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Chaetoglobosins, Cytotoxic 10-(Indo-3-yl)-[13]cytochalasans from *Chaetomium* spp. II.[1] Structures of Chaetoglobosins A, B, and D[2]

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The structures (Chart 7) of chaetoglobosins A, B, and D, 10-(indol-3-yl)-[13]cytochalasans, were elucidated by isomerization reactions and physical method including precise ^{1}H-NMR decoupling experiments.

Keywords——*Chaetomium globosum*; chaetoglobosins A, B, and D; 10-(indol-3-yl)-[13]cytochalasans; cytochalasins; ^{1}H-NMR; proton spin decoupling; mycotoxins; isomerization reactions

In the preceding paper[1] production and isolation of chaetoglobosins A—G and J, cytotoxic metabolites of *Chaetomium* spp., were reported, along with their biological effects. This paper describes in full detail the evidence which led to the structure elucidation of the major metabolite, chaetoglobosin A (**A**), and the two isomers, B (**B**) and D (**D**).[2]

The three compounds showed the same molecular formula, $C_{32}H_{36}O_5N_2$, as determined from high resolution mass spectra (MS) and elemental analyses.[1] The infrared (IR) specra of **A**, **B**, and **D** were similar to one another and showed absorptions due to >NH, –OH, C=O, aromatic rings, and *trans*-CH=CH– (see Table III of Part I[1]). The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra disclosed the presence of one secondary alcohol group in **A** (δ 5.01) and two in both **B** (δ 3.93, 5.04) and **D** (δ 4.59, 5.50); the presence of these groups was substantiated by the formation of **A** monoacetate (**A**-Ac), **B** diacetate (**B**-Ac), and **D** diacetate (**D**-Ac), respectively, upon treatment of **A**, **B** and **D** with acetic anhydride in pyridine. The ultraviolet (UV) spectra of **A**, **B**, **D**,[1] and their acetates are superimposable and the absorptions at around 270—295 nm indicate the presence of an indole chromophore. The positive Ehrlich reaction, the strong peaks at *m/e* 130 and 131 in the MS (cleavage of the bond situated α, β to the indole ring), and the ^{1}H-NMR data (*vide infra*) suggested the presence of a 3-substituted indole group in these compounds. The other >NH group of the two in these molecules was assigned to a γ-lactam ring on the basis of the non-basic nature of the compounds, the strong IR absorptions at around 1690 cm^{-1} (amide-I band),[1] and the ^{1}H-NMR data.

Chaetoglobosin A is unstable in acids and bases; for instance, when A was kept standing overnight in deuterated chloroform at room temperature, it was partly transformed into chaetoglobosins C (**C**) and **B** (see the legend to Fig. 1). In order to confirm such isomerization, the following reactions were carried out. Treatment of **A** with triethylamine in methanol afforded a mixture of **B** and **C**, while the same treatment of **A** in pyridine furnished **C** in good yield (the isomerization to **C** will be discussed in Part III). On treatment with boron trifluoride etherate in chloroform, **A** isomerized to a mixture of **B** and **D**, while warming in acetic acid transformed **A** into **B** in good yield. These reactions, along with the ^{1}H-NMR data (*vide infra*), indicated the presence of an epoxide group in **A** and the conversion of the group to allylic alcohols (**B** and **D**).

The remaining two oxygen functions in **A**, **B**, and **D** were suspected to exist in a conjugated enedione system, since subtraction of the UV absorption of the indole chromophores from those of **A**, **B**, and **D** gave absorption maxima at around 240 nm (log ε *ca.* 3.9), and the ^{1}H-NMR

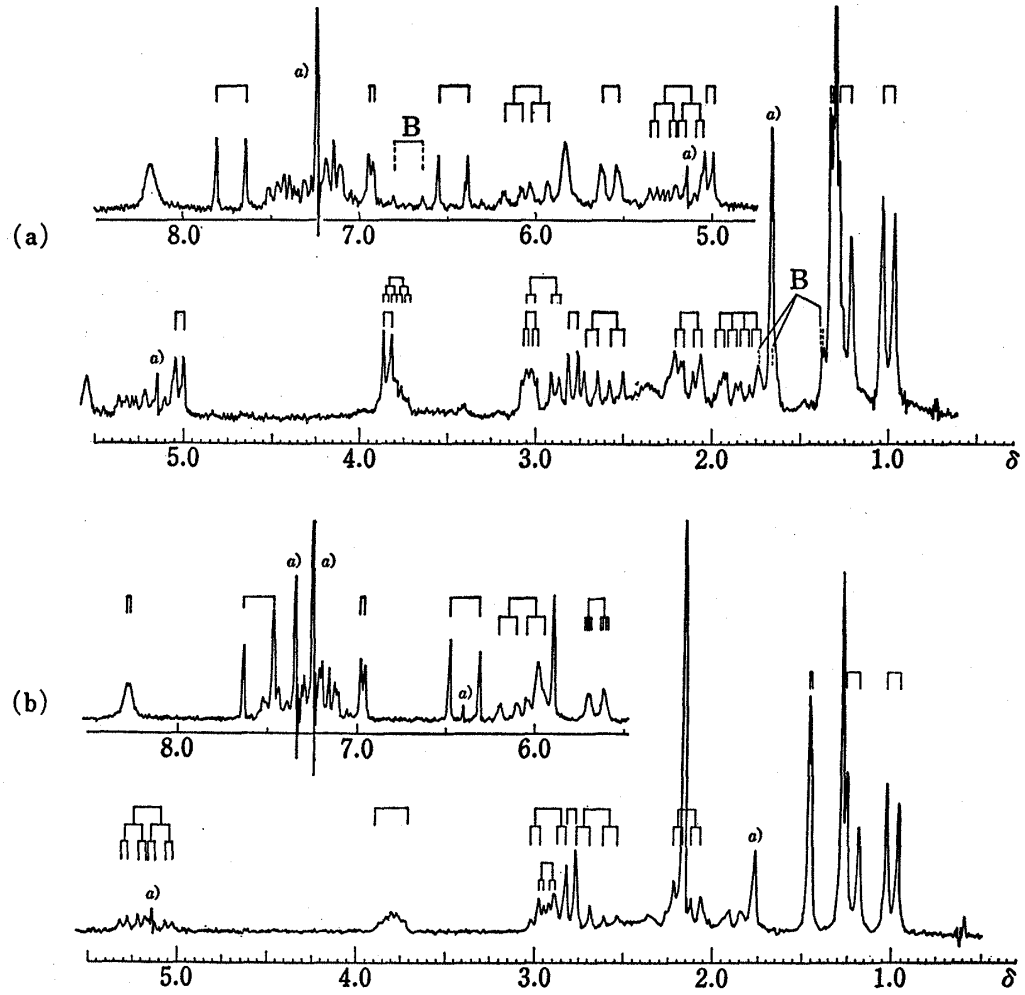


Fig. 1. ^{1}H-NMR Spectra of Chaetoglobosin A (a) and the Acetate (b) in $CDCl_3$ (100 MHz, Field Swept Mode)

