[Chem. Pharm. Bull. 30(5)1629—1638(1982)]

Chaetoglobosins, Cytotoxic 10-(Indol-3-yl)-[13]cytochalasans from *Chaetomium* spp. III.[1] Structures of Chaetoglobosins C, E, F, G, and J[2]

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(Received October 2, 1981)

The structures (Chart 1) of chaetoglobosins C, E, F, G, and J, 10-(indol-3-yl)-[13]-cytochalasans, were established on the basis of physical data, especially ^{1}H-NMR, and chemical correlations. The stereo-structural features of chaetoglobosins are discussed.

Keywords——*Chaetomium globosum*; chaetoglobosins C, E, F, G, and J; 10-(indol-3-yl)-[13]cytochalasans; cytochalasins; ^{1}H-NMR; conformations; mycotoxins

In the preceding papers[1] the structure elucidation of chaetoglobosins A (**A**), B (**B**), and D (**D**) as novel type [13]cytochalasans[3,4] containing tryprophan units was reported. This paper is concerned with the structures of other congeners, chaetoglobosins C (**C**), E (**E**), F (**F**), G (**G**), and J (**J**).[2]

Chaetoglobosins C and G showed the same molecular formula, $C_{32}H_{36}O_5N_2$, as **A**, **B**, and **D** and exhibited similar infrared (IR), ultraviolet (UV) and mass (MS) spectral properties, as reported in a previous paper (Table III in Part I).[1] Thus it was suggested that **C** and **G** were isomers of **A**, **B**, and **D**. Acetylation of chaetoglobosin C led to the recovery of **C**, while the same treatment of **G** gave a monoacetate (**G**-Ac). Chaetoglobosin C was formed from **A** by treatment with triethylamine. The same treatment of **B** and **D** afforded **G** and an isomer named isochaetoglobosin D (iso-D), respectively. When **C** was warmed in acetic acid under the same conditions as used to obtained **B** from **A**, **G** was obtained in a good yield. **G**-Ac was obtained by the treatment of **C** with sulfuric acid in acetic acid (Chart 1).

