Ester, Aldehyd, Keton, Lactam); 1640 (C=C konj.); 1610, 1500 (Arom.); 1380, 1240 (C—O—C); 1080 (C—O—H); 915 cm^{-1}.

13. *Haloform-Reaktion mit* **23**. Zu einer Lösung von 50 mg (0,099 mmol) **23** in 2,5 ml Dioxan und 0,5 ml 10proz. NaOH-Lösung wurde eine KJ/J_2-Lösung (2 g KJ, 1 g J_2, 10 ml H_2O) solange zugetropft bis die Braunfärbung bei 60° beständig war. Dann wurde die Lösung mit 10proz. NaOH-Lösung wieder entfärbt und mit Wasser verdünnt. Es entstand eine milchige Trübung, wobei der typische Jodoformgeruch wahrnehmbar wurde. Übliche Extraktion und Aufarbeitung lieferte ein braunes Harz, aus dem durch Sublimation (0,01 Torr/130°) 3,50 mg Jodoform (**25**) (9%) gewonnen wurde. **25** kristallisierte aus Methanol in kleinen, gelben Plättchen vom Smp. 120–121°, die nach Misch-Smp. und DC. mit einem authentischen Präparat identisch waren. Das radioaktive Jodoform (**25**) (3,50 mg) wurde mit inaktivem Jodoform (37,00 mg) verdünnt und das Gemisch aus Methanol umkristallisiert. Es resultierten 36 mg eines Jodoform-Präparats **25'**, welches für die Radioaktivitätsmessung verwendet wurde.

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191. Biosynthesis of the Cytochalasans. Part III. ^{13}C-NMR. of Cytochalasin B (Phomin) and Cytochalasin D. Incorporation of [1-^{13}C]- and [2-^{13}C]-Sodium Acetate[1])

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(26. VI. 74)

Summary. Sequential single frequency decoupling and partially relaxed *Fourier* transform (PRFT) are used to assign the natural abundance ^{13}C-NMR. spectra of cytochalasin B (phomin) (**1**) and cytochalasin D (**2**). Cultures of *Phoma spec.* S 298 were fed [2-^{13}C]-sodium acetate, and the distribution of this precursor in cytochalasin B (phomin) (**1**) was determined by ^{13}C-NMR. spectroscopy. Likewise, the labelling patterns in cytochalasin D (zygosporin A) (**2**) from *Zygos-*

[1]) Part. II. see [1].

posium masonii could be identified after incorporation of [2-^{13}C]-sodium acetate and [1-^{13}C]-sodium acetate. The results confirm previous proposals for the biogenesis of the cytochalasans from phenylalanine, methionine, and a C_{18} or C_{16} polyketide part.

1. Introduction. – Biosynthetic studies utilizing ^{13}C isotopic labelling are especially efficient since the position of the incorporated label can be determined directly by ^{13}C-NMR. spectroscopy instead of difficult and time-consuming degradations. The important biological activity of the cytochalasans [2] and the complexity of their structures make them natural subjects for such an investigation, particularly in light of previous work with radioactive precursors [3]. The present ^{13}C-NMR. studies of cytochalasin B (phomin) (**1**) and cytochalasin D (zygosporin A) (**2**) demonstrate the usefulness of sequential single frequency decoupling and partially relaxed *Fourier* transform (PRFT) [4] in making assignments of ^{13}C-NMR. peaks for complex organic compounds, and corroborate the biosynthetic proposals for the origin of these macrocyclic mould metabolites.

Cytochalasin B (**1**) was suggested to arise from one unit of phenylalanine, two units of methionine, and nine acetate units [2] [3]. Although the position of incorporation of radioactive phenylalanine and methionine could be completely determined by degradation experiments, the mode of utilization of [^{14}C]-sodium acetate was only partially accessible. These results are schematically summarized in Figure 1. Of special interest were carbon atoms C(1) and C(9) in the lactam ring, since they occur at the juncture of amino acid and polyketide biogenetic paths, and were inaccessible by degradation.

An analogous situation exists with the ^{13}C- and ^{3}H-labelling studies of cytochalasin D (**2**) [1]. This fungal metabolite has been proposed to come from one molecule of phenylalanine, three of methionine, and nine of acetate (Fig. 1). Location of acetate units could only be partially determined, but the portions derived from the other precursors could be identified by cleavage reactions.

2. Assignments of ^{13}C-NMR. Spectra of Cytochalasins B (1) and D (2). – The basis for assigning ^{13}C-NMR. signals for cytochalasins B (**1**) and D (**2**) are summarized in Tables 1 and 2. The techniques of partially relaxed *Fourier* transform [4] (PRFT), and especially that of sequential single-frequency decoupling were employed in assigning the natural abundance ^{13}C-NMR. peaks. The PRFT method (T_1 relaxation) was of great help in locating the quarternary carbon atoms and removing the interfering solvent bands (see inverted peaks in T_1 spectra, Fig. 3 and 6). However, in both (**1** and **2**) the T_1 relaxation time of carbon atoms other than quarternary and carbonyl were unusually fast, and the differences in relaxation times between methine, methylene, and methyl carbon atoms were so minimal that the method did not assist in distinguishing between these types of atoms. The rapid relaxation of signals may be due to the use of pyridine as solvent, but this should be further investigated.

Since the ^{1}H-NMR. signals [5] [6] for **1** and **2** (Fig. 2 and 5, top spectra) are spread out over a wide range, they were ideally suited for carrying out detailed single-frequency irradiations. This is evident on inspection of the following equation developed by *Ernst* [7] which correlates the ^{13}C-NMR. residual coupling J_r with $\Delta\nu$, the difference in frequency between the chemical shift of a particular proton signal and the decoupler frequency:

$$J_r = J\Delta\nu/(\gamma H_2/2\pi)$$

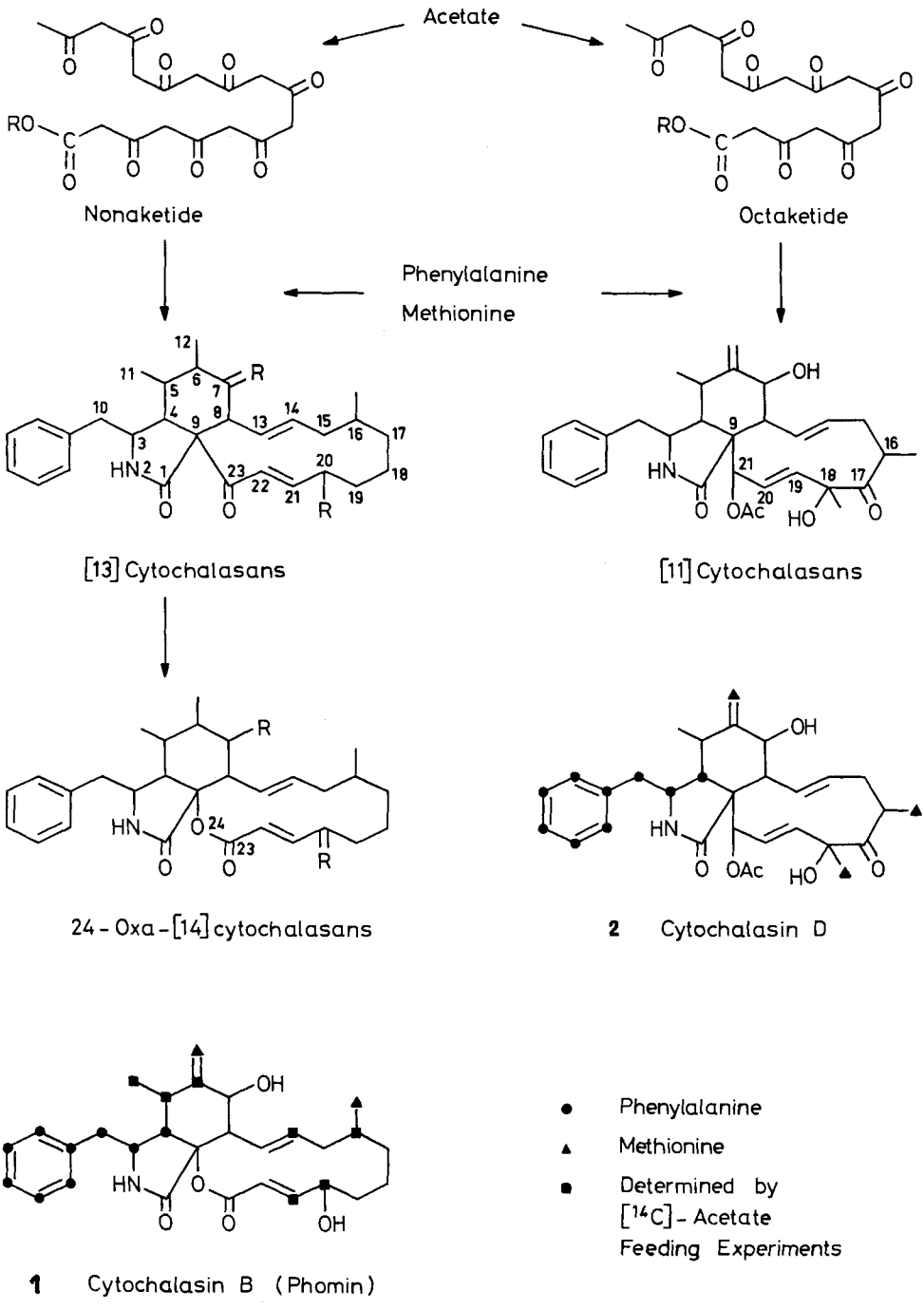

Fig. 1. *Biosynthetic Proposals*

where J is the ^{13}C–H coupling constant and $\gamma H_2/2\pi$ is the strength of the decoupling field [8].

Selected ^{13}C-NMR. spectra resulting from irradiations at positions indicated by IRR (1), IRR (2), etc. in the ^1H-NMR. spectra are shown in Figures 2 and 5. The numbers in the partially decoupled ^{13}C-NMR. spectra correspond to the carbon assignments and denote signals which became virtual singlets or peaks with very small J_r values upon irradiation at the frequency denoted by arrows (IRR (1), etc.) in the ^1H-NMR. spectra. Most of the ^{13}C-NMR. peaks were readily assigned by this technique. The assignments for C(5), C(10) and C(11) were established by comparing the spectra of cytochalasins B and D, assuming that the signals for the benzyl substituted perhydroisoindole portion of the molecule should be very similar. This proved to be the case, the difference in chemical shifts not exceeding 2.5 ppm with the exception of C(9) which is in a different oxidation state. All the ^{13}C-NMR. signals except for C(15), C(16) and C(17) in cytochalasin B, and C(14), C(19) and C(20) in cytochalasin D could be assigned by these methods; ^{13}C-incorporation results have been used for these remaining assignments.

3. Incorporation of [2-^{13}C]-Sodium Acetate in Cytochalasin B (1) by *Phoma spec.* S 298. – Sodium acetate labelled in the C(2) position with ^{13}C (isotopic purity = 90%) was fed to cultures of *Phoma spec.* S 298 in a concentration of 225 mg precursor per liter of culture. Fermentation of this mould and isolation of the resulting cytochalasin B (**1**) were carried out in the fashion previously described [6] [9].

The ^{13}C-NMR. spectra of unlabelled (natural abundance) and [2-^{13}C]-sodium acetate derived cytochalasin B (**1**) were measured under identical conditions of concentration (15 mg/ml), repetition time (2.1 s), and pulse width (15 μs) in order to obviate any differences in signal height resulting from the differing T_1's of the various carbon nuclei. Comparison of the two spectra (Fig. 4) shows the labelled carbons to be C(11), C(6), C(8), C(9), C(14), C(18), C(20) and C(22). It seems reasonable to assign the remaining labelled carbon with a resonance at 33.52 ppm to C(16) for biogenetic reasons. (Labelling at C(16) is corroborated by previous results from degradation of cytochalasin B (**1**) after feeding [^{14}C]-labelled sodium acetate and sodium malonate [2]). This allows the signals at 35.38 and 35.52 ppm to be assigned to C(15) and C(17), thus completing the ^{13}C-NMR. assignments for cytochalasin B (**1**).

Mass spectra analysis (see Section 4) showed the absolute incorporation rate to be 0.11%, in agreement with the observed ^{13}C-NMR. enrichment and previous experiments with [^{14}C]-sodium acetate (average incorporation rate = 0.123%).

The labelling pattern agrees with earlier feeding experiments with methionine and phenylalanine, and supports the biogenetic scheme outlined in Figure 1. Since C(9) is ^{13}C-labelled, it is possible that C(9) and C(1) are the terminus of the proposed C_{18} polyketide intermediate.