(a) **A** (24 mg) in $CDCl_3$ (0.5 ml).
(b) **A**-Ac (30 mg) in $CDCl_3$ (0.5 ml).
In (a) the signals marked B show the formation of **B** from **A**. The lower signal-to-noise ratio of the spectrum is due to the precipitation of **C** formed from **A** in the course of determination at room temperature.
a) indicates signals due to contaminating solvents.

spectra showed a pair of doublets due to an olefinic group at low field (for example, δ 6.50 and 7.72, J=16.5 Hz in **A**).

Thus all the oxygen and nitrogen functions in the molecules of **A**, **B**, and **D** were disclosed, but the carbon framework except for the indole ring was obscure. The ^{1}H-NMR spectra were quite informative for the structural analyses.[3] As shown in Figs. 1 and 2, the overall signals of these compounds are widespread. Thus, precise proton spin decoupling experiments including nuclear Overhauser effect (NOE) measurements were performed on **A** and **A**-Ac in deuterated chloroform ($CDCl_3$) and in pyridine (C_5D_5N) as shown in part in Figs. 3—5. They revealed the presence of the fragments (a), (b), and (c) in the molecules of **A** and **A**-Ac (Chart 1).

(a): The fragment contains a 3-substituted indole ring and a carbon chain composed of one methylene, three methine, and one secondary methyl. The vicinal and long-range couplings were confirmed by the following decoupling experiments.

When deuterium oxide was added to a $CDCl_3$ solution of **A**-Ac, one (δ 8.28) of the two NH groups was deuterized after 2 d, while the other (δ 6.00) was exchanged in about 12 h; thus the former was assigned to the indole NH and the latter was suggested to be amide NH

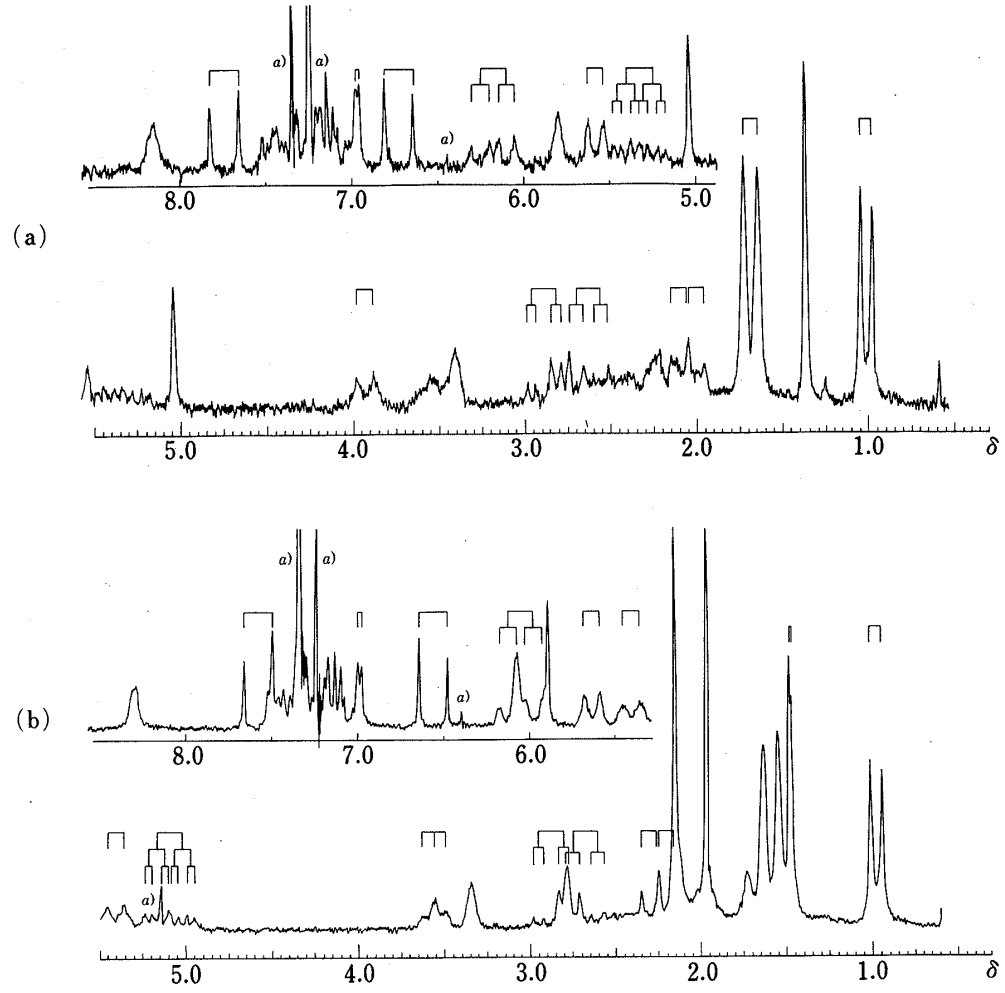


Fig. 2. ^{1}H-NMR Spectra of Chaetoglobosin B (a) and the Acetate (b) in $CDCl_3$ (100 MHz, Field Swept Mode)

(a) B (*ca.* 5 mg) saturated solution in $CDCl_3$ (0.6 ml).
(b) B-Ac (16 mg) in $CDCl_3$ (0.4 ml).
(*a*) See Fig. 1.

in γ-lactam. When the indole NH of **A** (δ 8.21) was irradiated (Fig. 3(a)), the doublet signal at δ 6.94 was changed into a singlet, which was assigned to $C_{2'}$-H on the indole ring. Upon weak irradiation of the $C_{2'}$–H, the ABX type methylene signals (δ 2.63 and 2.95) were sharpened (Fig. 4(a)). Strong irradiation at the center of the methylene signals (Fig. 4(c)) shapened the $C_{2'}$–H signal. Thus the ABX type methylene group was proved to be attached to the 3′-position of the indole ring.

