# 22. Unprecedented Ring Contractions in Cytochalasans: Formation of [10]Cytochalasans and a Cyclohepta[4,5]benz[1,2-*d*]isoindole Derivative

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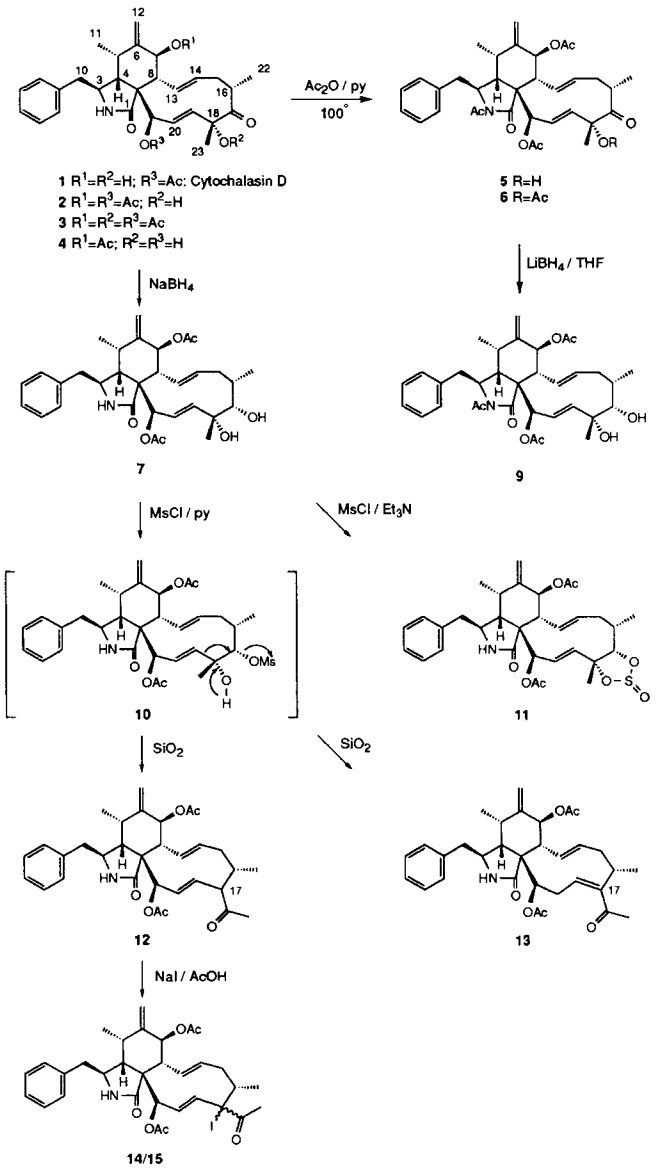
A series of transformations of cytochalasin D (**1**; zygosporin A) was carried out. After treatment of the diol **7** with mesyl chloride and pyridine, and subsequent chromatography on silica gel, the 17-acetyl derivatives **12** and **13**, the first members of the hitherto unknown [10]cytochalasans, were obtained. The alcohol **8** was converted to the chlorosulfinate **18** under the same conditions. Replacement of pyridine by triethylamine in the mesylation reaction led to the cyclohepta[4,5]benz[1,2-*d*]isoindole derivative **20**, also representing a novel ring system.

The cytochalasans are a class of fungal secondary metabolites which exhibit a variety of interesting biological activities, including inhibition of cell division and motility. They also have become important tools in cell biology. Structurally, they are characterized by the presence of a bicyclic, highly substituted hydrogenated isoindole nucleus, to which a 11- to 16-membered macrocyclic ring is fused. The latter is either a carbocycle (a lactone or a cyclic carbonate) or an oxalactone. The cytochalasins have a Ph group at C(10), while other similar compounds possess indolyl or isopropyl groups at this position. Cytochalasans occur in many groups of Ascomycotina and/or their anamorphic stages, including Xylarvales, but are not found in bacteria or plants. At present, *ca.* 60 naturally occurring compounds are known [1] [2].

In connection with studies on the relationship between chemical structure and biological activity, we have carried out a series of reactions on cytochalasin D (**1**; zygosporin A), which is the major metabolite of *Zygosporium masonii* [3], and on its derivatives with the aim to remove the O function at C(17). This goal was not attained, however, a series of unexpected reactions and rearrangements has been observed. The latter led to the hitherto unknown group of [10]cytochalasans and a cyclohepta[4,5]benz[1,2-*d*]isoindole derivative starting from [11]cytochalasans.