4. Incorporation of [1-^{13}C]-Sodium Acetate and [2-^{13}C]-Sodium Acetate in Cytochalasin D (2) by *Zygosporium masonii*. – A culture of *Zygosporium masonii* was grown under the usual conditions [1] in a medium containing 530 mg of [1-^{13}C]-sodium acetate (isotopic purity = 55%) per liter, and the resulting cytochalasin D (**2**) was isolated after four days. On the basis of mass spectral measurements, the absolute incorporation rate was 0.86%. Measurement of ^{13}C-NMR. spectra of unla-

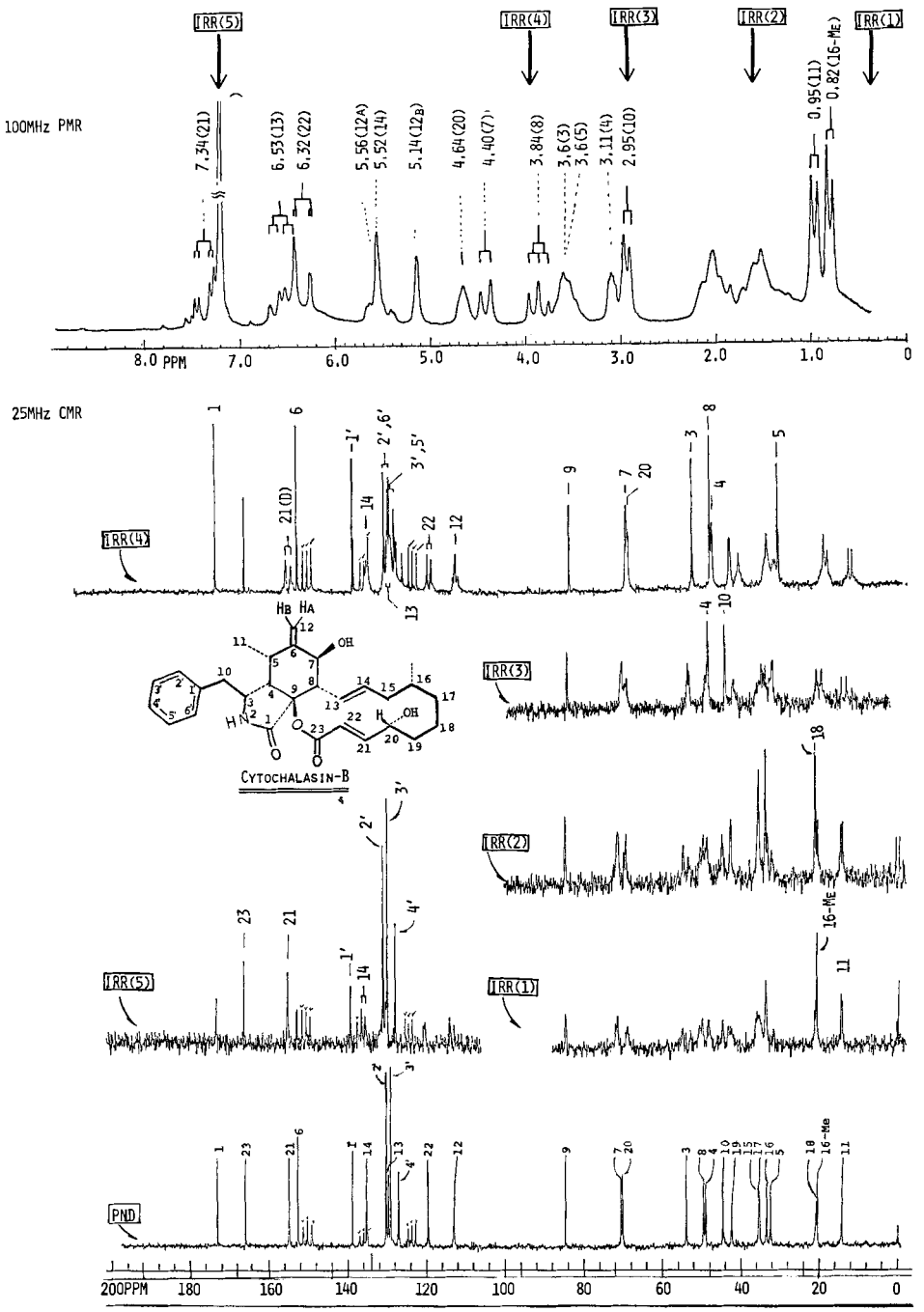

Fig. 2. *Cytochalasin B spectra.* IRR (1), IRR (2), etc. in the ^{13}C-NMR. charts show the pertinent portion of the spectra upon single-frequency irradiation at the regions designated by IRR (1), IRR (2), etc. in the 100 MHz ^{1}H-NMR.

Table 1. *^{1}H- and ^{13}C-NMR. Data of Cytochalasin B* [a])

	^{1}H (J, Hz)	^{13}C	Basis for Assignment			^{1}H (J, Hz)	^{13}C	Basis for Assignment
C(1)	–	172.3	–		C(15) (or 17)	1.2–2.2	35.38	–
N(2)	8.88	–	–		C(16)*	1.2–2.2	33.52	from ^{13}C-enrichment
C(3)	3.6	53.87	irr-4,	*cf.* irr-2	C(17) (or 15)	1.2–2.2	35.38	–
C(4)	3.11 (2.5, 1.5)	49.04	irr-3,	*cf.* irr-2	C(18)*	1.2–2.2	20.85	irr-2, γ-effect of 16(CH_3/20-OH)
C(5)	3.6	32.42	irr-4, cyto-D	*cf.* irr-2; (33.12)	C(19)	1.2–2.2	42.37	irr-2
C(6)*	–	152.0	PRFT		C(20)*	4.64	69.97	irr-4, *cf.* irr-2
C(7)	4.40 (10)	70.40	irr-4,	*cf.* irr-2	C(21)	7.34 (20, 4)	154.2	irr-5, *cf.* irr-4
C(8)*	3.84 (10, 10)	49.42	irr-4,	*cf.* irr-2	C(22)*	6.32 (20, 2)	119.2	irr-4
C(9)*	–	84.40	PRFT		C(23)	–	165.2	–
C(10)	2.95 (6)	44.64	irr-3, cyto-D	*cf* irr-2; (45.49)	C(1′)	–	138.3	PRFT
					C(2′); C(6′)	7.20	129.8	irr-5
C(11)*	0 95 (6)	14.26	irr-1; cyto-D	(13.65)	C(3′); C(5′)	7.20	128.7	irr-5
C(12)	5.56 (A) 5.14 (B)	112.7	–		C(4′)	7.20	126.7	irr-5
C(13)	6.53 (16, 10)	129.3	irr-4		C(16)CH_3	0.82 (6)	20.53	irr-1
C(14)*	5.52 (15, 10, 4)	134.8	irr-4,	irr-5				

[a]) ^{1}H-NMR. in pyridine-d_5, *Varian* HA-100, ppm from TMS; ^{13}C-NMR. in pyridine-d_5, *JEOLCO* PS-100, ppm from TMS. * = Carbons derived from [2-^{13}C]-sodium acetate. PRFT: Partially relaxed *Fourier* transform data (Fig. 2).