When the lactam NH (δ 5.85) was irradiated (Fig. 3(c) and 4(d)), a multiplet at δ 3.81 and a double doublet at δ 3.03 were somewhat sharpened. Fig. 4(b) shows the decoupling spectrum upon irradiation at δ 3.81, in which the ABX type methylene signals appeared as an AB-type quartet (J=15 Hz) and the signal at δ 3.03 was changed to a doublet. When the double doublet at δ 3.03 was irradiated (Fig. 5(c)), the signal at δ 3.81 was changed to a broad doublet and a quartet signal appeared at δ 1.85, which was assigned to C_5–H bearing a secondary methyl group. Thus, the sequence shown in (a) in Chart 1 was verified.

(b): The fragment consists of seven carbon atoms, including one *trans* double bond and one tertiary methyl group. Observation of a long-range coupling and NOE between C_6–CH_3 (δ 1.29) and C_7–H (δ 2.78) indicated the proximity of the two groups. When the C_7–H was irradiated, a double doublet type signal (δ 2.14) of an allylic proton was changed into a doublet (J=*ca.* 10 Hz), leading to its assignment to C_8–H (Fig. 4(c)). Strong irradiation at 2.14 ppm

(C_8–H and other allylic protons were assumed to be saturated, see Fig. 5(d)) collapsed two olefinic protons, the broad double doublet (δ 6.05) and the double double doublet (δ 5.20), to doublet (J=15 Hz) and double doublet-like (J=15, *ca.* 5 Hz) signals, respectively. Since the irradiation of the former proton collapsed the latter to a fused double doublet-like signal and the C_8–H to a doublet (Fig. 4(e)), they were assigned to C_{13}–H and C_{14}–H, respectively.

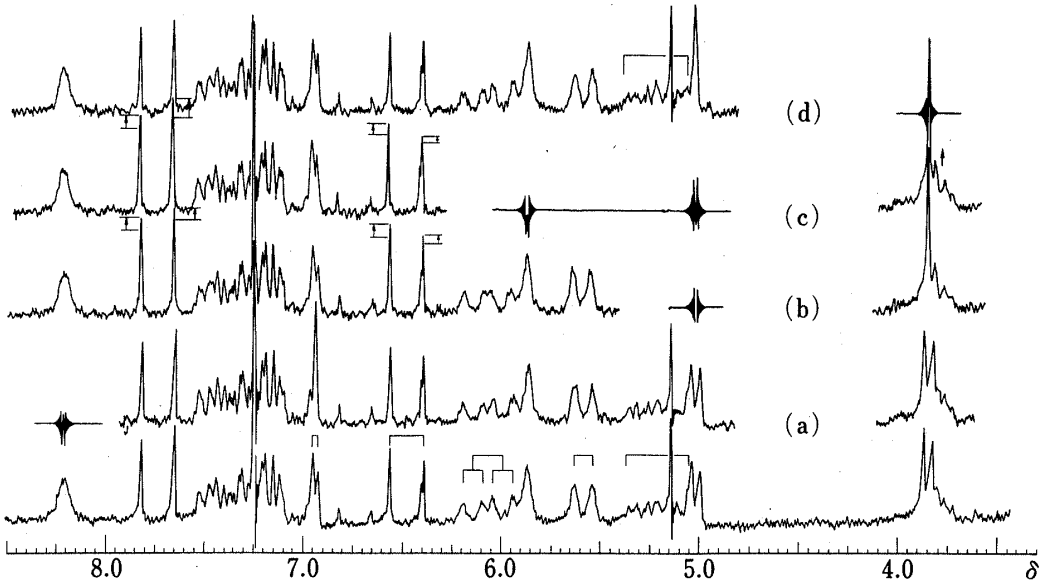


Fig. 3. Normal and Proton Decoupling Spectra of Chaetoglobosin A (in $CDCl_3$ at 100 MHz, Frequency Swept Mode) (1)

Double and triple resonance experiments were performed by irradiations as indicated by beating figures in the spectra; (a) 8.21 (1′-NH), (b) 5.01 (C_{19}–H), (c) 5.01 (C_{19}–H) and 5.85 (2-NH), and (d) 3.84 (C_{19}–OH) ppm.

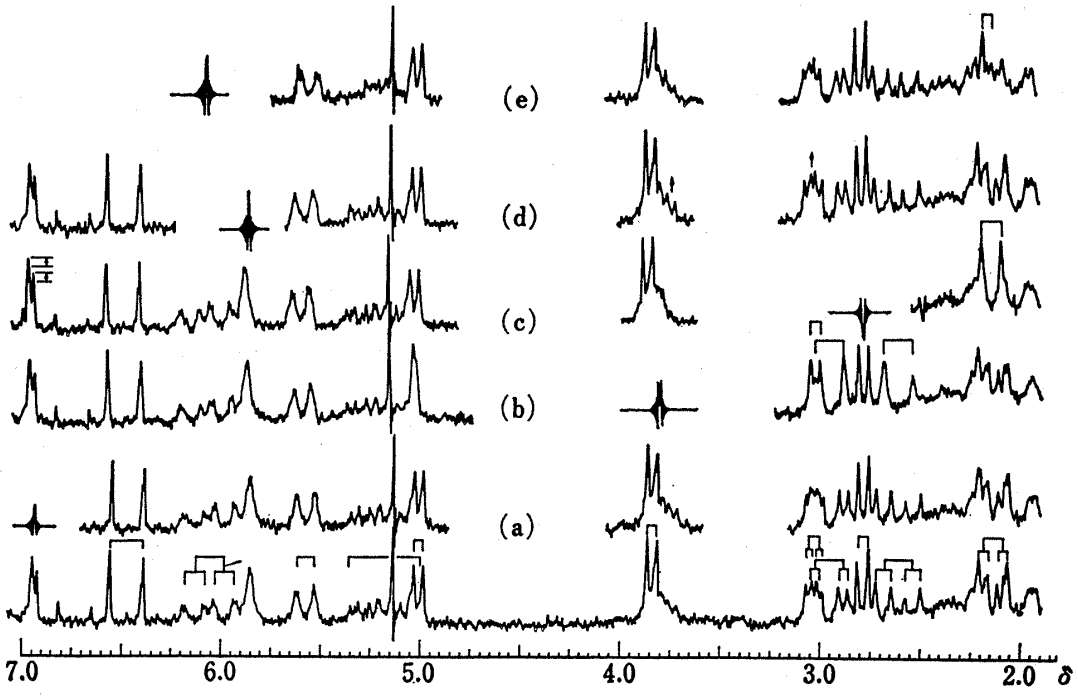


Fig. 4. Normal and Proton Decoupling Spectra of Chaetoglobosin A (in $CDCl_3$ at 100 MHz, Frequency Swept Mode) (2)

Irradiation at: (a) 6.94 ($C_{3'}$–H), (b) 3.81 (C_8–H), (c) 2.78 (C_7–H, C_{10a}–H and C_{10b}–H), (d) 5.85 (2-NH), and (e) 6.05 (C_{13}–H) ppm.