The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra gave much information on the structures of **C** and **G**. Precise double resonance experiments were performed for the assignments, and the overall results are shown in Table I. From these data it became clear that the frameworks of the two compounds are the same as in **A**, **B** and **D**; **C** has an epoxide ring at C_6–C_7 as does **A**, while **G** has a double bond at C_5–C_6 and an alcohol group at C_7 as does **B**. However the C_{19} carbinyl-H and the typical C_{21}–C_{22} double bond signals appearing at lower field in the case of **A**, **B**, and **D** were not observed; integration of the methylene protons in the δ 2.3—3.7 region showed an increase by four protons instead, and the C_{17}-olefinic-H and the C_{18}–CH_3 appeared at lower field than those of **A**, **B**, and **D**. The vicinal couplings between C_{15}–H and C_{16}–H, which were not obvious in the spectra of **A**, **B**, and **D**, were clearly assigned in **G** and iso-**D**, as shown in Chart 2. These observations and negative tetrazolium salt reactions for the three compounds, **C**, **G**, and iso-**D**, could reasonably be explained by postulating the structures shown in Chart 1. The formation of **C** from **A**, **G** from **B** as well as iso-**D** from **D** by base-catalyzed isomerization could be explained by a series of keto-enol tautomerizations as shown in Chart 3.

At this stage of the work, **C** was also isolated from *Penicillium aurantiovirens* by an American group and shown to be identical with our specimen by direct comparison. X-Ray analysis carried out by the American group revealed the correctness of the structure, and the results were simultaneously published.[2,5]

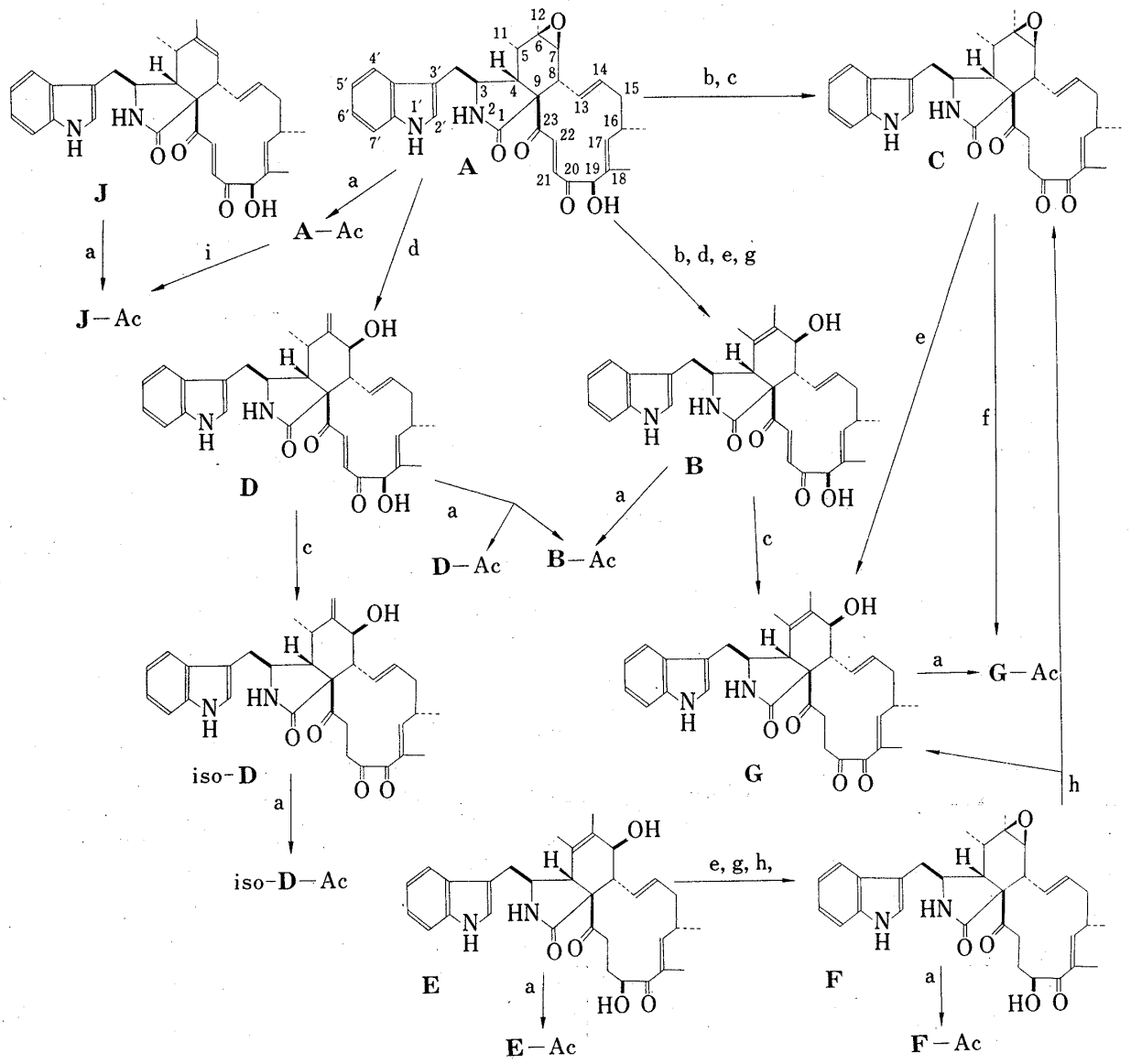
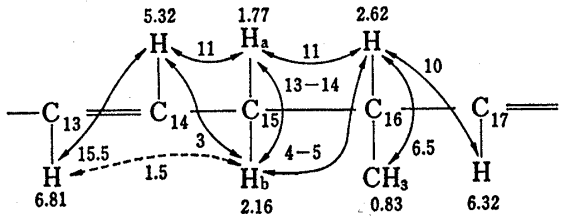
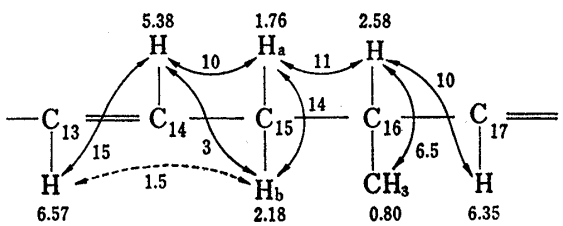


