pared according to general procedure A from 12 with trichloroethylsuccinoyl chloride in nearly quantitative yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 32 100). Anal. ($C_{60}H_{91}Cl_3SiO_{17}$) C, H.

5-*O*-(*tert*-Butyldimethylsilyl)-4″-*O*-[[(4-nitrophenyl)oxy]carbonyl]avermectin B_{1a} (21) was prepared according to general procedure A from 12 and 4-nitrophenyl chloroformate in 100% yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 243 nm (ϵ 35 600). Anal. ($C_{61}H_{89}O_{18}NSi$) C, H, N.

4″-*O*-Pivaloylavermectin B_{1a} (15). General Procedure B. A solution of 14 (95 mg, 0.088 mmol) in 8.0 mL of MeOH containing 80 mg (1%) of *p*-toluenesulfonic acid hydrate was stirred at 18 °C for 30 min. Then EtOAc was added, the solution was washed with dilute $NaHCO_3$ and H_2O (3 times), dried, and concentrated in vacuo. The crude product was purified immediately by PLC (CH_2Cl_2–THF–EtOH, 95:4.75:0.25) and gave 65 mg (75%) of 15: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 32 300). Anal. ($C_{53}H_{80}O_{15}\cdot 0.5H_2O$) C, H.

4″-*O*-Octanoylavermectin B_{1a} (17) was prepared from 16 according to general procedure B in 80% yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 31 100). Anal. ($C_{56}H_{86}O_{15}$) C, H.

4″-*O*-[3-[(2,2,2-Trichloroethoxy)carbonyl]propanoyl]avermectin B_{1a} (19) was prepared from 18 according to general procedure B in 93% yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 32 000). Anal. ($C_{54}H_{77}O_{17}Cl_3$) C, H, Cl.

4″-*O*-(Aminocarbonyl)avermectin B_{1a} (23) was prepared from 22 according to general procedure B in 73% yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 32 000). Anal. ($C_{49}H_{73}O_{15}N\cdot 2H_2O$) C, H, N.

4″-*O*-[(Dimethylamino)carbonyl]avermectin B_{1a} (25) was prepared from 24 according to general procedure B in 89% yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 32 700). Anal. ($C_{51}H_{77}O_{15}N\cdot 0.5H_2O$) C, H, N.

4″-*O*-[(Acetylamino)acetyl]avermectin B_{1a} (27) was prepared from 26 according to general procedure B in 82% yield: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 31 700). Anal. ($C_{52}H_{77}O_{16}N\cdot 0.5H_2O$) C, H, N.

4″-*O*-Succinoylavermectin B_{1a} (20). A solution of 19 (100 mg, 0.09 mmol) in 3.5 mL of acetic acid was stirred with 400 mg (6 mmol) of zinc dust for 1 h at 18 °C. The reaction mixture was filtered, and the solids were washed well with EtOAc. The filtrate was concentrated in vacuo to a white glass, which was dissolved in EtOAc, washed with dilute HCl and water, dried, and evaporated to give 80 mg of a clear glass. This was further purified by PLC (CH_2Cl_2–THF–AcOH, 90:9.5:0.5) to give 62 mg (69%) of 20: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 245 nm (ϵ 32 200). Anal. ($C_{52}H_{76}O_{17}\cdot H_2O$) C, H.

4″-*O*-[(Dimethylamino)carbonyl]-5-*O*-(*tert*-butyldimethylsilyl)avermectin B_{1a} (24). General Procedure C. A solution of 21 (50 mg, 0.044 mmol) in 4.0 mL of ether was cooled in an ice bath, and a stream of dimethylamine was bubbled into the solution for 1 min. The reaction mixture was kept 30 min at 0 °C, and then it was evaporated under a stream of N_2. The residue was taken up in ether, washed with H_2O (3 times), dried and again concentrated under a stream of N_2. The crude product was purified by PLC (CH_2Cl_2–THF, 95:5, two successive developments) to give 40 mg (87%) of 24 as a white foam: NMR, see Table IV; mass spectrum, see Table V; UV (MeOH) λ_{max} 244 nm (ϵ 31 650). Anal. ($C_{57}H_{71}O_{15}NSi$) C, H, N.

4″-*O*-(Aminocarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)avermectin B_{1a} (22) was prepared from 21 and NH_3 according to general procedure C in 87% yield, characterized after removal of the *tert*-butyldimethylsilyl protecting group (see 23).