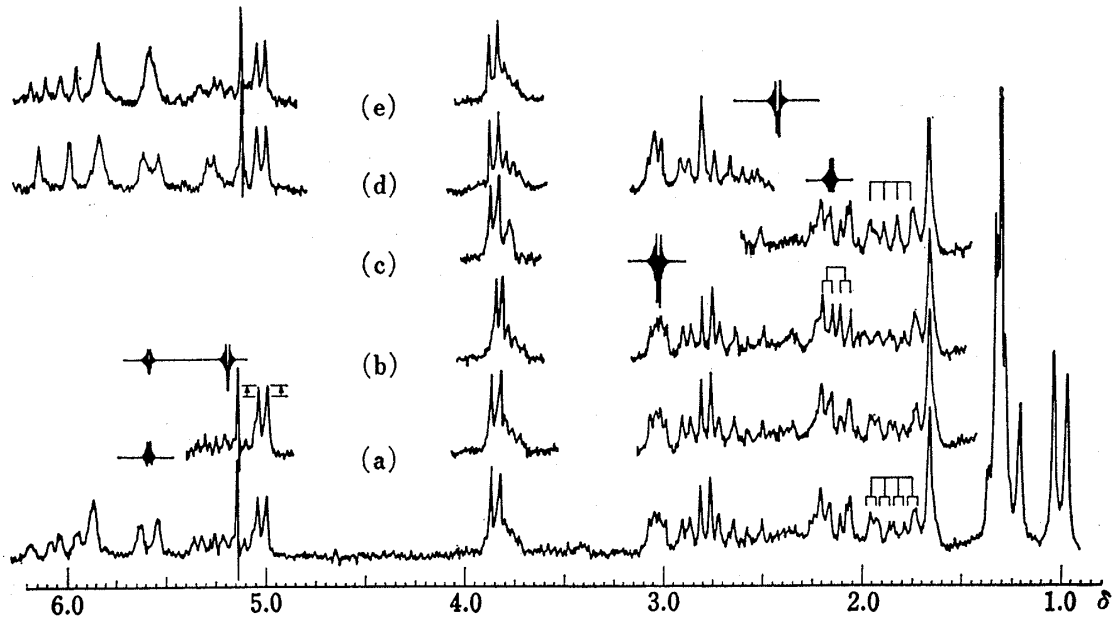


Fig. 5. Normal and Proton Decoupling Spectra of Chaetoglobosin A (in $CDCl_3$ at 100 MHz, Frequency Swept Mode) (3)

Irradiation at: (a) 5.57 (C_{17}–H), (b) 5.57 (C_{17}–H) and 5.20 (C_{14}–H), (c) 3.03 (C_4–H), (d) 2.14 (C_8–H and others), and (e) 2.42 (C_{16}–H) ppm.

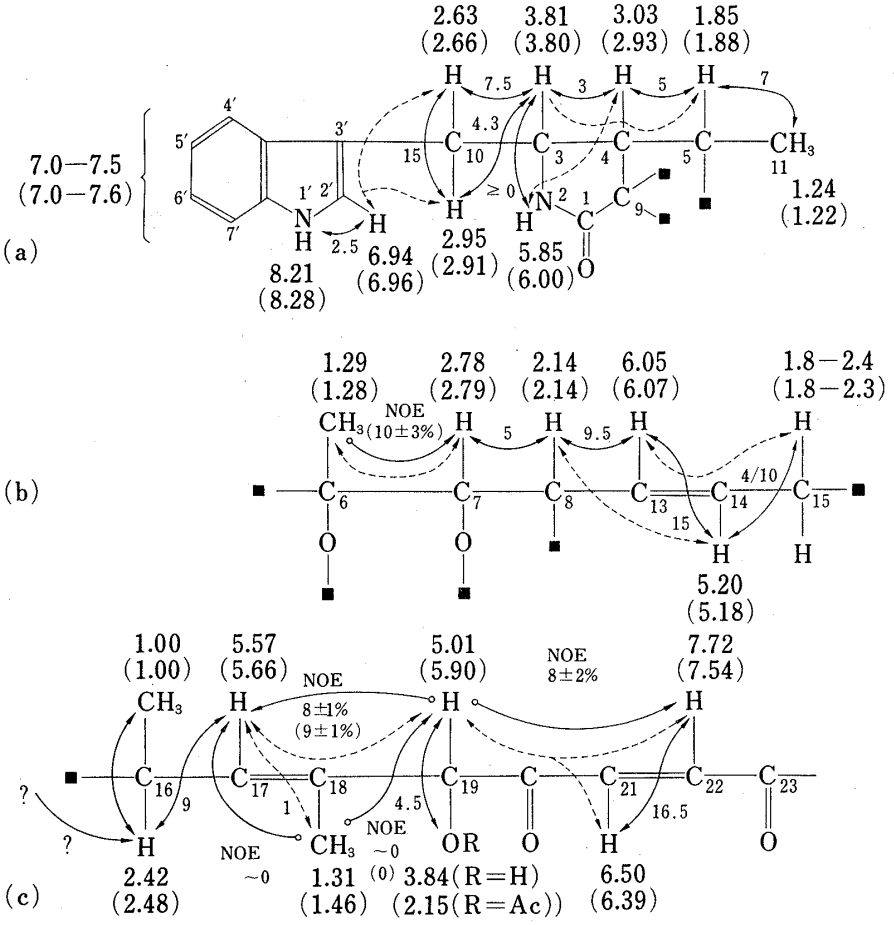


Chart 1. The Partial Structures (a), (b) and (c) and ^{1}H-NMR Parameters of Chaetoglobosin A (R=H) and the Acetate (R=Ac) (in $CDCl_3$)

The chemical shifts in parentheses are those for A-Ac. ⌒ indicates geminal or vicinal coupling, ⌒ long-range coupling, and ⌒ NOE.