Treatment of cytochalasin D (**1**) with $Ac_2O$ and pyridine at 50° led to 7-*O*-acetylcytochalasin (**2**) [4] (*Scheme 1*). The same reaction carried out at 100° gave the 2-*N*,7-*O*-diacetyl derivative **5** as major product (39%), and the 7-*O*-acetyl derivative **2** (25%), the 2-*N*,7,18-*O*-triacetyl derivative **6** (12%), and the 7,18-*O*-diacetyl derivative **3** (18%) as minor products. The *N*-acetyl group of **5** and **6** could selectively be removed by treatment with aqueous AcOH at 100° yielding 7-*O*-acetyl cyctochalasin D (**2**) and 7,18-*O*-diacetylcytochalasin D (**3**), respectively. Selective hydrolysis of the 18-AcO group leading from **3** to **2** was achieved with $NH_3$/MeOH at 55°. For the anticipated removal of the 17-oxo group, it was planned to convert it first to an OH group. Subsequent mesylation, substitution of the MsO group by I, and hydrogenolytic removal of the latter should lead

*Scheme 1*




to the desired 17-deoxo series. Treatment of **2** with $NaBH_4$/dioxane/$H_2O$ at 20° gave the vicinal diol **7** [5]. The selective reduction of the 17-oxo group was achieved also in the case of the *N*-acetyl derivative **5** leading to the diol **9**. The assignment of the configuration at C(17) is based on the subsequent conversions and by comparison with **7** [5].

Treatment of the known diol **7** with MsCl and pyridine led to the 17-MsO **10**. Surprisingly, it proved to be unstable. By chromatography on silica gel, it was converted to two isomeric compounds which were devoid of sulfur but contained a new oxo group

as an acetyl moiety. Structures **12** and **13** were assigned to these products on the basis of their mass and NMR spectra. The molecular formula $C_{32}H_{39}NO_6$ was deduced from the MS, showing *m/z* 533 as the highest mass corresponding to the $M^+$ ion, as well as $^1$H- and $^{13}$C-NMR spectra. In the $^1$H-NMR, the signal of new acetyl group was shifted downfield compared to that of the Me group at C(18) in **7** or **10**, respectively, and appeared at 2.15 ppm. In the $^{13}$C-NMR, the additional C=O group led to a signal at 208.8 ppm.

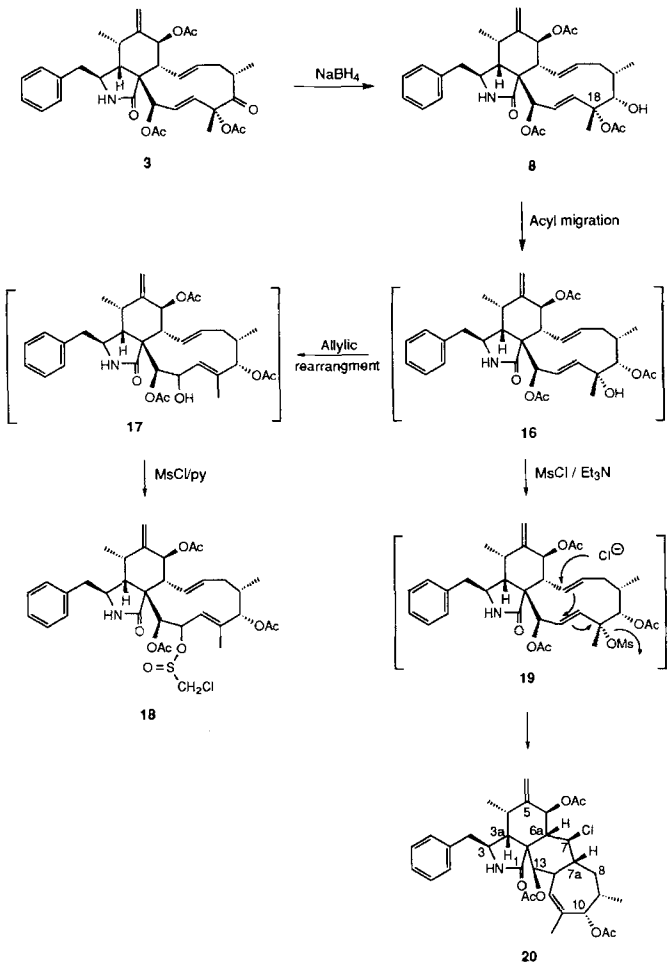
The 17-acetyl derivative **12** is formed by elimination of methanesulfonic acid, the removal of the MsO group being enhanced by the neighboring-group effect of the C(18)–C(19) bond and deprotonation of the 19-OH group as shown in formula **10**. By this pinacol rearrangement, the original [11]cytochalasan is transformed into a [10]cytochalasan by ring contraction. Isomerization of **12** led to the $\alpha\beta$-unsaturated ketone **13.** The [10]cytochalasans **12** and **13** represent a novel structural type in this class of microbial metabolites, since no natural product possessing this system has become known so far.