4″-*O*-(Acetylglycyl)-5-*O*-(*tert*-butyldimethylsilyl)avermectin B_{1a} (26). A solution of 12 (50 mg, 0.05 mmol), 4-(dimethylamino)pyridine (12.5 mg, 0.1 mmol), and *N*-acetylglycine (12 mg, 0.1 mmol) in 0.75 mL of CH_2Cl_2 was prepared at room temperature. After addition of a solution of dicyclohexylcarbodiimide (23 mg, 0.11 mmol) in 0.5 mL of CH_2Cl_2, the mixture was stirred for 90 min at room temperature, and then filtered and worked up with CH_2Cl_2. Purification by PLC (1.0 mm, CH_2Cl_2–MeOH, 95:5) gave 57 mg (100%) of amorphous 26: NMR, see Table IV; mass spectrum, see Table V.

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Structure–Activity Correlations of Cytochalasins. Novel Halogenated and Related Cytochalasin C and D Derivatives

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A series of halogenated and related analogues of cytochalasin C (CC) and D (CD) has been synthesized, and the biological activities of the analogues as inhibitors in a cell-free contractility model system obtained from Ehrlich ascites tumor cells were evaluated. The reaction sequence involved treatment of CD with phenyltrimethylammonium perbromide to give 6,12-dibromo-CD (2), dehydrohalogenation of 2 to 12-bromo-CC (3), and the subsequent conversions of 3 to 12-azido- (4), 12-iodo- (5), and 12-cyano-CC (6). The ID_{50} values for 5, 3, 4, 2, and 6 are 6.0, 7.4, 8.8, 45, and 77 × 10^{-7} M, respectively, in comparison to ca. 2.8 × 10^{-7} M for the parental compounds. The potential cell and molecular biological applications of these compounds are delineated.

The cytochalasins, a group of secondary fungal metabolites[1] of widespread distribution, exhibit profound effects upon eukaryotic cells and cell systems.[2] These manifestations, many of which are essentially reversible with drug removal or dilution, take place rapidly and at quite low concentrations (10^{-8}–10^{-6} M). The availability of high specific activity radiolabeled congeners and of potential affinity-labelling species could prove useful to the further identification of macromolecular drug receptors, including cytoskeletal elements[3,4] and transport carriers.[5] Toward these objectives, we describe in this article the preparation of cytochalasin C and D derivatives, functionalized with halogens, which maintain complete or partial biological

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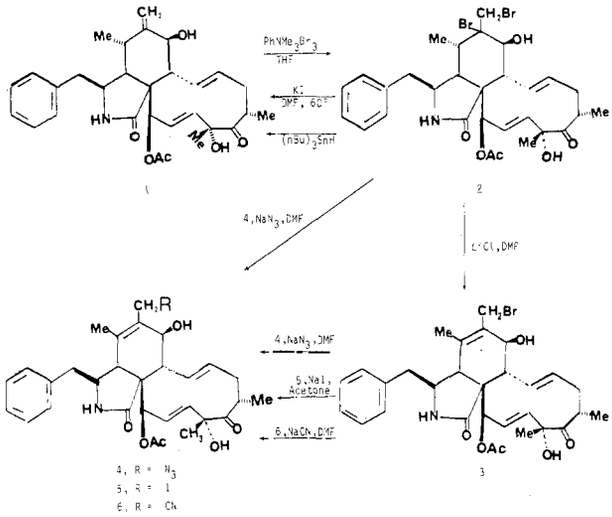
Scheme I



activity as inhibitors of contractility in a model cell-free system.

Chemistry. Treatment of cytochalasin D (1) with 2 molar equiv of phenyltrimethylammonium tribromide led to several products from which one major derivative (2) was isolated by HPLC. This reagent is reported[6] to selectively monobrominate α to keto groups. To our surprise, 2, by elemental analysis and molecular weight determination, was found to be a dibromo derivative. Extensive ^{1}H NMR (100 MHz), ^{13}C NMR,[2] and off resonance decoupling experiments indicated 2 to be (7*S*,16*S*,18*R*,21*R*)-21-acetoxy-6,12-dibromo-7,8-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-13,19-diene-1,17-dione (6,12-dibromo-CD).[7] This structure was further confirmed by the conversion of 2 back to 1 by treatment with *n*-butylstannic hydride[8,9] or by reaction with potassium iodide,[10] both reactions substantiating the presence of the vicinal dibromide. The initial step in the formation of 2 is similar to one postulated by Midland and Halterman[11] for addition of bromine to 3-penten-2-ols and presumably involves the formation of a bromonium ion as an intermediate.