Strong irradiation of C_{14}–H (Fig. 5(b)) showed an allylic long-range coupling of the proton to C_8–H (the signal at δ 2.14 was sharpened) and vicinal coupling to the allylic methylene protons at C_{15} (around δ 2.0) (Fig. 5(d)). Thus, the sequence shown in (b) in Chart 1 was confirmed.

(c): The fragment is composed of ten carbon atoms, including a secondary methyl and an allylic methyl group as well as a *trans* double bond, probably in the enedione. In the decoupling experiment, irradiation at the broadened doublet proton (δ 5.57) collapsed the allylic proton zone at around 2.4 ppm (Fig. 5 (a)). Conversely, upon irradiation at the allylic proton zone, the olefinic proton (δ 5.57) appeared as a broad singlet (Fig. 5 (e)) and the secondary methyl signal (δ 1.00) was changed into a singlet. A long-range coupling was observed between C_{17}–H and C_{18}–CH_3 and the sequence of C_{16}–C_{17}–C_{18} was confirmed. The complex coupling pattern of the proton at C_{16}–H remains, even under double irradiation at C_{16}–CH_3 and C_{17}–H. Thus, it was suggested that the C_{16} atom is adjacent to a methylene group. The proton at C_{19} (δ 5.01), which was shifted to lower field in the acetate (**A**-Ac), was assigned to that on the carbon bearing a hydroxyl group. When the hydroxyl proton (δ 3.84) was irradiated, the carbinyl proton was changed into a singlet (Fig. 3(d)). Although no vicinal coupling was observed for the carbinyl proton, irradiation at the proton clearly indicated the presence of long-range couplings to C_{17}–H (δ 5.57), C_{21}–H (δ 6.50), and C_{22}–H (δ 7.72 (Fig. 3(b)) as well as NOEs on C_{17}–H and C_{22}–H. Long-range coupling was also observed clearly for the carbinyl proton upon irradiation of C_{17}–H (Fig. 5(a)). These observations suggested the 17*E* structure. The presence of an α-ketol group in **A** was suggested by the positive tetrazolium salt reaction. As mentioned above, the *trans*-ethylene group appearing at lower field (C_{21}–C_{22})

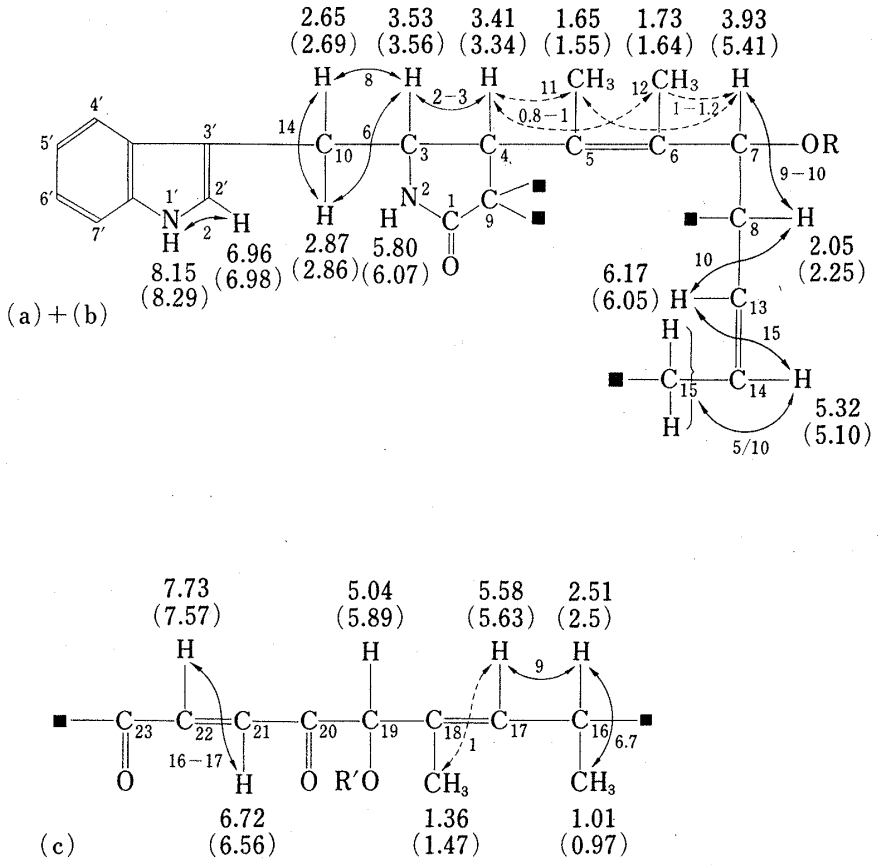


Chart 2. The Partial Structures (a), (b), and (c) and ^{1}H-NMR Parameters of Chaetoglobosin B (R=H) and the Diacetate (R=R′=Ac) (in $CDCl_3$)