Chart 1. The Structures and Correlation Reactions of Chaetoglobosins
a: Ac_2O/pyridine, b: Et_3N/MeOH, c: Et_3N/pyridine, d: $BF_3/CHCl_3$, e: HOAc, f: H_2SO_4/HOAc, g: $H^+(CHCl_3)$, h: Bi_2O_3/HOAc; i: WCl_6–BuLi.



isochaetoglobsin D



chaetoglobosin G

Chart 2. The Partial Structures and ^{1}H-NMR Parameters of Chaetoglobosin G and Isochaetoglobosin D (in C_5D_5N)

vicinal coupling, long-range coupling.

Table I. ^{1}H-NMR Spectral Data for Chaetoglobosins (at 100 MHz)

Compound	Solvent	Chemical Shifts (δ values in ppm)																								
		1′-NH	2′-H	2-NH	10H$_a$	10H$_b$	3-H	4-H	5-H	5-CH$_3$ (11)	6-CH$_3$ (12)	7-OR	8-H	7-H	13-H	14-H	15-H$_a$	15-H$_b$	16-H	16-CH$_3$	17-H	18-CH$_3$	19-OR	19-H	21-H	22-H
A	$CDCl_3$	8.21	6.94	5.85	2.95	2.63	3.81	3.03	(1.85)[a]	1.24	1.29	—	2.78	2.14	6.05	5.20	1.8—2.4		(2.42)[a]	1.00	5.57	1.31	3.84	5.01	6.50	7.72
	C_5D_5N	11.86	7.32	9.37	3.08	3.08	4.14	3.30	(2.07)	1.09	1.29	—	3.12	2.62	6.62	5.25	1.7—2.3		(2.43)	0.87	5.61	1.54	5.3	5.45	7.03	8.04
A-acetate	$CDCl_3$	8.28	6.96	6.00	2.91	2.66	3.80	2.93	(1.8)	1.22	1.28	—	2.79	2.14	6.07	5.18	1.8—2.3		(2.4)	1.00	5.66	1.46	2.15	5.90	6.39	7.54
	C_5D_5N	11.82	7.31	9.31	3.00	3.00	4.13	3.23	(2.04)	1.06	1.28	—	3.12	2.65	6.62	5.29			(2.46)	0.90	5.67	1.56	2.09	6.17	7.09	8.06
B	$CDCl_3$	8.15	6.96	5.80	2.87	2.65	3.53	3.41	—	1.65	1.73		3.93	2.06	6.17	5.32	1.7—2.4		(2.51)	1.01	5.58	1.36		5.04	6.72	7.73
	C_5D_5N	11.85	7.34	9.32	3.12	3.12	4.02	3.65	—	1.56	1.94		4.61	2.69	6.79	5.42			(2.46)	0.84	5.59	1.60		5.48	7.32	8.12
B-diacetate	$CDCl_3$	8.29	6.98	6.07	2.86	2.69	3.56	3.34	—	1.64	1.55	(1.96)[b]	5.41	2.25	6.05	5.10	1.5—2.3		(2.5)	0.97	5.63	1.47	(2.15)[b]	5.89	6.56	7.57
	C_5D_5N	11.85	7.33	9.42	3.14	3.07	3.98	3.54	—	1.48	1.54	(2.10)	5.99	2.46	6.67	5.30			(2.56)	0.88	5.63	1.65	(2.12)	6.19	7.41	8.06
D	C_5D_5N	11.82	7.30	9.06	3.18	2.97	3.88	3.30	3.14	1.23	5.21 5.66 (=CH_2)		4.59	2.92	6.53	5.44	1.7—2.2		2.44	0.83	5.70	1.54		5.50	6.97	8.43
D-diacetate	$CDCl_3$	8.24	6.90	5.85	2.95	2.61	3.41	2.90		1.20	5.06 5.12 (=CH_2)	1.87	5.27	2.45	5.71	5.05			(2.5)	0.87	5.58	1.36	2.06	5.88	6.36	7.76
J	$CDCl_3$	8.17	6.94	5.54	3.12	2.57	3.30	3.12	(2.45)	1.42	1.80	—	5.30	2.56	5.92	5.15	(2.25)	2.08	(2.45)	1.00	5.64	1.35	3.91	5.09	6.58	8.22
J-acetate	$CDCl_3$	8.25	6.97	5.65	3.09	2.59	3.31	3.09	(2.46)	1.41	1.79	—	5.29	(2.53)	5.94	5.12	(2.05)	(2.25)	(2.4)	0.99	5.75	1.46	2.13	6.03	6.49	8.11
C	C_5D_5N	12.02	7.34	9.50	3.20	3.05	4.16	2.78	(2.02)	1.08	1.28	—	3.06	2.77	6.70	5.20	1.5—2.0		(2.58)	0.83	6.31	1.90	—	—		
G	C_5D_5N	11.89	7.35	9.36	3.04	3.04	3.97	3.32	—	1.49	1.87	5.90	4.50	2.74	6.81	5.32	1.77	2.16	(2.62)	0.83	6.32	1.89	—	—	3.65	2.6
G-acetate	$CDCl_3$	8.56	7.01	7.07	2.81	2.70	3.60	2.98	—	1.54	1.52	1.96	5.33	2.43	6.05	5.03	2.34	2.73	(2.73)	1.05	6.05	1.83	—	—	3.6	2.6
	C_5D_5N	11.94	7.37	9.56	3.04	3.04	3.96	3.29	—	1.44	1.48	2.09	5.91	2.72	6.71	5.21			(2.60)	0.85	6.32	1.96	—	—	3.6	2.6
iso-**D**	C_5D_5N	11.98	7.34	9.22	3.24	2.98	3.82	2.71	3.08	1.12	5.17 5.58 (=CH_2)	6.21	4.47	3.33	6.57	5.38	1.76	2.18	(2.58)	0.80	6.35	1.91	—	—	3.3	2.4
																							20-OR	20-H		
F	$CDCl_3$	8.60	6.96	6.50	2.85	2.68	3.77	2.67	(1.80)	1.13	1.21	—	2.78	2.24	6.86	5.25	1.8—2.5		(2.71)	1.01	6.11	1.82		4.69	1.81	2.68
	C_5D_5N	11.89	7.30	9.25	3.07	3.07	4.09	2.91	(2.01)	0.97	1.25	—	3.12	2.68	6.95	5.33	1.7—2.4		(2.61)	0.85	6.26	1.93		5.14	2.27	2.95
F-acetate	$CDCl_3$	8.21	6.98	6.02	2.85	2.70	3.80	2.69	(1.79)	1.09	1.20	—	2.80	2.24	6.38	5.28			(2.71)	1.05	6.28	1.78	2.13	5.50		
	C_5D_5N	11.96	7.32	9.33	3.12	3.12	4.12	2.97	(2.01)	1.02	1.26	—	3.12	2.67	6.94	5.31			(2.62)	0.82	6.51	1.86	2.05	5.89	2.22	{3.12 2.98
E	C_5D_5N	11.82	7.30	9.16	3.10	2.99	3.96	3.44	—	1.49	1.90	5.98	4.56	2.69	7.02	5.46			2.62	0.83	6.34	1.93	6.10	5.29	2.41	3.41
E-diacetate	$CDCl_3$	8.40	7.01	6.32	2.73	2.73	3.55	3.13	—	1.50	1.50	(1.99)[b]	5.39	2.34	6.32	5.16			(2.71)	1.05	6.28	1.80	(2.11)[b]	5.59	2.03	2.96
	C_5D_5N	11.90	7.36	9.43	3.12	3.03	3.96	3.46	—	1.46	1.50	(2.04)	5.96	2.65	6.92	5.32			(2.60)	0.82	6.56	1.92	(2.11)	6.05	2.40	3.42

a) Value estimated from the center of decoupling.
b) The assignments may be reversed.