6,12-Dibromo-CD (2) underwent dehydrohalogenation with lithium chloride[12] to give 3, a white crystalline solid, mp 230–232 °C, which upon elemental analysis was found to contain one atom of bromine. From ^{1}H NMR (100 MHz) and ^{13}C NMR spectroscopy, the structure of 3 was deduced to be (7*S*,16*S*,18*R*,21*R*)-21-acetoxy-12-bromo-7,18-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-5,13,19-triene-1,17-dione (12-bromo-CC). Further reaction of 3 with sodium azide[13] displaced halogen by azide, yielding 4 [(7*S*,16*S*,18*R*,21*R*)-21-acetoxy-12-azido-7,18-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-5,13,19-triene-1,17-dione (12-azido-CC). The identical monoazido derivative was alternately obtained through reaction of 2 with sodium azide. It would appear that dehydrobromination occurred, as well as substitution.[13]

The interaction of 3 with sodium iodide[14] gave rise to the analogous monoiodo compound 5 [(7*S*,16*S*,18*R*,21*R*)-21-acetoxy-7,18-dihydroxy-16,18-di-

Table I. Relative Effectiveness of Cytochalasin Analogues for Inhibition of Cell-Free Gelation in Ehrlich Ascites Tumor Extracts[a]

no.	compound	$ID_{50} \times 10^7$, M
1	cytochalasin D	2.1
	cytochalasin C	3.5
5	12-iodocytochalasin C	6.0
3	12-bromocytochalasin C	7.4
4	12-azidocytochalasin C	8.8
2	6,12-dibromocytochalasin D	45
6	12-cyanocytochalasin C	77

[a] Reference 16. Each reaction mixture contained per 0.54 mL volume: protein, ~3.0 mg; KCl, 5.9×10^{-3} M; dithiothreitol, 2.4×10^{-3} M; EGTA, 2.4×10^{-3} M; $MgCl_2$, 3.9×10^{-3} M; phenylmethylsulfonyl fluoride, 2×10^{-4} M; ATP, 1.5×10^{-3} M. Cytochalasins were dissolved in Me_2SO (final concentrations were held at 0.10%) for addition to test mixtures. After 4 h at 37 °C, extent of gelation was assayed following centrifugation, for 2 min at 2000 rpm, by residual gel weights in tared test tubes (50 × 3 mm).

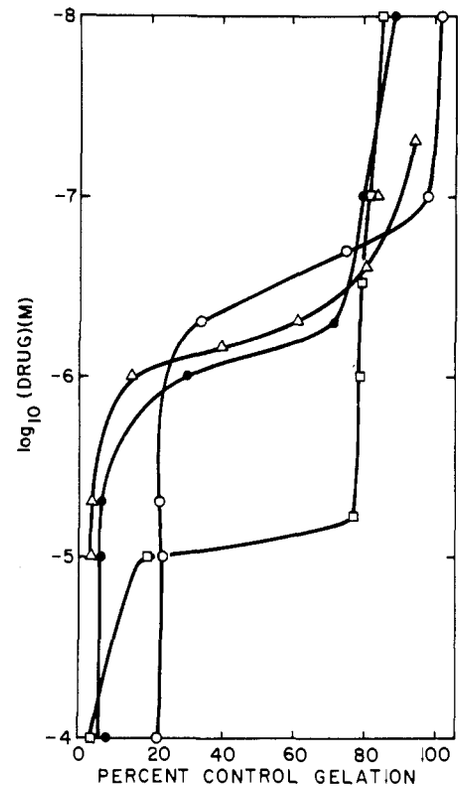


Figure 1. Dose–response curves for representative cytochalasin inhibitions of cell-free gelation: (○) cytochalasin C; (△) 12-iodo-CC (5); (□) 12-cyano-CC (6); (●) 6,12-dibromo-CD (2).

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methyl-12-iodo-10-phenyl[11]cytochalasa-5,13,19-triene-1,17-dione (12-iodo-CC)]. The monoiodo compound was very unstable in solution. Parallel reaction of **3** with sodium cyanide[15] gave **6** [(7*S*,16*S*,18*R*,21*R*)-21-acetoxy-12-cyano-7,18-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-5,13,19-triene-1,17-dione (12-cyano-CC)].

The foregoing chemical transformations, as well as analytical and spectroscopic evidence, suggest the reaction sequences collected in Scheme I.