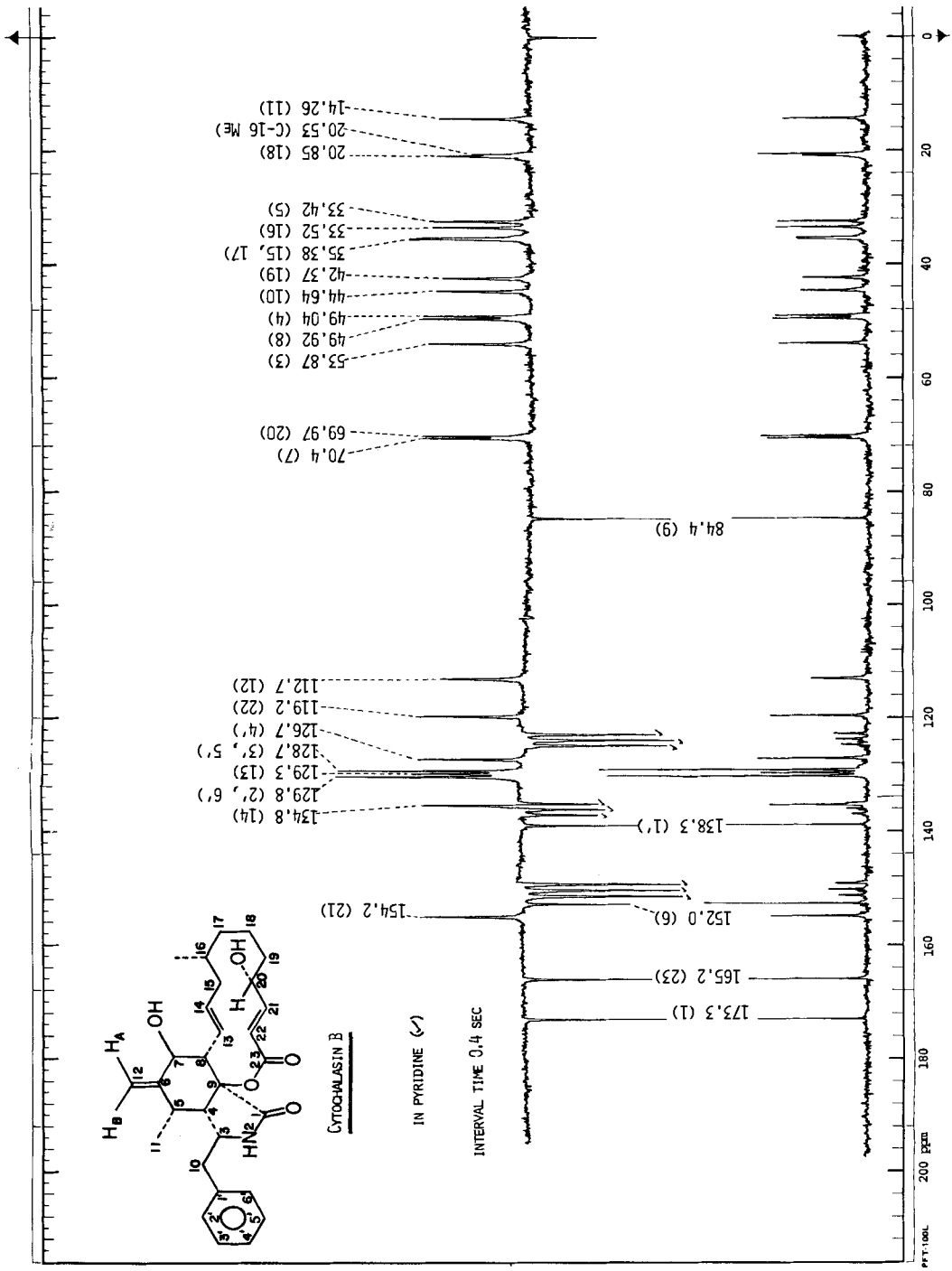

Fig. 3. *Proton noise decoupled (PND) and PRFT spectra of cytochalasin B, pyridine-d_5 (✓).* PRFT spectrum: interval time 0.4 sec, pulse width 19.08 μsec, repetition time 10 sec, 5144 scans; 270 mg.