Compound	Solvent	Coupling Constants (in H_2)																													
		1′–2′	10_a–10_b	3–10_a	3–10_b	2–3	3–4	4–5	5–11	4–11	4–12	11–12	7–11	7–12	7–7-OH	7–8	8–13	13–14	13–15_b	14–15_a	14–15_b	15_a–15_b	15_a–16	15–16_b	16–16-CH_3	16–17	17–18-CH_3	19–19-OH	21–22	Others
A	$CDCl_3$	2.5	15	4.3	7.5	≥1	3	5	7					≥0	—	5	9—10	15							6.5	9	1.2	4.5	16.5	*a,f,g,h,j,k*
	C_5D_5N	2.5		(5)	(7)	~1	2	5.5	7						—	5	10	15.5							6.5	9	1	4.5	16.5	*i,k*
A-acetate	$CDCl_3$	2.5	14	5	7		3	5	7.2					≥0	—	5.5	9—10	15—16		(10)	(5)				6.7	9.0	1.2	—	16.5	*i,j,k*
	C_5D_5N	2		(6.5)	(7)	~1	2.2	6	7					≥0		5	9.5	15.5							6.5	9	1.0	—	16.5	*i,j,k*
B	$CDCl_3$	2	14	6	8		2—3	—	—							9—10	10	15		(10)	(5)				6.7	9	1	16—17		
	C_5D_5N	2		(7)	(7)	>0	~2	—	—	≥0	1.3	≥0	1.7	0.5—1		9.5	10	15—16							6.5	9.5	1.2	15—16		*b)*
B-diacetate	$CDCl_3$	2.5	14	5	7		2	—	—	0.2	0.8	1.0	1.2	0.4	—	10	10	15.5							6.5	9	~1	—	16.5	*a,b,g,h*
	C_5D_5N	2—2.5	14	7.5	9		2	—	—		~1		~1		—	10	9	15—16		(9)	(3)				6.5	9	~1	—	16	*g,h*
D	C_5D_5N	2—2.5	14	5	8	~1	3	~5	6.5							10	10	15		(9)	(4)				6.5	~8	1.2		16.5	*d,g,h,k*
D-diacetate	$CDCl_3$	2.5	14	4.5	7		~2		6.5							10.5	10	15							6.9	9	1	—	16.5	
J	$CDCl_3$	2.5	15	3—4	9.5	~1	5	4	7.5					1	—	3	10	15.5	~2	10	4	13—14	11	4	6.5	9	~1	4.5	16.5	*a,d,f,g,h*
J-acetate	$CDCl_3$	2—2.5	14	3	9.5	~1	5	4	7.5					1—1.5	—	3	10	15	1.5	10	4	13—14	11	3	6.5	9—10	~1	--	16.5	*a,c,d,g,h*
C	C_5D_5N	~2	15	(5)	(6)	~1		~6	7					≥0	—	~5	9—10	15		(11)	(3—4)				6.5	9—10	~1	—		*e)*
G	C_5D_5N	2.5		(6—7)		~2	~1	—	—	≥0	1.6	0.6	1.8	1.1—1.3	6.5	~10	10	15.5	1.5	~11	~3	13—14	~11	4—5	~6.5	~10	1.3	—		*a,e)*
G-acetate	$CDCl_3$	2.5	~14	6	9	~1	≥1	—	—		>0		>0		—	10	10	15		(10)	(3)	~14			6.7	10	1.1	—		*a,e)*
	C_5D_5N	2—2.5		(6—8)		1—2	~1	—	—		>0		>0		—	10	10	14—15		(11)	(4)				6.5	10	1—1.5	—		
iso-**D**	C_5D_5N	2.5	15	~4	6	1—2	3.5	5	6.8					≥0	4—5	11	~9.5	15	1.5	10	3	~14	11		6.5	10	1.3	—		*a,e)*
F	$CDCl_3$	2.5	15	5	8		3	6	7.3					≥0	—	5	10	15		(12)	(4)				6.7	9	1.5	5—6	6—7	*e,i,l)*
	C_5D_5N	~2		(6)	(6)	~1	~2	6.5	6.5					≥0	—	5	9.5	16	≥0						6.5	9—10	1.2	5.5	6—7	*e,i,l)*
F-acetate	$CDCl_3$	~2				>0			7.5						—	5		16—17							6—7	9				
	C_5D_5N	~2		(5)	(8)		2	5.5	7						—	5.5	10	15.5							6.5	9	~1	6	7	*i,l)*
E	C_5D_5N	2.5	14	6	8	≥0	~1	—	—	~1	1.5	1.0	1.7	1—1.2	6	9	9.5	15.5—16							6	9	1—1.2	~6	6.5	*e,l)*
E-diacetate	$CDCl_3$	2.5		7	7			—	—						—	10	10	16							~6	9	1	~6	~7	
	C_5D_5N	2.5	14	7	8		>1	—	—		0.7		1.2		—	10	10	15.5							6.5	9	~1	6	7	*a)*

a—h) Long-range coupling: *a)* 2′-10_a and 2′-10_b; *b)* 4—7; *c)* 5—7; *d)*5—12; *e)* 8—14; *f)* 17—19; *g)* 19—21; *h)* 19—22.
i—l) NOE: *i)* 7—12; *j)* 17—19; *k)* 19—22; *l)* 17—20.

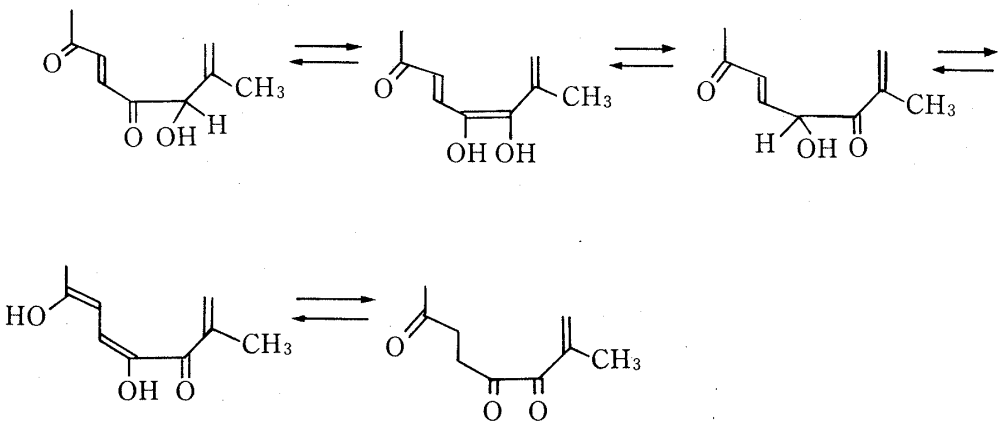
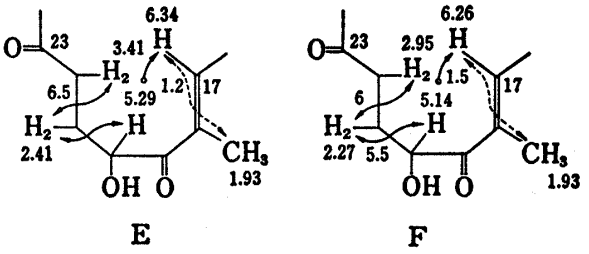


Chart 3

Chaetoglobosins E and F exhibited similar IR and UV spectral properties.[1] However their molecular formula, $C_{32}H_{38}O_5N_2$, suggested that the two compounds corresponded to the dihydro derivatives of **A**—**D** and **G**. Chaetoglobosin F formed a monoacetate (**F**-Ac), while **E** gave a diacetate (**E**-Ac). Precise ^{1}H-NMR examination was again performed on the two compounds and the acetates (Table I), revealing that the frameworks of **E** and **F** are the same as those of **B** and **A** except for the C_{19}–C_{22} part. The relationship between the two compounds was confirmed by acid-catalyzed isomerization as in the case of **A** to **B** and **C** to **G**. Chaetoglobosin F and the acetate were unstable in deuterated chloroform as in the case of **A**; **F** was changed into **E** after two days. Treatment of **F** with acetic acid afforded **E** in a good yield.