When pyridine was replaced by $Et_3N$ in the mesylation of **7**, no rearrangement took place. Structure **11** of the S-containing product was deduced from the spectral data. The MS, showing $[M + 1]^+$ at *m/z* 598, the $^{13}$C-NMR with a total of 32 signals, and the $^1$H-NMR were consistent with the structure of a cyclic sulfinate.

Still assuming that the stable product of the reaction of the diol **7** with MsCl and pyridine was the desired mesyl derivative **10**, it was treated with NaI and AcOH, hoping that the MsO group would be replaced by the I-atom. Indeed, two compounds were obtained which were devoid of sulfur but contained iodine according to the elemental analysis. They showed identical spectral data, and it was soon clear that they were derived from the rearranged 17-acetyl derivative **12**. Thus, structures **14** and **15** were assigned to the products. It was not possible to determine the configuration at C(17) unambiguously.

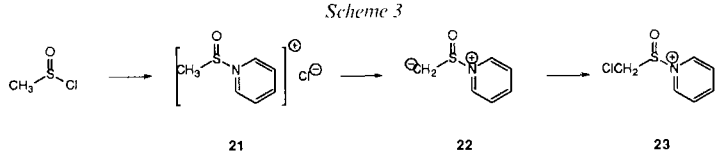
As it was not possible to remove the O function at C(17) in this way, we planned to protect the 18-OH group in order to eventually suppress the ring contraction. Acetylation of 7-*O*-acetylcytochalasin D (**2**) with $Ac_2O$ and pyridine at 100° yielded a mixture of the di-*O*-acetyl derivative **3** and tri-*N*,7,18-*O*-acetylcytochalasin D (**6**). Reduction of the oxo group of **3** with $NaBH_4$ in dioxane/$H_2O$ yielded the alcohol **8** (*Scheme 2*). The configuration at C(17) could not be determined on the basis of the spectral data, but complete hydrolysis of **8** as well as **7** gave the same compound. Therefore, the configuration at C(17) of **8** must be the same as in the known compound **7**. Treatment of **8** with MsCl in pyridine gave a product which surprisingly did not only contain sulfur but also chlorine according to the mass spectrum and elemental analysis. The molecular formula was $C_{35}H_{44}ClNO_9S$. On the basis of extended NMR studies, structure **18** is proposed for the product. In the $^1$H-NMR, the easily recognizable Me group at C(18) appeared as a *singlet* at 1.87 ppm, more than 0.5 ppm downfield when compared with **8**. This was a first indication for a shift of the double bond from C(19)=C(20) to C(18)=C(19). This assumption was confirmed, when a 'coupling chain' of protons could be determined, starting with the H–C(21) which showed coupling to the proton appearing at 6.40 ppm, which itself exhibited a coupling constant of $J$ = 11.5 Hz to the olefinic proton at 4.79 ppm. C,H Correlation showed that the protons at C(21) as well at C(20) were not attached to an olefinic C-atoms. This was only possible when the original C(20)=C(21) bond had migrated to C(19)=C(20). The prominent *AB* system at 4.54 ppm, which corresponded to an isolated $CH_2$ group according C,H correlation, indicates that the Me

*Scheme 2*




group of the Ms moiety had been chlorinated. Accordingly, **18** is an ester of chloromethanesulfinic acid. The formation of methylsulfinic chloride from MsCl, which would require a reduction step, cannot be readily explained considering the reaction conditions. We rather assume that the sample of MsCl which was used, had contained traces of methylsulfinic chloride as an impurity; however, we were not able to detect it analytically. The chlorination of the Me group proceeded in an analogous manner as described in the case of carboxylic acids and pyridine [6] *via* the formation of the salt **21**

*Scheme 3*



(*Scheme 3*). The H-atoms would be strongly acidic in order to allow deprotonation to the betain **22**. Subsequent chlorination of the carbanion by MsCl would lead to the reactive species **23**. The substrate **17** for the reaction with methylsulfinic chloride would have been formed from **8** by a 1,2-acyl migration leading to the 18-*O*-acetyl derivative **16**. It is converted to **17** by a subsequent allylic rearrangement.