Biological Activity. The compounds synthesized above were tested for biological activity in a temperature-sensitive, cell-free gelation extract[16] obtained from an Ehrlich ascites tumor line. This model system contains the elements of the cytoskeletal motility system, including actin, actin-network binding proteins, and control polymerization factors.[17] Its use obviates differential congeneric transport uncertainties which may be obtained with intact cell motility manifestations. In order to compare their relative effectiveness, 50% inhibition molarities (Table I) for each antagonist, as well as for CC and CD, were obtained from extrapolation of dose–response curves (Figure 1). These data demonstrate that the two parental congeners which differ from one another only by placement of the double bond at the perhydroisoindolone moiety are almost equally effective. Substitution of halogen or azide at C-12 results in but a 2- to 3-fold lowering of drug inhibitory potency. The lower order of magnitude of dibromo-CD (**2**) as an antagonist may reflect either its steric bulk or the loss of molecular rigidity following saturation of the exocyclic double bond. The dramatic and seeming anomalous ineffectiveness of 12-cyano-CC (**6**) presumably stems from its relative high electronegativety.

It can be anticipated that these newly described compounds may have pharmaceutical application, since it has been documented that transformed cell lines are differentially sensitive to congeneric cytochalasins.[18] Particularly in those cell biological probes which require high specific activity radiolabeled species, their subsequent displacement either with heavy halogens or with positron emitters may be useful. While the relative instability of 12-iodo-CC (**5**) may preclude its use for this specific purpose, its potential, along with that of **6**, for electrophilic affinity labeling of receptor macromolecules has yet to be ascertained. Additionally, compounds **4**–**6** provide alternative synthetic entree to the preparation of receptor-selective ligands. These approaches are presently under investigation in this laboratory.

Experimental Section

Melting points were measured with a Thomas-Hoover melting point apparatus and are not corrected. Separations were carried out using a Perkin-Elmer Series 2 HPLC with a semipreparative Whatman Partisil-10 Magnum 9 column, with ethyl acetate/hexane as eluant. IR spectra were recorded on Perkin-Elmer Infracord spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian XL-100 and Bruker WM-360 spectrometer, respectively (courtesy of Dr. Jack Melton, Bristol Laboratories). Chemical shifts are reported in parts per million, with tetramethylsilane as internal reference. Mass spectra were recorded on a Finnegan 4000 GC/MS. Elemental analyses and molecular weight determinations were carried out by the Galbraith Laboratories Inc., Knoxville, TN, and by Micro Analysis Inc., Wilmington, DE. Cytochalasin D was prepared by fermentation as described by Zabel et al.[19] Cytochalasin C was obtained from Aldrich Chemical Co. and was purified to homogeneity by HPLC.

6,12-Dibromocytochalasin D (2). To a solution of cytochalasin D (0.400 g, 0.78 mmol) in dry tetrahydrofuran (30 mL) was added, with magnetic stirring, a solution of phenyltrimethylammonium tribromide (Aldrich Chemical Co.; 0.600 g, 1.6 mmol) in tetrahydrofuran (15 mL) over 30 min. After complete addition, the reaction mixture was stirred at room temperature for 16 h, diluted with diethyl ether (50 mL), filtered, and repeatedly washed with aqueous HCl (5%) and brine. The combined organic layer was dried (anhydrous sodium sulfate), and the solvent was removed under reduced pressure. The residue, a yellow semisolid, was purified by repeated HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) eluant. Removal of solvent gave a white solid (0.260 g, 50%). Recrystallization from ethyl acetate/hexane (1:1) gave an analytical sample (**2**): mp 153–155 °C dec; mass spectrum (EI), *m/e*, no M^+ seen, 505 (M^+ – 2HBr); ^{1}H NMR ($CDCl_3$) δ 1.17 (m, 6 H, C_{11} and C_{16} CH_3), 1.47 (s, 3 H, C_{18} CH_3), 2.17 (m, 1 H), 2.23 (s, 3 H, CH_3Ac), 2.71 (m, 6 H), 3.71 (m, 3 H), 4.37 (m, 4 H), 5.25 (m, 4 H), 6.08 (m, 2 H), 7.2 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.1 (C_{11}), 19.3 (C_{16} CH_3), 20.7 (CH_3Ac), 24.1 (C_{18} CH_3), 34.1 (C_5), 34.4 (C_{12}), 38.1 (C_{15}), 42.4 (C_{16}), 46.4 (C_{10}, C_8), 50.7 (C_4), 51.9 (C_3), 54.6 (C_9), 55.1 (C_6), 76.3 (C_7), 77.8 (C_{21}), 78.5 (C_{18}), 127.5 (C_4), 127.8 (C_{19}), 127.9 ($C_{3'}$, $C_{5'}$), 129.3 (C_2, C_6, C_{13}), 132.5 (C_{14}), 136.7 (C_{20}), 137.1 ($C_{1'}$), 169.6 [C(=O)Ac], 173.9 (C_1), 210.8 (C_{17}). Anal. ($C_{30}H_{37}NO_6Br_2$) C, H, Br. M_r calcd, 667; obsd, 650 ($CHCl_3$).