In the ^{1}H-NMR spectra of these compounds, the typical AB type signals of the C_{21}–C_{22} double bonds seen at low fields in **A**, **B** and **D** were absent in the spectra of **E** and **F** and, instead, the presence of a –CH(OH)–CH_2–CH_2– group was confirmed by decouping experiments as shown in Chart 4. Irradiation at the carbinyl proton of this group exhibited NOE at the olefinic C_{17}–H of E and F. The signals of C_{17}–H and C_{18}–CH_3 were shifted to lower field than those of **A**, **B**, and **D**, as in the case of **C** and **G**. The presence of α-ketol groups in the compounds was suggested by the positive tetrazolium salt reactions. From these observations the structures shown in Chart 1 (except the C_{20} stereochemistry) were proposed for **E** and **F**.[2] In order to correlate these products with known compounds, bismuth trioxide oxidation of **F** in acetic acid was performed and the products were found to be identical with **C** and **G**.



E F

Chart 4. The Partial Structures and ^{1}H-NMR Parameters of Chaetoglobosins E and F (in C_5D_5N)

vicinal coupling, long-range coupling, NOE.

The C_{20} stereochemistry in **E** and **F** was suggested to be (*S*) for the following reasons. The conformation of the 13-membered rings in the crystalline state was revealed by X-ray analyses of **A**[1,6] and **C**.[5] As shown in Table I, the coupling constants of the protons up to C_{17} on the macrocyclic ring of **A** and **C** both in deuterated chloroform and in pyridine fit well with the values expected from the torsion angles in the solid state (this point will be discussed later). Since the ^{1}H-NMR data for **E**, **F** and the acetates (Table I) and inspection of a Dreiding model indicated that the conformation of the 13-membered ring of **E** and **F** was almost the same as those of other members of the group, the observed NOE between the olefinic C_{17}–H and the carbinyl C_{20}–H of **E** and **F** suggested the α-configuration of C_{20}–H (Chart 5).

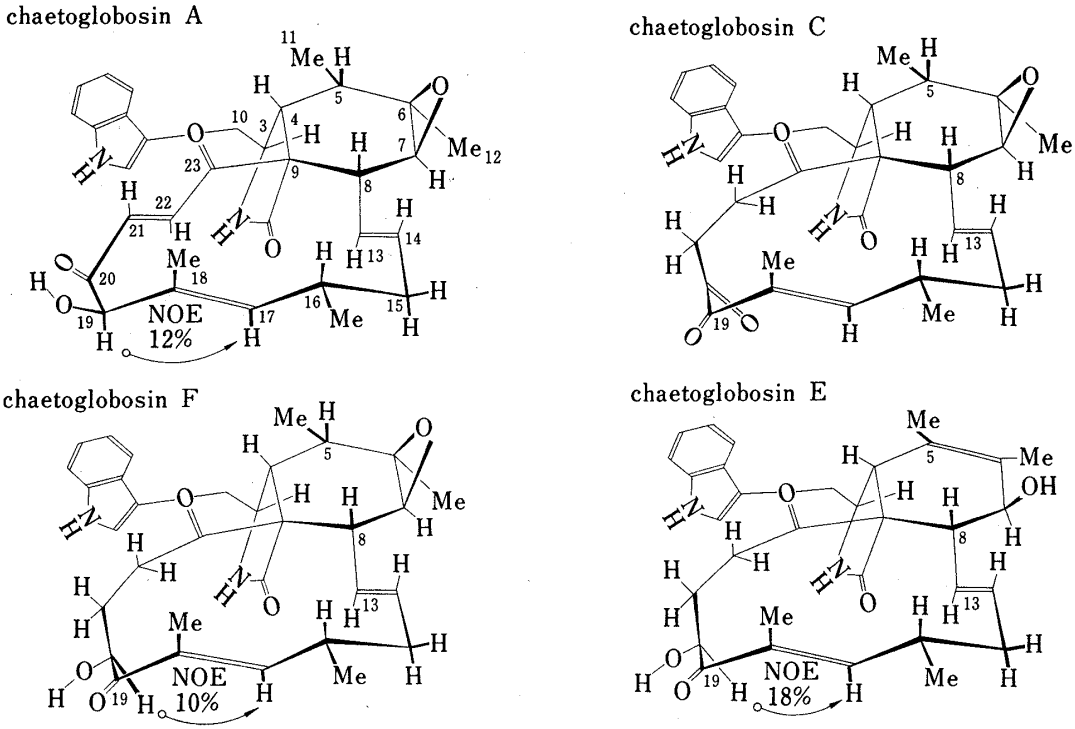


Chart 5. Conformations of Chaetoglobosins

The other new member of this class, **J** has the molecular formula $C_{32}H_{36}O_4N_2$, which corresponds to a deoxygenated product of **A**—**D**. It formed a monoacetate (**J**-Ac). Indeed, ^{1}H-NMR of J and **J**-Ac (Table I) showed that they have the same 13-membered ring as **A**, **B** and **D**, but the perhydroisoindolone part was assigned as shown in Chart 6. Zygosporin G (**1**)[7] and proxiphomin (**2**)[8] among 10-phenylcytochalasans are examples of compounds having such structures (Chart 7). Direct proof of the structure was obtained by the deoxygenation of chaetoglobosin A monoacetate[1] with tungsten hexachloride-butyllithium[9] to give **J**-Ac (Chart 1), and the structure was established for the new congener.