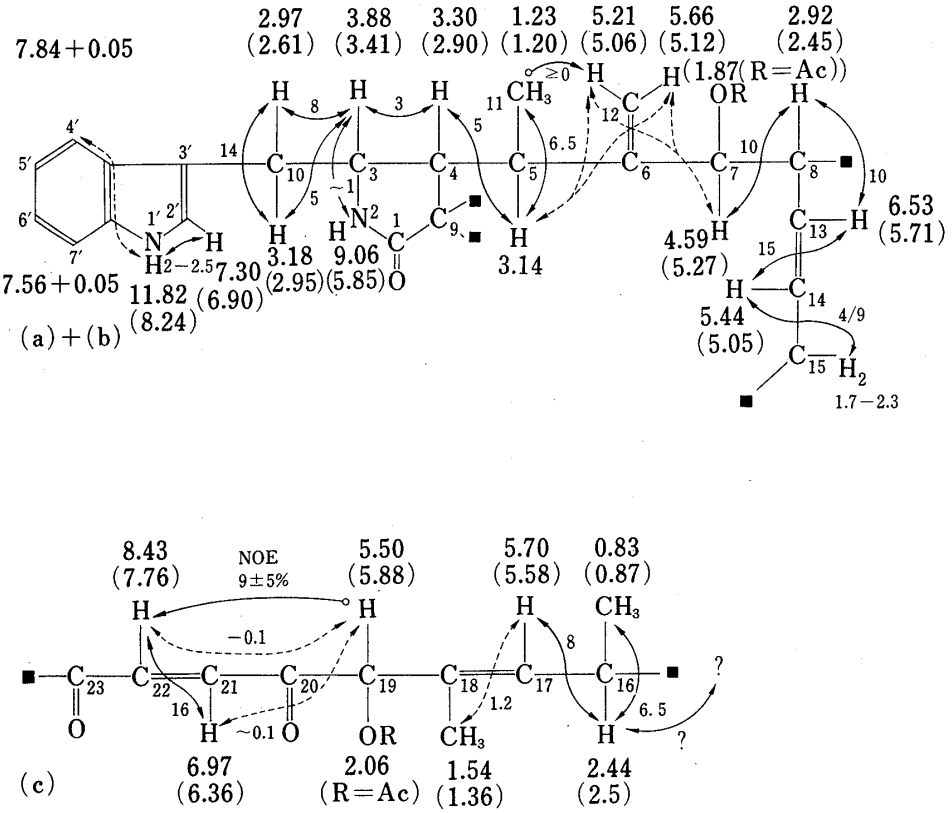
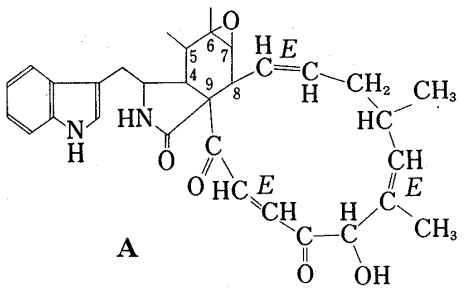


Chart 3. The Partial Structures (a), (b), and (c) and ^{1}H-NMR Parameters of Chaetoglobosin D (R=H) (in C_5D_5N) and the Acetate (R=Ac) (in $CDCl_3$)

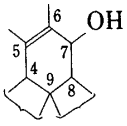
was assumed to be in a conjugated enedione system. Thus, the two double bonds and one secondary alcohol group were accommodated in fragment (c) as shown in Chart 1.

In the same manner, precise analyses of the spectra of **B**, **B**-Ac, **D**, and **D**-Ac were performed and the assignments are shown in Chart 2 and 3. Comparison of the ^{1}H-NMR spectra of **B** and **B**-Ac with those of **A** and **A**-Ac revealed that the secondary methyl group at C_5 (fragment (a)) and the tertiary methyl group at C_6 (fragment (b)) in **A** were replaced by two allyllic methyl groups in **B** and that a secondary alcohol group newly appeared at C_7 in **B**, but the other part of the molecule is essentially the same as that of **A** (Chart 2). In the case of **D** the two olefinic methyl groups at C_5 and C_6 in **B** were replaced by one secondary methyl group and one terminal methylene group (this group was also suggested by the IR absorption at 908 cm^{-1}) as shown in the partial formula (Chart 3). These observations were consistent with the assumption that **A** had an epoxide ring at the C_6–C_7 position, and the isomers **B** and **D** were the allylic alcohols bearing the hydroxyl group at C_7. Thus, the fragments (a) and (b) in **A** (Chart 1) were linked. Although first-order analysis was impossible due to the complicated couplings, the coupling patterns of the C_{15} and C_{16} protons suggested that these must be vicinal. Thus, the fragments (b) and (c) were linked. Finally C_8, C_9 and C_{23} were supposed to be mutually joined.

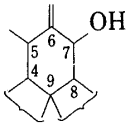
On the basis of these findings the structures shown in Chart 4 were put forward for chaetoglobosins A, B, and D as the preferred formulations.[2] These formulae suggested that the compounds belong to a group of cytotoxic mold metabolites known as cytochalasans,[4–7] such as cytochalasins A[5] (dehydrophomin[6]), B[5] (phomin[6]), and D[5] (zygosporin A[7]) (Chart 5); the phenylalanine unit in these is replaced by a tryptophan unit in our compounds.



A

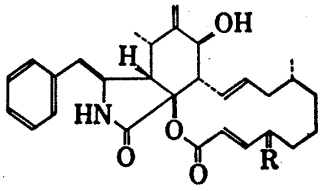


B



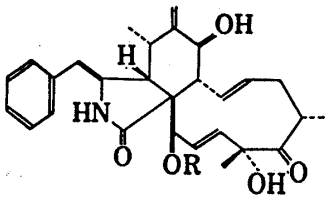
D

Chart 4



cytochalasin A : R=O
(dehydrophomin)

cytochalasin B : R= 
(phomin)



cytochalasin D : R=Ac
(zygosporin A)