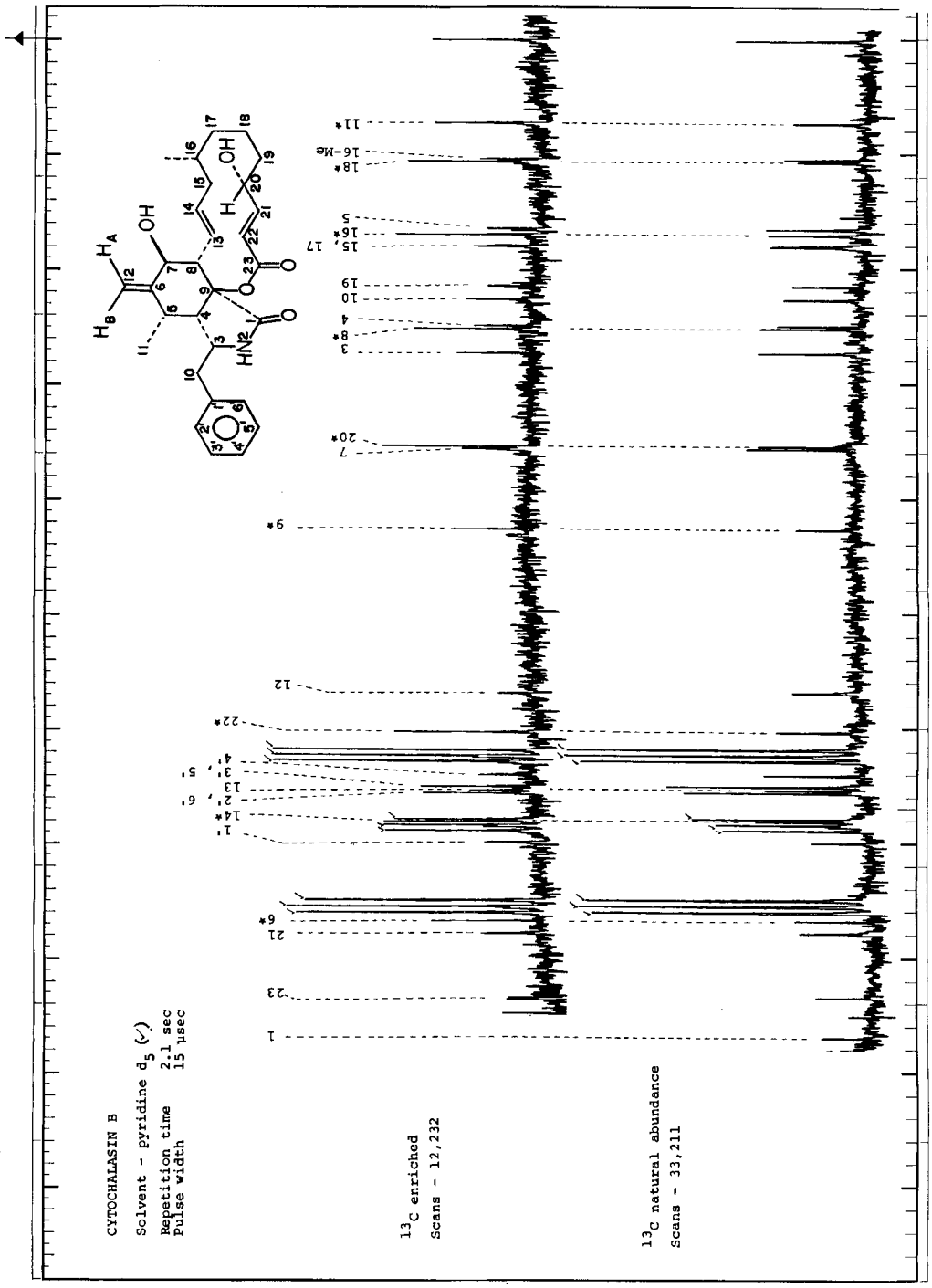

Fig. 4. *PND spectra of natural and [2-^{13}C]-acetate derived cytochalasin B in pyridine-d_5 (✓), pulse width 15 µsec, repetition time 2.1 sec.*

belled (natural abundance) and labelled material was done under identical conditions of concentration (46 mg/ml), repetition time (2.1 s) and pulse width (9.5 μs). Comparison of the spectra showed labelled carbons at C(1), C(5), C(7), C(13) (see IRR-5, Fig. 5), C(15), C(17), C(21) and the carbonyl group of the O-acetyl group. For biogenetic reasons the remaining labelled carbon at 127.7 ppm was assigned to C(19). This leaves the unassigned olefinic resonances at 133.7 and 132.7 ppm in the natural abundance ^{13}C-NMR. spectrum of cytochalasin D to be assigned to C(20) and C(14). Single frequency off-resonance decoupling (IRR-5, Fig. 5) linked the carbon signal at 133.7 ppm to the proton signal at 6.70 ppm, thus identifying it as C(20). This completes the assignment of the ^{13}C-NMR. natural abundance spectrum of cytochalasin D.

Incorporation of [2-^{13}C]-sodium acetate (isotopic purity = 90%) at a concentration of 519 mg of precursor per liter of growth medium confirmed these results. In this case, comparison of spectra for natural abundance and labelled cytochalasin D (Fig. 7) showed carbons C(11), C(6), C(8), C(9), C(14), C(16), C(18), C(20) and the methyl of the O-acetyl group to be enriched. The absolute incorporation rate was 1.5%.

Previous studies indicated that the C(18) and C(16) methyl groups and C(12) arise from methionine, and that the aromatic residue, C(10), C(3) and C(4) originate from phenylalanine. Viewed together with the current ^{13}C experiments, these results support the scheme for the biosynthesis of cytochalasin D (**2**) outlined in Figure 1. Additional work to explore the detailed biogenesis of the C_{16} polyketide part, or its biogenetic equivalent, and its linking to the phenylalanine residue is in progress.

5. Determination of the Incorporation Rates by Mass Spectrometry. – The absolute incorporation rate and the expected average enhancement of the ^{13}C-NMR. integral per labelled atom were determined by comparison of the mass spectra of labelled and unlabelled material. Cytochalasin D (**2**) (molecular weight = 507.26) shows a natural abundance mass spectrum of ions, I, in the ratio:

$$I_{507} : I_{508} : I_{509} : I_{510} = 100 : 35 : 7 : 1$$

The sample obtained after incorporation of [2-^{13}C]-sodium acetate showed an ion abundance of:

$$I_{507} : I_{508} : I_{509} : I_{510} = 100 : 62 : 23 : 6$$

which leads to a distribution as follows:

Additional ^{13}C atoms	I_{507}	I_{508}	I_{509}	I_{510}	% of Sample
0	100	35	7	1	74
1	–	27	9	2	20
2	–	–	7	2	5
3	–	–	–	1	1
	100	62	23	6	100