A different but also surprising result was obtained, when the mesylation of **8** was carried out in the presence of $Et_3N$ in place of pyridine. The product obtained did not contain sulfur but chlorine. The molecular formula $C_{34}H_{42}ClNO_7$ was deduced from the MS ($[M + 1]^+$ at $m/z$ 612) and from the elemental analysis. The NMR data were compatible with structure **20** of a cyclohepta[4,5]benz[1,2-*d*]isoindole. In the $^1$H-NMR, only 3 olefinic protons were detected which could be explained only as a result of the proposed rearrangement. The signal of the Me group at C(11) was shifted downfield by 0.44 ppm as compared to compound **8**. In the $^{13}$C-NMR, the absence of a third C=C bond was obvious as well. The signal of C(7a) was shifted upfield and appeared at 42.6 ppm, C(7) experienced the deshielding influence of the Cl-atom, appearing at 75.6 ppm. The formation of **20** can be explained by a rearrangement of the intermediate **19** accompanied by a ring contraction induced by a nucleophilic attack of $Cl^-$ and the removal of the MsO group. Compound **20** also represents a novel type of a cyclohepta[4,5]benz[1,2-*d*]isoindole.

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## Experimental Part

*General.* Water- and air-sensitive reactions were carried out under Ar or $N_2$. THF was freshly distilled over Na-K alloy. All org. extracts were dried ($Na_2SO_4$) and evaporated below 40°. TLC: silica gel *60 F254* (*Merck*). Column chromatography (CC): silica gel (60–200 μm, *Chemische Fabrik Uetikon*). $[\alpha]_D$: *Perkin-Elmer-141* polarimeter. IR Spectra [cm$^{-1}$]: *Perkin-Elmer-781* IR spectrometer. NMR: *Varian-VXR-400* ($^1$H, 400 MHz; $^{13}$C, 101 MHz); chemical shifts in ppm rel. to internal TMS or to residual non-deuterated solvent. MS (*m/z* (%)): *VG 70-250* spectrometer (Cl with $NH_3$, FAB with NBA).

*Acetylation of Cytochalasin D* (**1**). To a soln. of **1** (1.04 g, 2.05 mmol) in pyridine (20 ml), $Ac_2O$ (10 ml) was added. After stirring at 100° for 14 h, ice was added to the reaction mixture, followed by extraction with $CH_2Cl_2$ and evaporation *in vacuo*. The crude product was purified on silica ($CH_2Cl_2$/acetone): 280 mg (0.51 mmol; 25%) of *(7S,16S,18R,21R,13E,19E)-18-hydroxy-16,18-dimethyl-1,17-dioxo-10-phenyl[11]cytochalasa-6(12),13,19-triene-7,21-diyl diacetate* (**2**), 180 mg (0.37 mmol; 18%) of *(7S,16S,18R,21R,13E,19E)-16,18-dimethyl-1,17-dioxo-10-phenyl[11]cytochalasa-6(12),13,19-triene-7,18,21-triyl triacetate* (**3**), 470 mg (0.80 mmol; 39%) of *(7S,16S,18R,21R)-2-acetyl-16,18-dimethyl-18-hydroxy-1,17-dioxo-10-phenyl[11]cytochalasa-6(12),13,19-triene-7,21-diyl diacetate* (**5**), and 150 mg (0.24 mmol; 12%) of *(7S,16S,18R,21R,13E,19E)-2-acetyl-16,18-dimethyl-1,17-dioxo-10-phenyl[11]cytochalasa-6(12),13,19-triene-7,18,21-triyl triacetate* (**6**), were obtained.

*Selective Hydrolysis of the* N*-Acetyl Derivatives* **5** *and* **6**. A mixture of **5**, AcOH, pyridine, and $H_2O$ was stirred for 20 h at 95°. After the addition of ice, the mixture was extracted with $CH_2Cl_2$, dried, and evaporated *in vacuo*. Pure **2** was obtained. Treatment of **6** for 6 h under the same conditions gave **3**.

*(7S,16S,17S,18R,21R,13E,19E)-17-Hydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-6(12),13,19-triene-7,18,21-triyl Triacetate* (**8**). To a soln. of **3** (319 mg, 0.54 mmol) in dioxane (30 ml), $NaBH_4$ (104 mg, 2.77 mmol) in $H_2O$ (25 ml) was added. After stirring at r.t. for 7 h, the reaction mixture was acidified with 2N $H_2SO_4$ until pH ~1. After stirring for an additional h, the mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$/acetone 9:1. The extracts were washed with $H_2O$, dried ($Na_2SO_4$), and evaporated *in vacuo*. The crude product was purified by CC (160 g of silica, $CH_2Cl_2$/acetone 85:15→65:35): **8** (105 mg, 33%) and unreacted starting material **3** (106 mg, 33%) were obtained. $[\alpha]_D^{25} = +25.7$ (*c* = 2.0, $CHCl_3$). $^1$H-NMR (400 MHz, $CDCl_3$): 0.88 (*d*, *J* = 6.5, Me–C(5)); 1.11 (*d*, *J* = 7, Me–C(16)); 1.30 (*s*, Me–C(18)); 1.72 (*d*, *J* = 6, H–C(15)); 1.93 (*s*, AcO–C(7)); 2.02 (*m*,