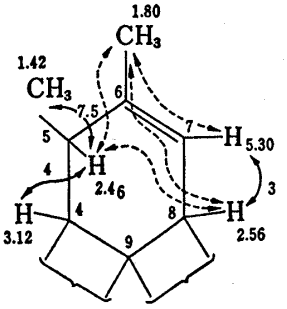


Chart 6. The Partial Structure and ^{1}H-NMR Parameters of Chaetoglobosin J (in $CDCl_3$)

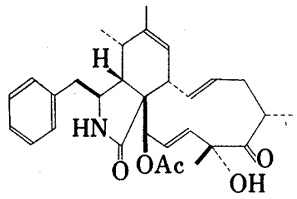
vicinal coupling. long-range ing.coupl

According to the systematic nomenclature adopted in Chemical Abstracts based on the proposal[10] chaetoglobosins C, E, F, G, and J (Chart 1) can be expressed as (7*S*, 13*E*, 16*S*, 17*E*)-6,7-epoxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-13,17-diene-1,19,20,23-tetrone, (7*S*, 13*E*, 16*S*, 17*E*, 20*S*)-7,20-dihydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-5,13,17-triene-1,19,23-trione, (7*S*, 13*E*, 16*S*, 17*E*, 20*S*)-6,7-epoxy-20-hydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-13,17-diene-1,19,23-trione, (7*S*, 13*E*, 16*S*, 17*E*)-7-hydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-5,13,17-triene-1,19,20,23-tetrone, and (13*E*, 16*S*, 17*E*, 19*R*, 21*E*)-19-hydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-6,13,17,21-tetraene-1,20,23-trione, respectively.

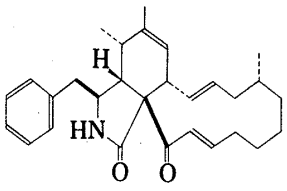
In the preceding papers[1] and this report, the structures of eight cytochalasans isolated from *Chaetomium* spp. were elucidated. All thirty-six cytochalasans so far known[4,11,12] have a common framework of [11]cytochalasan (**3**), [13]cytochalasan (**4**), 21,23-dioxa-[13]-cytochalasan (**5**), or 24-oxa-[14]cytochalasan (**6**) (Chart 7).[10] Chaetoglobosins belong to the

[13]cytochalasan group and bear an indol-3-yl group at the 10-position instead of the phenyl group present in the all cytochalasans known at the time of our preliminary report.[2] Quite recently, another type of cytochalasan having an isopropyl group at C_{10} (aspochalasins A—D) was also reported.[13] Four modifications of the six-membered ring of the perhydroisoindolone part of the cytochalasans are known as illustrated in the case of chaetoglobosins; i) $\Delta^{6,7}$ (**J**), ii) 6,7-epoxide (**A**, **C** ,and **F**), iii) $\Delta^{6,12}$-7β-ol (**D**), and iv) $\Delta^{5,6}$-7β-ol (**B**, **G**, and **E**). Although the epoxides (ii) are unstable to acids and bases, forming allylic alcohols (iii and iv), careful extraction with various solvents and TLC examination of the culture excluded the possibility of the formation of the latter from the former in the course of the separation.

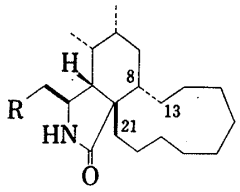
Finally, the conformations of chaetoglobosins will be discussed based on the ^{1}H-NMR data shown in Table I. Among the cytochalasans so far known, the conformations in the solid state have been determined by X-ray analyses for three [11]cytochalasans (**7**,[14] **8**,[15] **9**[16]), three [13]cytochalasans (**A**,[6] **C**,[5] **10**[17]), one dioxa-[13]cytochalasan (**11**[18]), and two oxa-[14]-cytochalasans (**12**,[19] **13**[20]) (Chart 7). The six-membered rings of these compounds are modified to either ii) or iii) type. The X-ray analyses showed that the conformations of the perhydroisoindolone rings in these compounds are all similar in the solid state; the five-membered rings are slightly modified in each compound and those of chaetoglobosins A and C are enantiomeric,[6] but as a whole the five-membered rings show nearly flat structures, while the six-membered rings exist in boat or twisted boat conformations.[5,6,14–20] As shown in Table I, the coupling constants (J_{2-3}, J_{3-4}, and J_{4-5}) are almost the same for all chaetoglo-



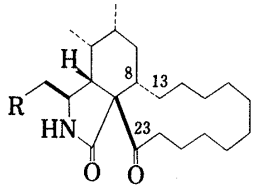
zygosporin G (**1**)



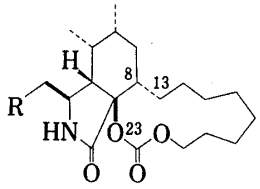
proxiphomin (**2**)



3



4



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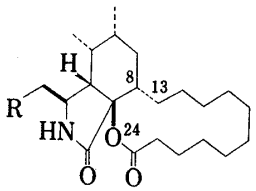

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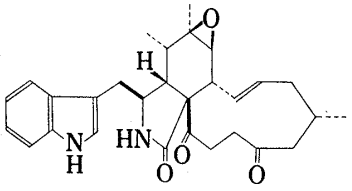
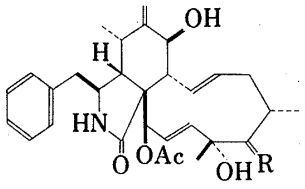
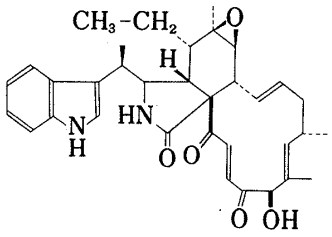


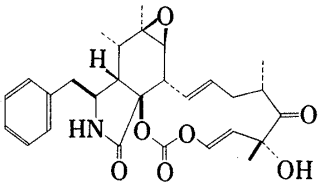
cytochalasin G (**7**)



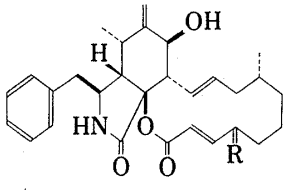
cytochalasin D(**8**) : R=O
cytochalasin H(**9**) : R=H$_2$



chaetoglobosin K (**10**)



cytochalasin E (**11**)



cytochalasin B(**12**): R=H, OH
cytochalasin A(**13**) : R=O

Chart 7. Structures of Cytochalasans

bosins and the acetates and are in good accord with the values expected from the torsion angles in the solid state.[6] The constant (J_{7-8}) varies with modification of the six-membered ring such as ring strain due to the formation of an epoxide ring or introduction of a double bond; the value for $\Delta^{6,7}$ compounds (i) is 3 Hz, that for 6,7-epoxy compounds (ii) is 5—6 Hz, and that for $\Delta^{6,12}$-7-ols (iii) and $\Delta^{5,6}$-7-ols (iv) is 10 Hz. In the case of **A** and **C** ((ii) type), the values were in good accord with those expected from the torsion angles in the solid state. Inspection of a Dreiding model indicated that the rings of **J** ((i) type), **A**, **C**, and **F** ((ii) type), and **D** ((iii) type) exist in almost the same twisted boat conformations, while **B**, **G** and **E** ((iv) type) exist in a half-chair conformation, where C_8–H is axial. As a whole, the stereo-structural relationship of C_4, C_8, C_9, C_{13}, and C_{23} is rather similar in all chaetoglobosins both in the solid state and in solution.