Regeneration of 1. A. Sodium borohydride (0.0030 g, 0.08 mmol) was suspended in dry ethanol (2 mL). A solution of tri-*n*-butylstannic chloride (60 μL, excess)[8] in dry ethanol (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 30 min, and then a solution of 6,12-dibromocytochalasin D (**2**; 0.050 g, 0.07 mmol) in dry ethanol (2 mL) was added. The resulting reaction mixture was stirred at 60 °C for 2 h, cooled, poured into aqueous hydrochloric acid (2%, 20 mL), and repeatedly extracted with chloroform. The organic layer was dried (anhydrous sodium sulfate), and the solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white crystalline solid: yield 0.030 g (78%); mp 255 °C dec. All analytical constants were identical with those recorded for the parent compound.[1]

B. 6,12-Dibromocytochalasin D (**2**; 0.050 g, 0.07 mmol) and potassium iodide (0.150 g, 0.8 mmol) were dissolved in DMF (2 mL) and stirred at 55–60 °C for 15 h. The reaction mixture was cooled, and DMF was removed under reduced pressure. The residue was extracted with dichloromethane, and the organic layer was repeatedly washed with aqueous saturated sodium thiosulfate solution. The resulting organic layer was dried (anhydrous sodium sulfate), and the solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white solid: yield 0.020 g (52%); mp 255 °C dec. The compound was identified as cytochalasin D (**1**).

12-Bromocytochalasin C (3). 6,12-Dibromocytochalasin D (**2**; 0.400 g, 0.600 mmol) and anhydrous lithium chloride (0.600 g, excess) were dissolved in dry DMF (5 mL) and stirred at room temperature for 48 h. After solvent removal under reduced pressure, the residue was extracted with dichloromethane, washed repeatedly with aqueous hydrochloric acid (5%) and brine, and then dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white solid (**3**): yield 0.19 g (55%). Recrystallization from ethyl acetate gave an analytical sample: mp 230–232 °C dec; mass spectrum (CI), *m/e* 587 (M^+ + 1); ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 3 H, C_{16} CH_3), 1.52 (m, 6 H, C_{11} and C_{18} CH_3), 2.06 (m, 1 H), 2.26 (s, 3 H, CH_3Ac), 2.89 (m, 7 H), 4.28 (m, 5 H), 5.59 (m, 6 H), 7.25 (m, 5 H); ^{13}C NMR (Me_2SO-d_6) δ 16.0 (C_{11}), 19.1 (C_{16} CH_3), 20.5 (CH_3Ac), 24.5 (C_{18} CH_3), 37.9 (C_{15}), 40.4 (C_{12}), 41.4 (C_{16}), 43.7 (C_{10}), 48.8 (C_8), 49.1 (C_4), 59.3 (C_3), 52.3 (C_9), 66.0 (C_7), 74.8 (C_{21}), 77.5 (C_{18}), 126.8 ($C_{4'}$), 127.9 (C_{19}), 128.7 ($C_{3'}$, $C_{5'}$), 129.4 ($C_{2'}$, $C_{6'}$), 130.5 (C_{13}), 131.6 (C_{14}), 132.2

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(C_{20}), 133.9 (C_6), 137.6 ($C_{1'}$), 134.3 (C_5), 170.4 (C(=O)Ac), 173.7 (C_1), 210.1 (C_{17}). Anal. ($C_{30}H_{36}NO_6Br$) C, H.