H–C(15)); 2.15 (*m*, H–C(4)); 2.27 (*s*, AcO–C(21)); 2.33 (*s*, AcO–C(18)); 2.73 (*m*, 2 H–C(10)); 2.81 (*m*, H–C(5)); 3.18 (*dd*, $J$ = 11, 10, H–C(8)); 3.25 (*m*, H–C(3)); 4.63 (*d*, $J$ = 2, H–C(17)); 5.05 (*s*, H–C(12)); 5.21 (*m*, H–C(14)); 5.25 (*s*, H–C(12)); 5.25 (*d*, $J$ = 10, H–C(7)); 5.35 (*dd*, $J$ = 2, 16, H–C(19)); 5.55 (*dd*, $J$ = 2.5, 2.5, H–C(21)); 5.78 (*dd*, $J$ = 10, 15.5, H–C(13)); 5.99 (br. *s*, NH); 6.13 (*dd*, $J$ = 16, 3, H–C(20)); 7.22 (*m*, Ph). $^{13}$C-NMR (101 MHz, $CDCl_3$): 13.6 (C(11)); 20.9, 21.10, 21.13 (3 MeCOO); 24.5 (C(22)); 25.9 (C(23)); 33.1 (C(5)); 33.4 (C(16)); 36.2 (C(15)); 44.3 (C(8)); 45.2 (C(10)); 50.0 (C(4)); 51.3 (C(9)); 53.6 (C(3)); 72.3 (C(7)); 72.8 (C(18)); 77.8 (C(21)); 85.2 (C(17)); 114.9 (C(12)); 127.0 ($C_p$); 128.2 (C(20)); 128.8, 129.2 ($C_o$, $C_m$); 129.1 (C(13)); 132.7 (C(19)); 134.6 (C(14)); 137.2 (C(6)); 145.7 ($C_i$); 169.7, 170.2, 172.3, 173.8 (4 CO).

*(7S,16S,17S,18R,21R,13E,19E)-2-Acetyl-17,18-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-6(12),13,19-triene-7,21-diyl Diacetate* (**9**). To a soln. of **5** (102 mg, 0.17 mmol) in dry THF (3 ml), 0.75 ml of a 1.7M $LiBH_4$ in THF were added under Ar at −78°. After warming to −50°, the mixture was stirred for 45 h, then acidified with cold 2N $H_2SO_4$, warmed to r.t., and extracted with $CH_2Cl_2$. The crude product (91 mg) was purified on silica gel ($CH_2Cl_2$/acetone 9:1): 50 mg (0.084 mmol; 49%) of **9** ($[\alpha]_D^{25}$ = +98.2 ($c$ = 0.7, $CHCl_3$)) were obtained, as well as **7** (10 mg; 10%).