Chart 5

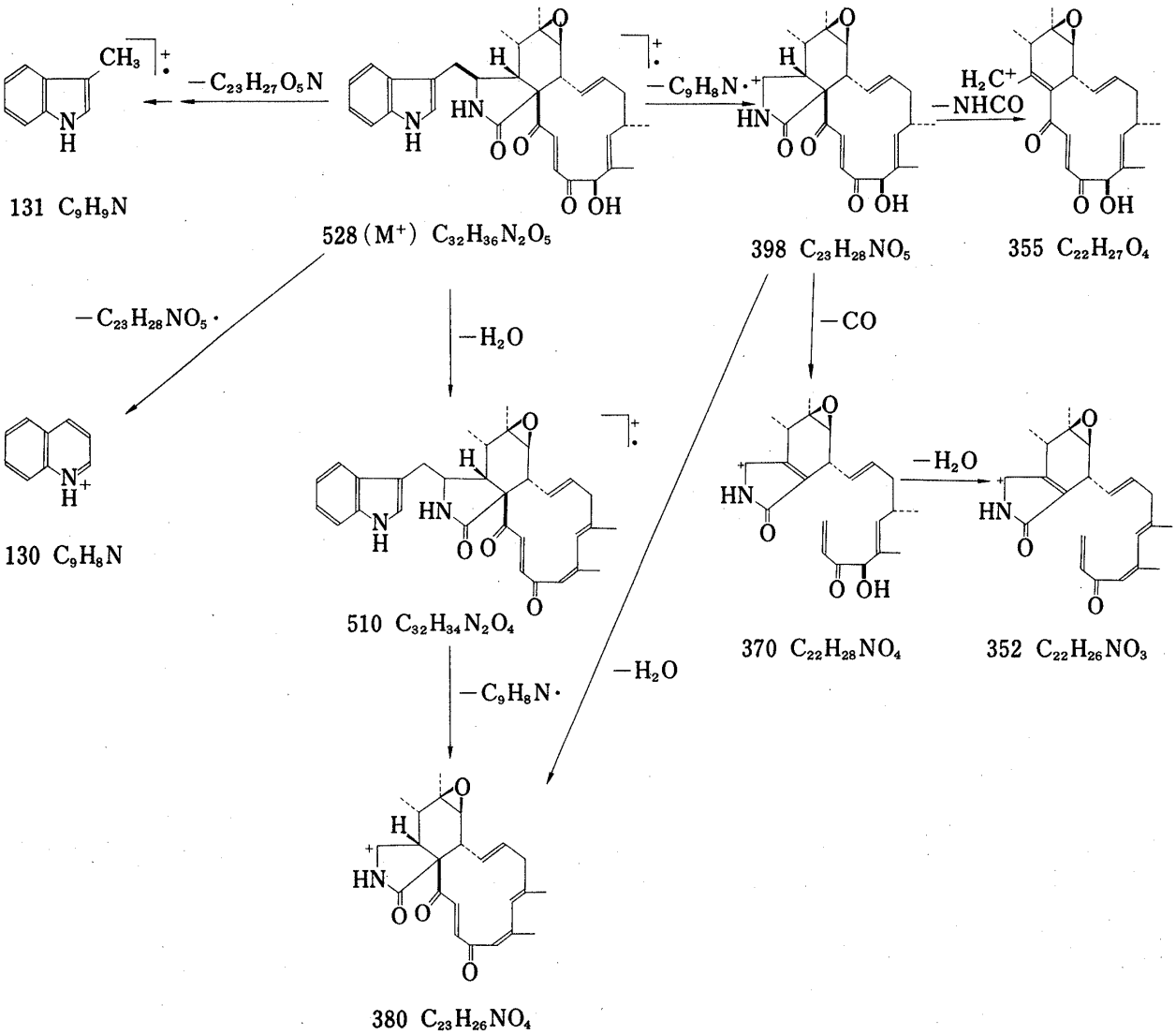


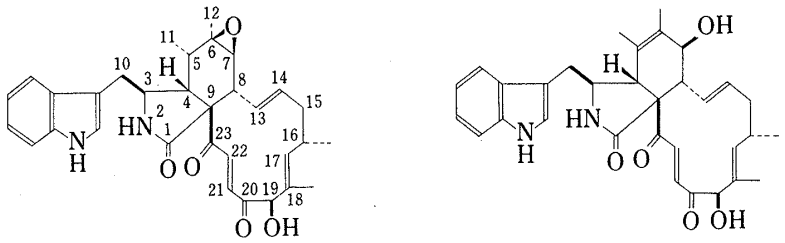
Chart 6. Mass Fragmentation of Chaetoglobosin A

As shown in the case of **A** in Chart 6, the MS fragmentations of chaetoglobosins showed good accord with those reported for the cytochalasins.[6] The structures are also reasonable in terms of possible biosynthesis from one unit of tryptophan, nine units of acetate-malonate, and three C_1 units.[8]

At this stage of the work we proposed plain structures for **A** and **B** in a preliminary communication.[2] Although there was no direct evidence for the streochemistry of the compounds, ^{1}H-NMR data can be harmoniously interpreted on the assumption that the perhydroisoindole part of the molecules has the same stereo-structure as the known cytochalasans.[5–7]

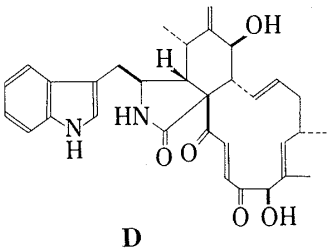
To confirm the structures and to determine the absolute configuration, a single crystal of chaetoglobosin A monohydrate, obtained by recrystallization from acetone (pale yellow prisms of mp 188°C[9]) was analyzed by X-ray crystallography. The structure was determined by direct methods, making use of a technique which uses the reflections occurring most often in the negative quartets as a starting set in the multi-solution approach. The absolute configuration was determined by means of the anomalous scattering of oxygen. The results verified the proposed structure for **A** and established the absolute stereochemistry of the compound, which is the same as that of the known cytochalans, as shown in Chart 7.[10] The five-membered ring in the isoindole unit is *cis*-fused to the six-membered ring, while the thirteen-membered ring is *trans*-fused to the six-membered ring. As was expected from the presence of an epoxide ring, the six-membered ring adopts a slightly twisted boat conformation.[10]

Since the coupling constant (10 Hz) of the C_7-carbinyl proton to the C_8 proton in both **B** and **D** suggests a *trans*-diaxial relation, the C_7 hydroxyl group was shown to be β and the stereostructures of the compounds were established as shown in Chart 7.



A

B



D

Chart 7

According to the systematic nomenclature adopted in Chemical Abstracts based on the proposal[11] chaetoglobosins A, B, and D are designated (7*S*, 13*E*, 16*S*, 17*E*, 19*R*, 21*E*)-6,7-epoxy-19-hydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-13,17,21-triene-1,20,23-trione, (7*S*, 13*E*, 16*S*, 17*E*, 19*R*, 21*E*)-7,19-dihydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-5,13,17,21-tetraene-1,20,23-trione, and (7*S*, 13*E*, 16*S*, 17*E*, 19*R*, 21*E*)-7,19-dihydroxy-10-(1*H*-indol-3-yl)-16,18-dimethyl-[13]cytochalasa-6(12),13,17,21-tetraene-1,20,23-trione, respectively.

Experimental

Melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. UV, IR, MS, and $[\alpha]_D$ were measured with Hitachi 200-10, Nihon Bunko DS-403G, JEOL 01SG-2, and Nihon Bunko DIP-180 machines, respectively. ^{1}H-NMR spectra were recorded on a Varian HA-100 spectrometer using the field and/or frequency swept mode and the internal Me_4Si-locked mode. Successive double and triple resonance experiments were achieved with two Hewlett Packard 200ABR audio frequency oscillators, and the line positions were determined with a Hewlett Packard 5521A electronic counter suitable for use with the HA-100 system. For thin-layer chromatography (TLC), silica gel $60F_{254}$ plates were used.