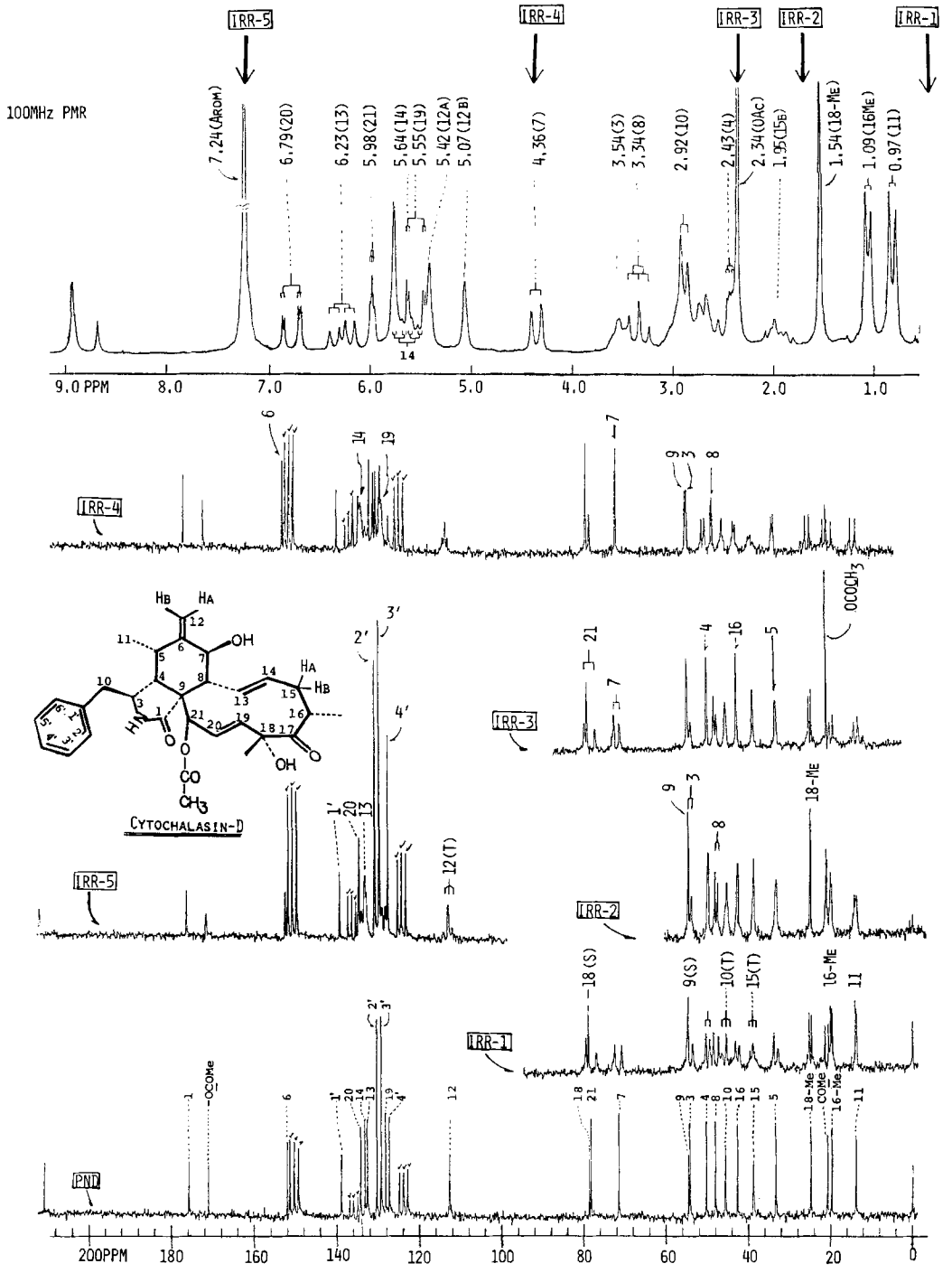

Fig. 5. *Cytochalasin D spectra.* IRR (1), IRR (2), etc. in the ^{13}C-NMR. charts show the pertinent portion of the spectra upon single-frequency irradiation at the regions designated by IRR (1), IRR (2), etc. in the 100 MHz ^{1}H-NMR.

Table 2. *^1H- and ^{13}C-NMR. Data of Cytochalasin D*[a])

	^1H (J, Hz)	^{13}C	Basis for Assignment			^1H (J, Hz)	^{13}C	Basis for Assignment
C(1)	–	174.9	–		C(16)*	2.0	42.45	irr-3, *cf.* irr-1
N(2)	8.92	–	–		C(17)	–	210.7	–
C(3)	3.54	54.00	irr-4,	*cf.* irr-2	C(18)*	–	78.32	irr-1
C(4)	2.43 (6, 3)	50.00	irr-3,	*cf.* irr-1	C(19)	5.55 (16, 2.2)	127.7	irr-4, irr-5
C(5)	2.7	33.12	irr-3, cyto-B	*cf.* irr-1; (32.42)	C(20)*	6.79 (16, 2.5)	133.7	irr-4
					C(21)	5.98 (2.5, 2.2)	77.92	irr-3
C(6)*	–	151.4	PRFT					
					C(1′)	–	138.3	PRFT, irr-5
C(7)	4.36(10)	71.20	irr-4,	*cf.* irr-3				
					C(2′); C(6′)	7.24	129.9	irr-5
C(8)*	3.34 (10, 10)	47.8	irr-4,	*cf.* irr-3				
					C(3′); C(5′)	7.24	128.7	irr-5
C(9)*	–	54.37	PRFT					
					C(4′)	7.24	126.8	irr-5
C(10)	2.92 (7)	45.49	irr-1;	*cf.* cyto-B (44.64)				
					C(16)CH_3	1.09	19.44	irr-2
C(11)*	0.97	13.65	irr-1;	*cf.* cyto-B (14.26)	C=O (Ac)	–	170.3	–
					CH_3 (Ac)*	2.35	20.61	irr-3
C(12)	5.42 (A) 5.07 (B)	112.2	–		C(18)CH_3	1.54	24.64	irr-2
C(13)	6.23 (15, 9)	132.1	irr-5					
C(14)*	5.64	132.7	irr-4,	irr-5				
C(15)	2.7, 1.95	38.58	irr-1					

a) See footnote to Table 1.