*(7S,16S,17S,18R,21R,13E,19E)-16,18-Dimethyl-10-phenyl-17,18-(sulfinyldioxy)[11]cytochalasa-6(12),13,19-triene-7,21-diyl Diacetate* (**11**). MsCl (0.11 ml, 1.41 mmol) was added to a soln. of **7** (74 mg, 0.125 mmol) and $Et_3N$ (0.5 ml, 3.6 mmol) in $CH_2Cl_2$ (5 ml) at 0°. After stirring for 1.25 h at r.t., ice was added to the mixture, which was then extracted with $CH_2Cl_2$/acetone 9:1. The org. extracts were washed with 2N HCl and $H_2O$, dried ($Na_2SO_4$), and evaporated. The crude material (90 mg) was purified by CC (30 g of silica, $CH_2Cl_2$/acetone 95:5→70:30 and $CH_2Cl_2$/$Et_2O$ 85:15→70:30) to give **11** (30 mg, 40%). $[\alpha]_D^{25}$ = +7.8 ($c$ = 1.40, $CHCl_3$). $^1$H-NMR (400 MHz, $CDCl_3$): 0.94 (*d*, $J$ = 6.5, Me–C(11)); 1.22 (*d*, $J$ = 7.5, Me–C(16)); 1.56 (*s*, Me–C(18)); 1.93 (*s*, AcO–C(7)); 1.98 (*m*, H–C(16)); 2.15 (*m*, H–C(4)); 2.29 (*s*, AcO–C(21)); 2.59 (*td*, $J$ = 11, 14, 2 H–C(15)); 2.69 (*dd*, $J$ = 9, 10.5, H–C(10)); 2.84 (*dd*, $J$ = 5, 13,5 H–C(5), H–C(10)); 3.21 (*dd*, $J$ = 10.5, 11, H–C(8)); 3.26 (*m*, H–C(3)); 4.56 (*s*, H–C(17)); 5.05 (*s*, H–C(12)); 5.11 (*dd*, $J$ = 2, 15.5, H–C(19)); 5.20 (*m*, H–C(7)); 5.21 (*m*, H–C(14)); 5.25 (*s*, H–C(12)); 5.55 (*d*, $J$ = 2.5, H–C(21)); 5.66 (*s*, NH); 5.73 (*ddd*, $J$ = 1.5, 10, 15, H–C(13)); 5.92 (*dd*, $J$ = 3, 15.5, H–C(20)); 7.24 (*m*, Ph). $^{13}$C-NMR (101 MHz, $CDCl_3$): 13.5 (C(11)); 20.9, 21.0 (2 *Me*COO); 24.4 (C(23)); 25.7 (C(22)); 30.5 (C(16)); 33.1 (C(5)); 34.9 (C(15)); 44.1 (C(8)); 45.4 (C(10)); 50.0 (C(4)); 50.5 (C(9)); 53.6 (C(3)); 72.2 (C(7)); 77.4 (C(21)); 91.0 (C(17)); 91.2 (C(18)); 115.3 (C(12)); 127 ($C_p$); 128.5 (C(20)); 128.7 (C(19)); 128.9 (C(13)); 129.1, 129.14 ($C_o$, $C_m$); 134.6 (C(14)); 137.1 (C(6)); 145.4 ($C_i$); 169.6, 169.9 (2 Me*C*OO); 173.3 (C(1)). FAB-MS: 598 (18, $[M + 1]^+$).

*(7S,16S,17ξ,21R,13E,19E)-17-Acetyl-16-methyl-10-phenyl[10]cytochalasa-6(12),13,19-triene-7,21-diyl Diacetate* (**12**). A soln. of MsCl in pyridine (1.7 ml, 2.1M) was added to **7** (664 mg, 1.21 mmol) in pyridine (10 ml) at −20°. After stirring for 19 h at r.t., ice was added to the reaction mixture (0.5 h), which was diluted with $H_2O$ and finally extracted with $CH_2Cl_2$/acetone 9:1. The org. extracts were washed with 2N HCl, 2N $NaHCO_3$, and $H_2O$, dried ($Na_2SO_2$) and evaporated *in vacuo*. The crude product 690 mg) was purified by CC (250 g of silica, $CH_2Cl_2$/acetone 95:5→75:25). **12** (146 mg, 23%) as well as **13** (66 mg) and **10** (398 mg, 52%) were obtained. $[\alpha]_D^{25}$ = +53.8 ($c$ = 1.37, $CHCl_3$). IR ($CCl_4$): 3430, 3090, 3060, 3030, 2970, 2935, 2880, 1745, 1715, 1690, 1370, 1225 $cm^{-1}$. $^1$H-NMR (400 MHz, $CDCl_3$): 0.97 (*d*, $J$ = 7, Me–C(5)); 1.03 (*d*, $J$ = 7, Me–C(16)); 1.70–1.80 (*m*, H–C(16)); 1.93 (*s*, AcO–C(7)); 2.01–2.05 (*m*, H–C(15)); 2.09 (*dd*, $J$ = 4, 4.5, H–C(4)); 2.15 (*s*, MeCO–C(17)); 2.30 (*s*, AcO–C(21)); 2.63 (*ABX*, $J$ = 9.5, 13.5, H–C(10)); 2.83 (*ABX*, $J$ = 4.5, 13.5, H–C(10)); 2.86–2.89 (*m*, H–C(5)); 3.18–3.27 (*m*, H–C(3), H–C(15)); 3.33 (*dd*, $J$ = 10, 11, H–C(8)); 3.41–3.43 (*m*, H–C(17)); 5.05 (*m*, H–C(12)); 5.18–5.23 (*m*, H–C(7), H–C(14), H–C(19)); 5.24 (*m*, H–C(12)); 5.51 (*dd*, $J$ = 2, 4.5, H–C(12)); 5.53 (br. *s*, NH); 5.80 (*ddd*, $J$ = 0.5, 1.5, 16.5, H–C(20)); 7.11–7.33 (*m*, Ph). $^{13}$C-NMR (101 MHz, $CDCl_3$): 13.9 (C(11)); 20.9, 21.2 (2 *Me*COO); 21.5 (*Me*–C(16)); 32.2 (*Me*CO–C(17)); 33.0 (C(16)); 33.1 (C(5)); 37.5 (C(15)); 44.8 (C(8)); 45.3 (C(10)); 49.2 (C(4)); 50.0 (C(9)); 53.5 (C(3)); 58.2 (C(17)); 72.0 (C(7)); 77.7 (C(21)); 115.0 (C(12)); 126.5 (C(14)); 127.0 ($C_p$); 128.0 (C(13)); 128.1 (C(20)); 128.8, 129.3 ($C_o$, $C_m$); 137.2 ($C_i$); 138.7 (C(19)); 145.9 (C(6)); 170.0 (2 Me*C*OO); 173.9 (C(1)); 208.8 (Me*C*O–C(17)). EI-MS (70 eV): 533 ($M^+$), 490, 473, 442.