In contrasts, the coupling constants (J_{3-10a}, J_{3-10b}) are different from the values expected from the torsion angles in the solid state, This suggests that the conformation of the bonds connected to the aromatic ring is flexible.

The remarkable feature of the conformation of the cytochalasans revealed by X-ray analyses is that a portion of the large ring, starting at C_8 and running to C_{19}, has a fairly constant chair-like conformation in spite of the different sizes of the rings and different functionalities over C_{19} as well as the expected flexibility of these rings.[16,20] It was also suggested that the framework can be assumed to be a stable, relatively rigid structural unit and is expected to be maintained even in solution.[16] This assumption was supported by the ^{1}H-NMR observations. As shown in Table II, chemical shifts of the protons from C_8–H to C_{18}–CH_3 appear at nearly the same fields for all the compounds, when solvent effects and the effects of the functionalities at C_7 and C_{19} are taken into account. All the compounds exhibit values of 9—10 Hz for J_{8-13} and J_{16-17}, indicating *anti* conformation. Accordingly, C_8–H and C_{16}–H are eclipsed with the C_{13-14} and C_{17-18} double bonds, respectively. Although the coupling patterns were clearly observable only in the case of **G**, iso-**D**, and **J**, the value of 9—12 Hz for J_{14-15a} and J_{15a-16} indicate *anti* conformation of the protons concerned, while those of 3—5 Hz for J_{14-15b} and J_{15b-16} indicate *gauche* conformation. The C_{15}–H_a appears at considerably higher fields than C_{15}–H_b, and long-range couplings were observed between the latter and C_{13}–H. These findings indicate that the skeleton starting from C_8 and running to C_{19}, including two (*E*)-double bonds, exists in a zig-zag form and the ring is stabilized.

There are three varieties of chain from C_{19} to C_{22} among the eight chaetoglobosins and this region shows variation in cytochalasans as a whole. However the flexibility of the conformation of this part is assumed to be restricted by the rigidity of other parts of the molecules. As shown in Table II, NOEs were observed among the protons of these regions, and the proximity of C_{17}–H, C_{19}–H, and C_{22}–H in **A**, **B**, and **D**, and of C_{17}–H and C_{20}–H in **E** and **F** was indicated.

Table II. Nuclear Overhauser Effects observed in Chaetoglobosins
(% Enhancement in (a) $CDCl_3$ and in (b) C_5D_5N)

Saturated proton and observed proton	Compound								
	A		**A-Ac**		**D**	**E**	**F**		**F-Ac**
	(a)	(b)	(a)	(b)	(b)	(b)	(a)	(b)	(b)
C_{17}–H→C_{20}–H	—	—	—	—	—	11	—		
C_{18}–CH_3→C_{17}–H			0	0		0	0	0	
C_{18}–CH_3→C_{19}–H			0	0		—	—	—	—
C_{19}–H→C_{17}–H[a]	8	8	9	8		—	—	—	—
C_{19}–H→C_{22}–H[b]	8	10	8	10	9	—	—	—	—
C_{20}–H→C_{17}–H	—	—	—	—	—	18	10	8	>0

a,b) Atomic distances between the protons in the solid state in chaetoglobosin A have been calculated as *a*) 2.23Å and *b*) 2.46Å respectively.[6]

The conformations of chaetoglobosins are illustrated in Chart 5; those in the solid state and in solution are suggested to be almost the same except for the indol-3-yl side chain part.

Experimental

Physical determinations were carried out in the same way as reported in the preceding paper.[1]

Chaetoglobosins C, E, F, G, and J——The details of the isolation and the analytical and spectral data were in the previous papers.[1] ^{1}H-NMR data are shown in Table I.

Acetylation of Chaetoglobosins E, F, G and J——Chaetoglobosins E, F, G, and J were acetylated by the same procedure as reported previously.[1]

Chaetoglobosin E diacetate was recrystallized from MeOH as colorless needles, mp 267°C. MS *m/e*: 619.295 (M^+), (calcd. for $C_{36}H_{42}O_7N_2$, 619.299). IR ν_{max}^{KBr} cm^{-1}: 3370, 2925, 1735, 1705, 1689, 1620, 1438, 1375, 1239, 1029, 981, 748. ^{1}H-NMR (Table II).

Chaetoglobosin F monoacetate was recrystallized from CH_2Cl_2 as colorless crystals, mp 268°C. MS *m/e*: 572.289 (M^+), (calcd. for $C_{34}H_{40}O_6N_2$, 572.282). IR ν_{max}^{KBr} cm^{-1}: 3395, 2990, 1746, 1692, 1638, 1431, 1377, 1244, 1034, 979, 755. ^{1}H-NMR (Table II).

Chaetoglobosin G monoacetate was recrystallized from MeOH as colorless crystals mp 177°C. MS *m/e*: 570.272 (M^+), (calcd. for $C_{34}H_{38}O_6N_2$, 570.272). IR ν_{max}^{KBr} cm^{-1}: 3370, 1700 (br), 1665, 1632, 1428, 1370, 1235 (br), 1024, 980, 745. ^{1}H-NMR (Table II).