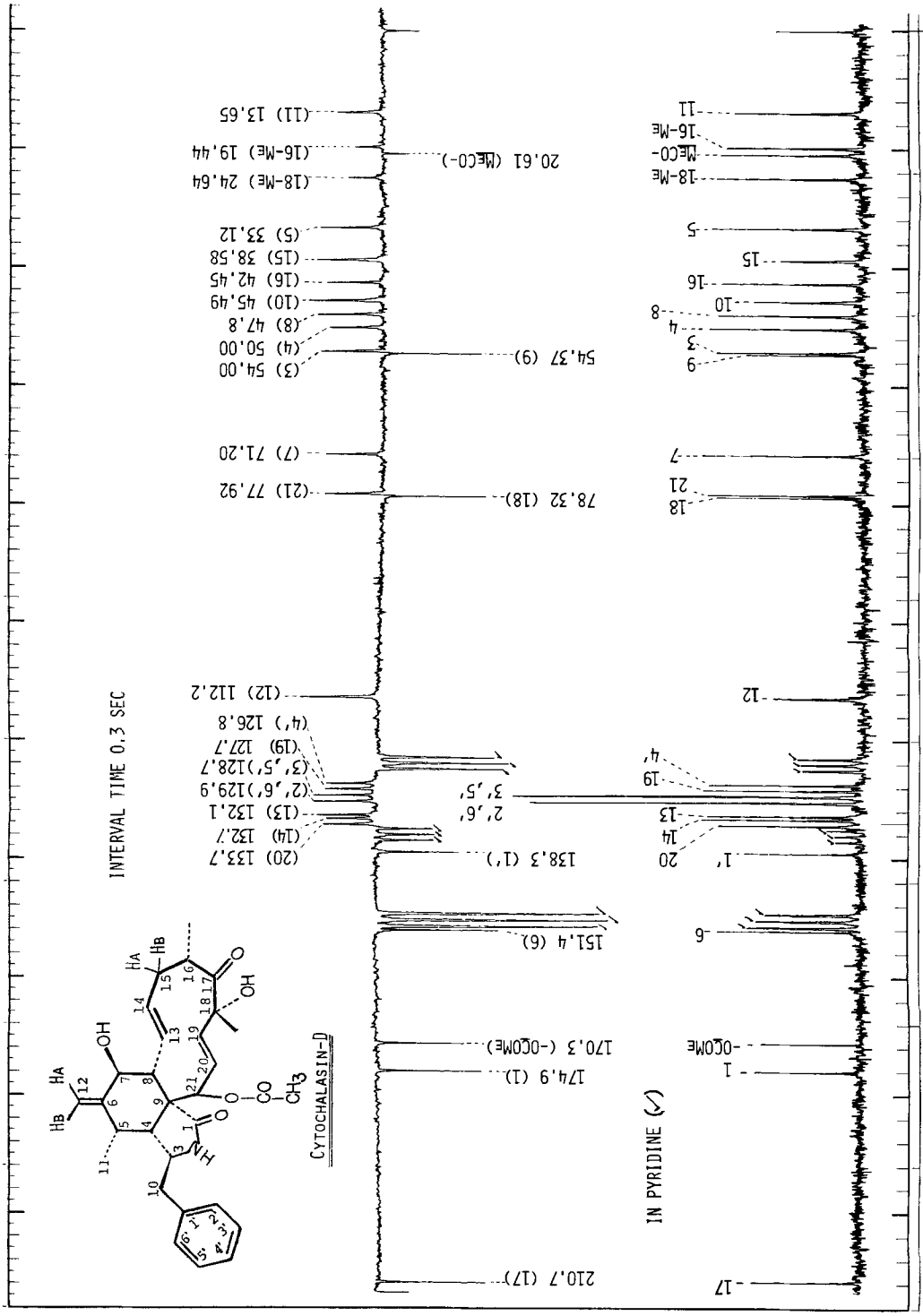

Fig. 6. *Proton noise decoupled (PND) and PRFT spectra of cytochalasin D, pyridine-d_5 (✓).* PRFT spectrum: interval time 0.3 sec, pulse width 19.7 μsec, repetition time 5.0 sec, 5494 scans; 266 mg.

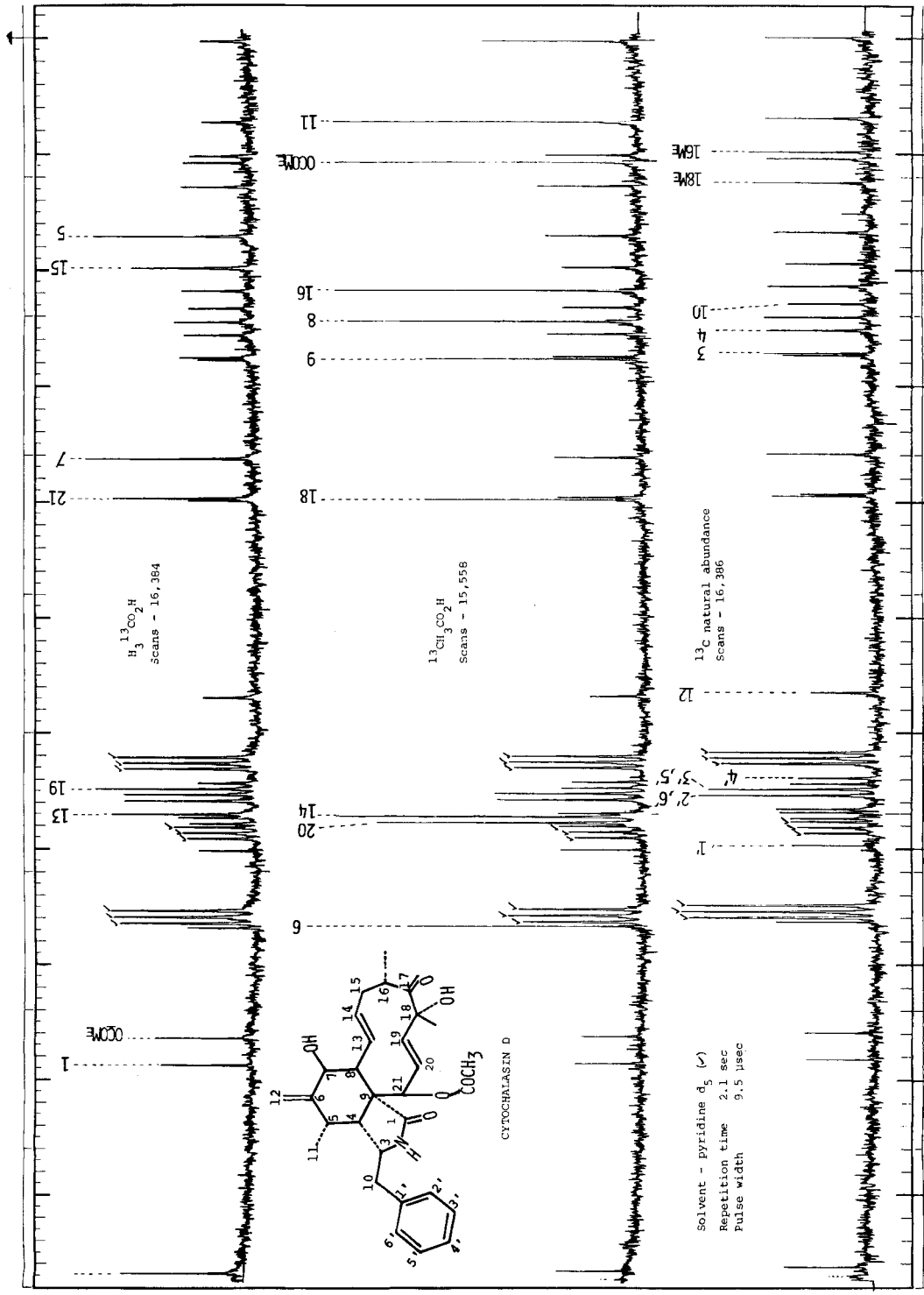

Fig. 7. *PND spectra of natural,* [7-^{13}C]*-acetate derived and* [2-^{13}C]*-acetate derived cytochalasin D in pyridine-d_5* (✓), pulse width 9.5 µsec, repetition time 2,1 sec.