12-Azidocytochalasin C (4). 6,12-Dibromocytochalasin D (**2**; 0.040 g, 0.05 mmol) and sodium azide (0.100 g, excess) were dissolved in dry DMF (5 mL), the reaction mixture was stirred at room temperature for 48 h, and the solvent was removed under reduced pressure. The residue was extracted with dichloromethane and repeatedly washed with brine. The resulting organic layer was dried (anhydrous sodium sulfate), and solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white solid: yield 0.022 g (70%). Recrystallization from acetonitrile gave an analytical sample (**4**): mp 236–237 °C dec; mass spectrum (EI), *m/e*, no M^+ seen, 520 ($M^+ - N_2$); IR (KBr) 2100 (azide) cm^{-1}. Anal. ($C_{30}H_{36}N_4O_6$) C, H, N. Under identical conditions, 12-bromocytochalasin C (**3**) gave the same monoazido derivative.

12-Iodocytochalasin C (5). 12-Bromocytochalasin C (**3**; 0.080 g, 0.13 mmol), sodium iodide (0.200 g, excess), and acetone (20 mL) were stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The residue was repeatedly extracted with dichloromethane, and the resulting organic layer, after washing with aqueous sodium thiosulfate solution and brine, was dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant. The major peak was collected, the solvent was removed, and the residue was crystallized from ethyl acetate/hexane (1:1) to give a pale yellow solid (**5**; 0.026 g, 30%). Repeated recrystallization from ethyl acetate/hexane (1:1) and preparative TLC (silica gel; benzene/acetone, 3:2) gave an analytical sample: mp 173–175 °C dec; ^1H and ^{13}C NMR shifts were consistent with this structure; mass spectrum (EI), *m/e* no M^+ seen, 505 ($M^+ - HI$). Anal. ($C_{30}H_{36}NO_6I$) C, H. Except in the dry state, **5** underwent rapid decomposition in solution to yield a variety of transformation and substitution products.

12-Cyanocytochalasin C (6). 12-Bromocytochalasin C (**3**; 0.180 g, 0.3 mmol) and sodium cyanide (0.400 g, excess) in DMF (15 mL) were stirred at room temperature for 24 h. After solvent removal under reduced pressure, the residue was extracted repeatedly with dichloromethane. The organic layer was repeatedly washed with aqueous hydrochloric acid (5%) and brine and dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure. The residue was purified by HPLC on a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white solid (**6**): yield 0.073 g (45%). Repeated recrystallization from acetonitrile gave an analytical sample as a white solid: mp 240–242 °C dec; IR (KBr) 2250 (CN) cm^{-1}; mass spectrum (EI), *m/e* 532 (M^+); ^1H and ^{13}C shifts were in accord with the structure as given. Anal. ($C_{31}H_{36}N_2O_6$) C, H.

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Structure–Activity Relationships for 2-Substituted Imidazoles as α_2-Adrenoceptor Antagonists[1]

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Several 2-[(1,4-benzodioxan-2-yl)alkyl]imidazoles were prepared and evaluated for their blocking activity and relative selectivity on presynaptic (α_2) and postsynaptic (α_1) receptors in the isolated rat vas deferens. 1-Ethyl-2-[(1,4-benzodioxan-2-yl)methyl]imidazole (**13**) was the most selective α_2-adrenoceptor antagonist of the series and was, for practical purposes, devoid of α_1-adrenoceptor antagonist activity. The lipophilicity of **13** (log D = 2.31) indicated that it would have an excellent chance to enter the central nervous system. Compound **13** was selected for clinical evaluation as an antidepressant agent.

The pharmacological and functional differences between prejunctional α-adrenoceptors of the postganglionic sympathetic neurons and postjunctional α-adrenoceptors of the effector cells originally led to the designation α_1 and α_2, for the post- and prejunctional α-adrenoceptors, respectively, of noradrenergic neuroeffector junctions.[2] Subsequently, it has been recommended that the classification α_1 and α_2 should be used independently of the location and function of α-adrenoceptors and instead according to the relative affinity for agonists and antagonists, i.e., exclusively on the basis of their pharmacological specificity.[3,4] In general, α-adrenoceptors characterized as α_1 are only found at postjunctional locations, whereas α_2-adrenoceptors are located both prejunctionally and postjunctionally. Two examples that illustrate the varied roles and locations of α-adrenoceptors[5] are the inhibitory feedback effect on norepinephrine (NE) release at nerve endings[6] and the inhibition of adenylate cyclase in human platelets.[7]

The study and therapeutic manipulation of α-adrenergic receptors are facilitated by having well-defined, selective receptor agonists and antagonists.[5a] Phenylephrine, a classic α_1-adrenoceptor agonist, operates as a vasoconstrictor and is used as a nasal decongestant. Prazosin, an

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