Chaetoglobosin J monoacetate was recrystallized from hexane–benzene as pale yellow needles, mp 156—158°C. MS *m/e*: 554.277 (M^+), (calcd. for $C_{34}H_{38}O_5N_2$, 554.277). IR ν_{max}^{KBr} cm^{-1}: 3358, 3000, 1733, 1692, 1613, 1432, 1374, 1300, 1230, 1186, 1029, 970, 745. ^{1}H-NMR (Table II).

Isomerization of Chaetoglobosins A, B, and D with Triethylamine in Pyridine——Chaetoglobosin A (30 mg) was treated with triethylamine (0.5 ml) in pyridine (0.5 ml) at room temperature overnight. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was recrystallized from MeOH to give colorless needles (10 mg), mp 260°C, which were identical with **C** (IR and TLC).

By the same procedure, **G** (8 mg) was obtained from **B** (30 mg) and iso-**D** (28 mg), from **D** (47 mg).

Iso-**D** was recrystallized from MeOH as colorless crystals of mp 264—266°C (dec.), $[\alpha]_D$ +41° (c=0.10, MeOH). MS *m/e*: 528.254 (M^+), (calcd. for $C_{32}H_{36}O_5N_2$, 528.262). UV λ_{max}^{EtOH} nm (log ε): 222 (4.53), 275 (3.82), 281 (3.82), 291 (3.76). IR ν_{max}^{KBr} cm^{-1}: 3450, 3330, 1692, 1649, 1627, 982, 917, 851, 748. ^{1}H-NMR (Table II). Acetate: Prepared by Ac_2O–pyridine treatment. Colorless crystals, mp 173°C, from MeOH.

Isomerization of Chaetoglobosin C with Acids——i) Chaetoglobosin C (15 mg) was warmed for 75 min in 90% HOAc (1 ml) in a water bath. H_2O was added, and the resulting precipitate was separated and recrystallized from MeOH to give colorless needles (10 mg), mp 251°C, which were identical with **G** (IR and TLC).

ii) Conc. H_2SO_4 (0.5 ml) was added in an ice-bath to a solution of **C** (100 mg) in HOAc (3 ml) and the reaction mixture was kept overnight at room temperature then poured into ice water. The precipitate was separated and purified by silica gel column chromatography using benzene and EtOAc as developing solvents. From the benzene–EtOAc (9: 2) fraction, **G**-Ac (16 mg) was obtained. It was shown to be identical with an authentic sample by IR and TLC comparisons.

Isomerization of Chaetoglobosin F with Acetic Acid——Chaetoglobosin F (17 mg) was dissolved in HOAc (0.5 ml) and the solution was warmed in a water bath for 30 min. After 1 day, the precipitate formed was filtered off and washed with water. The mother liquor was diluted with water and extracted with EtOAc. The extract was dried and concentrated. The residue and the precipitates were combined and recrystallized from MeOH to give colorless needles (6 mg), mp 280°C, which were identical with **E** (IR and TLC).

Bi_2O_3 Oxidation of Chaetoglobosin F——Bi_2O_3 (120 mg) was added to the solution of F (96 mg) in HOAc (2 ml). The reaction mixture was heated on a water bath for 45 min, filtered, and diluted with water. The precipitate formed was filtered off, dried, and passed through a silica gel column using $CHCl_3$ as the developing solvent. Chaetoglobosin C (35 mg), mp 260—261°C, **G** (15 mg), mp 252°C, and **E** (20 mg), mp 280°C, were obtained and identified.

Deoxygenation of Chaetoglobosin A Acetate——Tungsten hexachloride (116 mg) was added to tetrahydrofuran (1.2 ml) precooled to −78°C, followed by addition of *n*-butyllithium (0.36 ml). The mixture was allowed to warm to 15°C and then **A** acetate[1] (72 mg) was added. After standing for 45 min, the reaction mixture was quenched by the addition of 20% NaOH solution. The reaction mixture was extracted with EtOAc. The extract was dried and concentrated. The residue was purified on a silica gel column using benzene and EtOAc. From the benzene–EtOAc (10: 1) fraction, **J**-Ac (21 mg) was obtained. It was recrystallized from hexane–benzene as pale yellow needles, mp 156—158°C, and shown to be identical with an authentic sample (IR and TLC).

Acknowledgement The authors are indebted to the analytical laboratories of the Faculty of Pharmacy, Kanazawa University, and Faculty of Pharmacy, Fukuoka University, and Dr. K. Kanohta of this institute

for some physical determinations. The authors' thanks are also due to Prof. Ch. Tamm, Dr. H. Minato, and Dr. D.C. Aldridge for generous gifts of samples and for providing information. They are also grateful to Prof. J. Clardy for providing details of his work on chaetoglobosin C and for suggesting simultaneous publication, and to Dr. T. Akiyama for discussions.

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Added in Proof (February 8, 1982)——Quite recently, the isolation of two new metabolites, 19-*O*-acetylchaetoglobosin B and 19-*O*-acetylchaetoglobosin D, along with chaetoglobosins A and C and 19-*O*-acetylchaetoglobosin A from a strain (Lederle H-124) of *Chaetomium globosum* was reported (A. Probst and Ch. Tamm, *Helv. Chim. Acta*, **64**, 2056 (1981). The two major metabolites of the strain, chaetoglobosin A and 19-*O*-acetylchaetoglobosin A, had been shown to be identical with our specimens by direct comparison as early as in 1974 (Dr. G.A. Ellestad, Lederle Laboratories, private communication; see Ref. 4)). Although there exist some differences of melting points between our data and those reported by the Swiss workers, they claimed that the differences arise from the presence of crystal modifications due to the use of different solvents for crystallization and their use of a non-ideal solvent system (Prof. Ch. Tamm, University of Basel, private communication).

The ^{1}H-NMR assignments made for the C_{21} and C_{22} protons of chaetoglobosins A and B in our preliminary communication (S. Sekita, K. Yoshihira, S. Natori, and H. Kuwano, *Tetrahedron Lett.*, **1973**, 2109) were reversed after the establishment of the stereochemistry of these compounds, as discussed in Part II and Part III of this series. The assignments shown in the paper by Probst and Tamm and also in some other papers on related compounds (e.g. T. Fex, *Tetrahedron Lett.*, **22**, 2703 (1981)) should also be reversed.