Assuming that the number of labelled atoms in the precursor in excess of natural abundance is approximately equal to the total number of labelled atoms in the precursor for high activities, we obtain:

$$\text{Absolute Incorporation Rate} = \frac{(\text{Total Activity Product}) \cdot 100\%}{(\text{Total Activity Precursor})}$$

$$= \frac{\left(\begin{matrix}\text{Number of } {}^{13}\text{C Atoms in Product in Excess of} \\ \text{Natural Abundance}\end{matrix}\right) \cdot 100\%}{(\text{Number of Labelled Atoms in Precursor})}$$

$$= \frac{\dfrac{(\text{mg of Product}) \cdot 100\%}{(\text{Molecular Weight of Product})} (x_1 + 2x_2 + 3x_3 + \ldots n x_n)}{\dfrac{(\text{mg of Precursor})}{(\text{Molecular Weight of Precursor})} \left(\begin{matrix}\text{Isotopic} \\ \text{Purity}\end{matrix}\right) \left(\begin{matrix}\text{Number of Labelled} \\ \text{Atoms/Molecule Precursor}\end{matrix}\right)}$$

where x_n is the fraction of molecules in the product possessing n additional ^{13}C atoms. This yields an absolute incorporation rate of 1.50% for [2-^{13}C]-sodium acetate, which corresponds to an average expected enhancement for the ^{13}C-NMR. signals of about 3.5 times the natural abundance signals.

The support of these investigations in Basel (*Ch. T.*) by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* (Projects No. 2.675.72 and 2.0550.73) and in New York (*K. N.*) by a *NIH* Grant No. CA 11 572 is gratefully acknowledged. *J. C. V.* thanks the *American Philosophical Society* (*Penrose Fund*) for a travel grant.

Experimental Part

1. *General Methods.* The ^{13}C-NMR. spectra were measured on a *JEOLCO* PS-100 instrument (25.149 MHz). Partially relaxed *Fourier* transform spectra were obtained by the 180°-τ-90°-T pulse sequence. The single frequency decoupled spectra were obtained by using approximately 5% of the PND field strength.

We are grateful to Dr. *H. Lichti, Sandoz AG,* Basel, for all mass spectral measurements for the determination of ^{13}C content. The spectra were measured on a *CEC* 21-110B instrument at 70 eV.

Sodium acetate with ^{13}C label was purchased from *Radium Chemie,* 9053 Teufen AR, Switzerland. The purity of all isolated substances was checked by thin layer chromatography on silica gel F 254 (*E. Merck,* AG, Darmstadt) with a variety of solvent systems, including methanol/ether 5:95, methanol/methylene chloride 10:90, chloroform/acetone 75:25, and benzene/methanol 90:10.

2. *Incorporation of [2-^{13}C]-Sodium Acetate into Cytochalasin B* (**1**) *by* Phoma spec. *S 298.* Fermentation of *Phoma spec.* S 298 and isolation of the resulting cytochalasin B (phomin) (**1**) was carried out in the fashion previously described [8]. The culture medium (2 l) was treated with 450 mg of [2-^{13}C]-sodium acetate (90% isotopic purity) before innoculation. After 12 days at 18°, the culture filtrate and micelle were worked up. Chromatography of the extracts on silica gel and multiple recrystallizations from acetone produced 15 mg of pure cytochalasin B (**1**).

3. *Incorporation of [1-^{13}C]-Sodium Acetate into Cytochalasin D* (**2**) *by* Zygosporium masonii. Prior to fermentation of *Zygosporium masonii* in the usual way [1], 530 mg of [1-^{13}C]-sodium acetate (55% isotopic purity) were added to the culture medium (1 l). After 4 days of aeration and stirring at 28°, the culture was extracted. The crude extract was chromatographed on silica gel, and the 97 mg of cytochalasin D (**2**) isolated was recrystallized three times from acetone/hexane to yield 60 mg of pure material.

4. *Incorporation of [2-^{13}C]-Sodium Acetate into Cytochalasin D* (**2**) *by* Zygosporium masonii. The method described above was used, starting with 519 mg of [2-^{13}C]-sodium acetate (90% isotopic purity), to produce 131 mg of cytochalasin D (**2**). An 85 mg portion was recrystallized as above to give 56 mg of pure material.

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192. Spezifisch $\pi \rightarrow \pi^*$-induzierte Reaktionen von γ-Dimethoxymethylcyclohexen-2-onen: 1,3-Umlagerung und Wasserstoffabstraktion durch das α-Kohlenstoffatom[1])

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(10. VI. 74)

Summary. When α,β-unsaturated γ-dimethoxymethyl cyclohexenones are excited to the $S_2(\pi,\pi^*)$ state, certain unimolecular reactions can be observed to compete with $S_2 \rightarrow S_1$ internal conversion. These reactions do not occur from the $S_1(n,\pi^*)$ or the lowest $T(\pi,\pi^*$ and $n,\pi^*)$ states. They comprise the radical elimination of the formylacetal substituent (*cf.* **8**, **9** → **32** + **33**), $\gamma \rightarrow \alpha$ formylacetal migration (*cf.* **6** → **27**, **8** → **30**, **9** → **34**, **12** → **37**), and a cyclization process involving the transfer of a methoxyl hydrogen to the α carbon and ring closure at the β position (*cf.* **6** → **28**, **8** → **31**, **12** → **38**, **20** → **40** + **41**).

The quantum yield of the ring closure **20a** → **40a** + **41a** is 0.016 at ≤ 0.05M concentration. It is independent of the excitation wavelength within the $\pi \rightarrow \pi^*$ absorption band (238–254 nm), but Φ(**40a** + **41a**) decreases at higher concentrations. According to the experimental data the reactive species of these specifically $\pi \rightarrow \pi^*$-induced transformations is placed energetically higher than the $S_1(n,\pi^*)$ state, and it is either identical with the thermally equilibrated $S_2(n,\pi^*)$ state, or reached *via* this latter state.

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