha]^{20}$ −84 (*c* 0.44 in MeOH); ν_{max}/cm^{-1} ($CHCl_3$) 3420, 1690, 1250, 1055, 1020, 960, 940; δ_H 0.00 and 0.05 (each 9 H, s, 3 × SiMe), 0.9 and 1.0 (each 2 H, m, CH_2Si), 1.06 (3 H, d, *J* 8, 16-CH_3), 1.14 (3 H, d, *J* 7, 5-CH_3), 1.16 (3 H, s, 18-CH_3), 1.65 (3 H, m, 16-H, 19-H_2), 1.72 (3 H, 2, 6-CH_3), 1.80 (1 H, m, 15-H), 1.90 (1 H, m, 20-H), 2.40 (1 H, m, 5-H), 2.42 (1 H, dd, *J* 14, 10, 10-H), 2.49 (1 H, m, 8-H), 2.55 (1 H, m, 15-H), 2.70 (1 H, dd, *J* 14, 4, 10-H), 3.05 (1 H, m, 4-H), 3.25 (1 H, m, 3-H), 3.39 (1 H, s, 17-H), 3.53 (1 H, m, HC*H*CH_2Si), 3.63 (2 H, m, 2 × HC*H*CH_2Si), 3.93 (1 H, m, HC*H*CH_2Si), 4.66 (1 H, m, 20-H), 4.68, 4.72, 4.83 and 4.93 (each 1 H, d, *J* 7, OHC*H*O), 5.25 (1 H, ddd, *J* 15, 11, 4, 14-H), 5.39 (1 H, br s, NH), 5.45 (1 H, br s, 7-H), 6.35 (1 H, ddd, *J* 15, 10, 1.5, 13-H), 7.07–7.38 (5 H, m, ArH); *m*/*z* (CI) 784 (M^+ + 73, 12%), 729 (M^+ + 18, 43), 712 (M^+ + 1, 3), 594 (35), 564 (43), 536 (29), 506 (21), 464 (100) and 416 (90).

(16*S*,17*S*,18*R*)-16,18-Dimethyl-17,18-methylenedioxy-10-phenyl[11]cytochalasa-6(7),13-diene-1,21-dione 27

Aqueous hydrogen fluoride in acetonitrile (150 μl from a stock solution comprising 40% hydrogen fluoride, 1 cm^3 in acetonitrile 3 cm^3) was added to a solution of the macrocycle **26** (15 mg, 0.02 mmol) in acetonitrile (150 cm^3) and the mixture stood at room temperature for 6 h before diluting with dichloromethane (5 cm^3), washing with water (2 cm^3), drying ($MgSO_4$) and concentrating under reduced pressure. Chromatography of the residue using light petroleum–ether (1:3) as eluant gave the *title compound* **27** (5 mg, 55%) as a white solid, mp 216–217 °C (Found: M^+ 463.2722. $C_{29}H_{37}NO_4$ requires *M*, 463.2725); ν_{max}/cm^{-1} 3420, 1700 1085 and 990; δ_H 1.18 (3 H, d, *J* 6.5, 16-CH_3), 1.19 (3 H, d, *J* 6, 5-CH_3), 1.23 (3 H, s, 18-CH_3), 1.73 (3 H, s, 6-CH_3), 1.80–1.95 (4 H, m, 15-H, 16-H, 19-H_2), 2.02 (1 H, m, 20-H), 2.40 (1 H, dd, *J* 13.5, 9.5, 10-H), 2.42 (1 H, m, 5-H), 2.52 (1 H, m, 8-H), 2.72 (2 H, m, 10-H, 15-H), 3.00 (1 H, dd, *J* 6.5, 3, 4-H), 3.24 (1 H, m, 3-H), 3.32 (1 H, br s, 17-H), 4.09 (1 H, ddd, *J* 19, 11.5, l, 20-H), 4.90 and 5.23 (each 1 H, s, OHC*H*O), 5.24 (1 H, ddd, *J* 16, 12, 4, 14-H), 5.32 (1 H, br s, NH), 5.49 (1 H, br s, 7-H), 6.26 (1 H, ddd, *J* 16, 10.5, 3, 13-H) and 7.07–7.38 (5 H, m, ArH); *m*/*z* (CI) 481 (M^+ + 18, 3%), 464 (M^+ + 1, l00) and 434 (12).

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