*(7S,16S,17ξ,21R,13E,19E)-17-Acetyl-17-iodo-16-methyl-10-phenyl[10]cytochalasa-6(12),13,19-triene-7,21-diyl Diacetate* (**14** and **15**). NaI (250 mg, 1.68 mmol) and AcONa (25 mg, 0.30 mmol) were added to a soln. of **12** (148 mg, 0.28 mmol) in $AcOH_4$ (1.25 ml). After stirring at 55° for 5 h, $CH_2Cl_2$ was added and the mixture washed with $NaHSO_3$ and $K_2HPO_4$ soln. The org. layer was dried ($Na_2SO_4$) and evaporated *in vacuo*. Purification of the crude product (190 mg) by CC (silica, acetone/$CH_2Cl_2$) gave **14**/**15** (96 mg combined; 53%) as well as starting material **12** (28 mg) and rearranged **13** (10 mg). Anal. calc. for **14**/**15**: C 58.27, H 5.81; found: 58.32, H 6.37.

*(7S,16S,17S,20ξ,21R,13E,18E)-20-(Chloromethylsulfonyl)-16,18-dimethyl-10-phenyl[11]cytochalasa-6(12),13,18-triene-7,17,21-triyl Triacetate* (**18**). A soln. of **8** (521 mg, 0.88 mmol) in pyridine (10 ml) was added to MsCl (1.3 ml, 1.67 mmol) in pyridine (8.7 ml) at −20°. After warming to r.t., the mixture was stirred for 21 h. After

addition of ice to the mixture, it was diluted with 1N $Na_2CO_3$, extracted with $CH_2Cl_2$/acetone 9:1, and the org. extracts were washed with 2N HCl and $H_2O$, dried ($Na_2SO_4$), and evaporated *in vacuo*. The crude product (610 mg) was purified by CC (180 g of silica, $CH_2Cl_2$/acetone 95:5→50:50). The desired product was rechromatographed (90 g of silica, $Et_2O$/pentane 1:1) to give **18** (140 mg, 23%). $[\alpha]_D^{25} = +122$ ($c = 0.78$, $CHCl_3$). IR ($CCl_4$): 3430, 3340, 3060, 3040, 2970, 2930, 1740, 1695, 1370, 1230, 1120, 1030. $^1$H-NMR (400 MHz, $CDCl_3$): 0.93 (*d*, $J = 6.5$, Me–C(5)); 1.00 (*d*, $J = 6$, Me–C(16)); 1.87 (*s*, Me–C(18)); 1.95 (*s*, AcO–C(7)); 2.15 (*m*, H–C(4), 2 H–C(15), H–C(16)); 2.25 (*s*, AcO–C(21)); 2.34 (*s*, AcO–C(18)); 2.71 (*m*, H–C(5)); 2.82 (*d*, $J = 7.5$, 2 H–C(10)); 2.99 (*dd*, $J = 10.5$, 10.5, H–C(8)); 3.25 (*m*, H–C(3)); 4.48, 4.61 (*AB*, $J_{AB} = 12$, $CH_2SO_2$); 4.79 (*dd*, $J = 11.5$, 1, H–C(19)); 5.05 (*s*, H–C(12)); 5.23 (*s*, H–C(12)); 5.30 (*dd*, $J = 11$, 1, H–C(7)); 5.40 (*m*, H–C(14)); 5.64 (*s*, H–C(17)); 5.75 (*d*, $J = 4.5$, H–C(21)); 5.94 (*s*, NH); 6.08 (*ddd*, $J = 15$, 10, 1.5, H–C(13)); 6.41 (*dd*, $J = 11.5$, 4.5, H–C(20)); 7.25 (*m*, Ph). $^{13}$C-NMR (101 MHz, $CDCl_3$): 14.1 (C(11)); 20.6, 21.2, 21.5 (3 *Me*COO); 21.9 (C(22)); 24.6 (C(23)); 33.4 (C(5)); 34.8 (C(16)); 38.2 (C(15)); 42.4 (C(8)); 45.0 (C(10)); 51.1 (C(4)); 53.3 (C(9)); 53.8 (C(3)); 55.5 (*C*$H_2SO_2$); 62.4 (C(20)); 72.0 (C(7)); 75.2 (C(21)); 78.3 (C(17)); 112.2 (C(19)); 114.6 (C(12)); 127.0 ($C_p$); 128.9, 129.4 ($C_o$, $C_m$); 129.1 (C(13)); 132.5 (C(14)); 137.2 (C(6)); 144.8 (C(18)); 145.5 ($C_i$); 170.0, 170.6, 171.0 (3 Me*C*OO); 173.2 (C(1)). FAB-MS: 690 (2, $[M + 1]^+$).