Chaetoglobosins A, B, and D——The details of the isolation procedures and UV and IR spectra were given in the preceding paper.[1] ^{1}H-NMR data are shown in Chart 1—3. MS data are as follows:

Chaetoglobosin A: MS *m/e*: 528.263 (M^+) (calcd for $C_{32}H_{36}N_2O_5$, 528.262), 510.254 (M^+-H_2O) (calcd for $C_{32}H_{34}N_2O_4$, 510.252), 398.198 ($M^+-C_9H_8N$) (calcd for $C_{23}H_{28}NO_5$, 398.197), 380.185 ($398-H_2O$) (calcd for $C_{23}H_{26}NO_4$, 380.186), 370.203 (398−CO) (calcd for $C_{22}H_{28}NO_4$, 370.202), 355.190 (370−NH) (calcd for $C_{22}H_{27}O_4$, 355.191), 352.184 ($370-H_2O$) (calcd for $C_{22}H_{26}NO_3$, 352.191), 131.073 (3-methylindol ion) (calcd for C_9H_9N, 131.074), 130.065 (quinolinium ion) (calcd for C_9H_8N, 130.066).

Chaetoglobosin B: MS *m/e*: 528.265 (M^+) (calcd for $C_{32}H_{36}N_2O_5$, 528.262), 398.194 (calcd for $C_{23}H_{28}O_5N$, 398.197), 355.184 (calcd for $C_{22}H_{27}O_4$, 355.191), 131.104 (calcd for C_9H_9N, 131.074).

Chaetoglobosin D: MS *m/e*: 528.261 (M^+) (calcd for $C_{32}H_{36}N_2O_5$, 528.262), 510.252 (calcd for $C_{32}H_{34}O_4N_2$, 510.252), 398.195 (calcd for $C_{23}H_{28}O_5N$, 398.197), 380.185 (calcd for $C_{23}H_{26}NO_4$, 380.186), 370.204 (calcd for $C_{22}H_{28}NO_4$, 370.202), 352.192 (calcd for $C_{22}H_{26}NO_3$, 352.191), 131.138 (calcd for C_9H_9N, 131.074), 130.104 (calcd for C_9H_8N, 130.066).

Acetylation of Chaetoglobosins A, B, and D——Chaetoglobosin A (90 mg) was treated with Ac_2O (2.5 ml) in pyridine (3.5 ml) at room temperature overnight. The precipitate was applied to a silica gel column using benzene–ether as developing solvents. From the benzene–ether (8: 2) fraction, an acetate (14 mg) was obtained and identified as **B**–Ac (*vide infra*). From the benzene–ether (7: 3) fraction, **A**–Ac (62 mg) was obtained and recrystallized from benzene as pale yellow needles of mp 252°C. UV λ_{max}^{MeOH} nm (log ε): 222 (4.63), 275 (3.83), 281 (3.83), 292 (3.72); IR ν_{max}^{KBr} cm^{-1}: 3395, 2970, 1738, 1698 (br), 1618, 1243, 1031, 974, 745; MS *m/e*: 570.273 (M^+) (calcd for $C_{34}H_{38}N_2O_6$, 570.273). ^{1}H-NMR (*cf.* Chart 1).

By the same procedure, **B**–Ac and **D**–Ac were obtained. They had the following physical properties:

Chaetoglobosin B Diacetate: Pale yellow needles from benzene, mp 257—258°C. UV λ_{max}^{MeOH} nm (log ε): 212 (4.33), 271 (3.55), 280 (3.53), 290 (3.47). IR ν_{max}^{KBr} cm^{-1}: 3400, 2918, 1746, 1736, 1703 (br), 1620, 1373, 1246, 1229, 1031, 979, 745. MS *m/e*: 612.282 (M^+) (calcd for $C_{36}H_{40}O_7N_2$, 612.283). ^{1}H-NMR (*cf.* Chart 2).

Chaetoglobosin D Diacetate: Pale yellow needles from benzene, mp 158—159°C. IR ν_{max}^{KBr} cm^{-1}: 3398, 2915, 1735 (br), 1680, 1368, 1230 (br), 1035, 975, 740. MS *m/e*: 612.282 (calcd for $C_{36}H_{40}O_7N_2$, 612.283). ^{1}H-NMR (*cf.* Chart 3).

Isomerization of Chaetoglobosin A——i) With Triethylamine in MeOH: Chaetoglobosin A (15 mg) was treated with triethylamine (0.5 ml) in MeOH (3 ml) at room temperature for 1 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was passed through a silica gel column using benzene, $CHCl_3$, and EtOAc successively as developing solvents. The fractions eluted with benzene–$CHCl_3$ (1: 1) and benzene–EtOAc (8: 2) afforded compounds a (8 mg) and b (3 mg), respectively. Compound a was recrystallized from $CHCl_3$ as colorless crystals, mp 263—265°C, identical with an authentic sample of **C** (IR and TLC). Compound b was recrystallized from benzene as yellow needles, mp 186°C, and its identity with **B** was established by IR and TLC.

i) With Triethylamine in Pyridine: See Part III.

iii) With BF_3–etherate in $CHCl_3$: A solution of chaetoglobosin A (27 mg) in $CHCl_3$ (3 ml) was added to a solution of $BF_3O(C_2H_5)$ (0.2 ml) in dry $CHCl_3$ (1 ml) at room temperature. After 5 min, the reaction mixture was diluted with $CHCl_3$ (100 ml), then it was washed with aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was passed through a silica gel column using $CHCl_3$ and EtOAc as developing solvents. The fractions eluted with $CHCl_3$–EtOAc (8: 2) and $CHCl_3$–EtOAc (1: 1) gave compounds a (7 mg) and b (5 mg), respectively. Compound a was recrystallized from benzene to give yellow needles, mp 186°C, identical with an authentic sample of **B** (IR and TLC). Compound b was recrystallized from CH_2Cl_2 as yellow prisms, mp 215°C, and found to be identical with **D** by IR and TLC.

iv) With Acetic Acid: Chaetoglobosin A (18 mg) was warmed for 40 min in 90% AcOH (1 ml) in a water bath. After addition of H_2O, the resulting precipitate was separated, recrystallized from benzene as pale yellow needles, mp 185—187°C, and identified as **B** (13 mg). The mother liquor was extracted with CH_2Cl_2, dried, and concentrated. TLC of the residue showed the presence of **D**.

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