*(3*R*,3a*S*,4*S*,6*S*,6a*R*,7*S*,7a*R*,9*S*,10*S*,12a*ξ*,13*R*,13a*S*)-3-Benzyl-7-chloro-2,3,3a,4,5,6,7,7a,8,9,10,12a,13-tetradecahydro-4,9,11-trimethyl-5-methylidene-1*H*-cyclohepta[4,5]benz[1,2-d]isoindole-10,13-diyl Diacetate* (**20**). To a soln. of **8** (75 mg, 0.126 mmol) and $Et_3N$ (0.5 ml, 3.6 mmol) in $CH_2Cl_2$ (5 ml), MsCl (5 ml) was added at 0°. After stirring for 1.2 h at 0°, ice was added to the mixture, which was subsequently extracted with $CH_2Cl_2$/acetone 9:1. The org. extracts were washed with 2N HCl and $H_2O$, dried ($Na_2SO_4$), and evaporated *in vacuo*. The crude product (101 mg) was purified by CC (30 g of silica, $CH_2Cl_2$/acetone 95:5→80:20). Recrystallization ($Et_2O$/pentane) afforded **20** (28 mg, 36%). $^1$H-NMR (400 MHz, $CDCl_3$): 0.79 (*d*, $J = 7$, Me–C(4)); 0.96 (*d*, $J = 7$, Me–C(9)); 1.53 (*dt*, $J = 13.5$, 11, H–C(8)); 1.74 (*s*, Me–C(11)); 2.00 (*s*, AcO–C(6)); 2.04 (*m*, H–C(9)); 2.08 (*s*, AcO–C(10)); 2.11 (*m*, H–C(7a)); 2.12 (*m*, H–C(3a)); 2.29 (*s*, AcO–C(13)); 2.42 (*dd*, $J = 13.5$, 4.5, H–C(8)); 2.61 (*m*, H–C(4)); 2.67 (*m*, H–C(6a)); 2.78 (*dd*, $J = 13.5$, 6.5, H–C(14)); 2.87 (*dd*, $J = 13.5$, 8.5, H–C(14)); 3.12 (*m*, H–C(12)); 3.32 (*m*, H–C(3)); 4.79 (*dd*, $J = 10.5$, 10.5, H–C(7)); 4.92 (*s*, H–C(16)); 5.08 (*d*, $J = 3$, H–C(12)); 5.25 (*s*, H–C(16)); 5.26 (*s*, H–C(10)); 5.31 (*d*, $J = 2.5$, H–C(6)); 5.53 (*d*, $J = 8.5$, H–C(13)); 5.65 (*s*, NH); 7.23 (*m*, Ph). $^{13}$C-NMR (101 MHz, $CDCl_3$): 12.3 (C(15)); 19.4 (C(17)); 21.0, 21.1, 22.0 (3 *Me*COO); 23.9 (C(18)); 31.9 (C(4)); 35.8 (C(8)); 42.5 (C(6a)); 42.6 (C(7a)); 43.1 (C(12)); 43.9 (14)); 47.4 (C(3a)); 52.3 (C(13a)); 53.2 (C(3)); 65.8 (C(13)); 75.1 (C(6)); 75.6 (C(7)); 76.2 (C(12)); 114.5 (C(16)); 125.6 (C(12)); 127.0 ($C_p$); 128.9, 129.1 ($C_o$, $C_m$); 137.5 (C(5)); 138.1 (C(11)); 144.8 ($C_i$); 170.1, 170.9, 171.2 (3 Me*C*OO); 174.9 (C(1)). FAB-MS: 612 (1, $[M + 1]^+$).

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