Tetrahedron Letters, Vol.22, No.28, pp 2703 - 2706, 1981
Printed in Great Britain

0040-4039/81/282703-04$02.00/0

STRUCTURES OF CYTOCHALASIN K, L AND M, ISOLATED FROM *CHALARA MICROSPORA*

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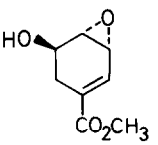
Abstract - The structures of cytochalasin K, L and M, isolated from the fungus *Chalara microspora*, have been determined by spectroscopic methods, primarily ^{1}H NMR and ^{13}C NMR.

In an investigation of toxic metabolites produced by the fungus *Chalara microspora* (Corda) Hughes, three new cytochalasins have been isolated. Previously, the methyl ester of (+)-3,4-anhydroshikimic acid (1)[1], chaloxone (2)[2,3] and chalmicrine (3)[4] were isolated from the same fungus.



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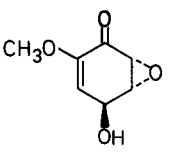

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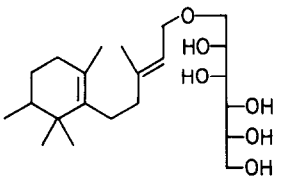

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The fungus was grown in a stationary culture[4], and both medium and mycelium were extracted with EtOAc. The cytochalasins were isolated using reversed phase chromatography. Cytochalasin K (4) was amorphous, $[\alpha]_D^{25}$ -177°(EtOH); mol.formula $C_{32}H_{37}NO_6$ (High res. MS: 531.2660; calcd. 531.2621); UV (abs. ethanol): 232 nm (11300); IR (KBr): 3380 (OH), 1750, 1700(broad) (C=O). 270 MHz ^{1}H NMR (Fig. 1), including decoupling experiments, established chemical shifts and coupling constants for nearly all protons. A comparison of these data with those of chaetoglobosin A (7) and its acetate[5], indicated that cytochalasin K is identical with the acetate of chaetoglobosin A, except that the indolyl group of the latter is replaced by a phenyl group. ^{13}C NMR of cytochalasin K (Fig. 1) is also consistent with the proposed structure 4[6].

Cytochalasin L (5) was also amorphous, $[\alpha]_D^{25}$ -165°(EtOH); mol.formula $C_{32}H_{37}NO_7$ (High res. MS: 547.2535; calcd. 547.2570); UV (abs. ethanol): no characteristic absorption maxima were discerned; IR (KBr): 3400 (OH), 1720(broad) (C=O). ^{1}H NMR and ^{13}C NMR of cytochalasin L

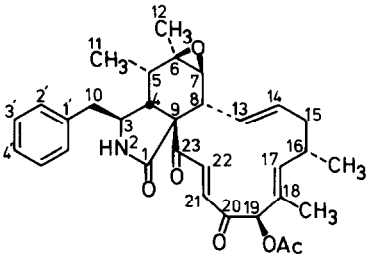


Fig. 1 Cytochalasin K 4

^{1}H NMR ($CDCl_3$) δ, J (Hz): NH 5.85; C(3)H 3.66, J_{3-10a}=5.5, J_{3-10b}=8, J_{3-4}=2.5; C(4)H 2.99 J_{4-5}=5.5; C(5)H 1.83, J_{5-11}=6.5; C(7)H 2.83, J_{7-8}=5.0; C(8)H 2.21, J_{8-13}=10.0; C(10)H_a 2.71 $J_{10a-10b}$=13.5; C(10)H_b 2.53; C(11)H_3 1.03; C(12)H_3 1.28; C(13)H 6.16, J_{13-14}=15.5; C(14)H 5.27, J_{14-15a}=10.2, J_{14-15b}=3.5; C(15)H_a 2.07, $J_{15a-15b}$=13.5; C(15)H_b 2.32; C(16)H 2.5, $J_{16-16CH_3}$=7.3, J_{16-17}=9.0; C(17)H 5.73; C(19)H 5.94; C(21)H 7.66, J_{21-22}=15.5; C(22)H 6.71; 16-CH_3 1.09; 18-CH_3 1.50; -OOCCH_3 2.18; C(2')H, C(3')H, C(4')H 7.1-7.4.

^{13}C NMR ($CDCl_3$) δ: C(1) 172.9; C(3) 53.7; C(4) 48.0[a]; C(5) 32.3[b]; C(6) 58.0; C(7) 62.2; C(8) 46.4[a]; C(9) 63.0; C(10) 44.3; C(11) 13.1[c]; C(12) 19.8[d]; C(13) 128.1[e]; C(14) 134.1[f]; C(15) 41.2; C(16) 36.2[b]; C(17) 133.6[f]; C(18) 128.1[e]; C(19) 83.3; C(20) 194.5[g]; C(21) 142.4; C(22) 134.9[f]; C(23) 196.9[g]; 16-CH_3 11.5[c]; 18-CH_3 20.8[d]; -OO$\underline{C}CH_3$ 169.8; -OOC$\underline{C}H_3$ 20.8[d]; C(1') 136.2; C(2') 129.4; C(3') 128.9; C(4') 127.1[e]. (a-g: may be interchanged)

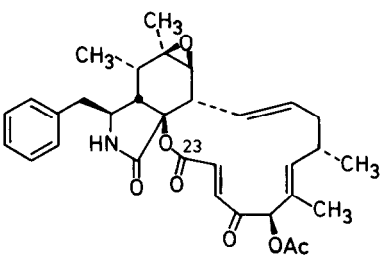


Fig. 2 Cytochalasin L 5

^{1}H NMR ($CDCl_3$) δ, J (Hz): NH 6.00; C(3)H 3.71, J_{3-10a}=8.8, J_{3-10b}=4.8, J_{3-4}=3.3; C(4)H 2.80, J_{4-5}= 4.5; C(5)H 2.24, J_{5-11}=7.5; C(7)H 2.67; C(8)H 2.68, J_{8-13}=10.0; C(10)H_a 3.02, $J_{10a-10b}$=13.3 C(10)H_b 2.89; C(11)H_3 1.03; C(12)H_3 1.29; C(13)H 6.17, J_{13-14}=14.5; C(14)H 5.40, J_{14-15a}=10.0, J_{14-15b}=3.0; C(15)H_a 2.23, $J_{15a-15b}$=13.0; C(15)H_b 2.35; C(16)H 2.6, $J_{16-16CH_3}$=7.0, J_{16-17}=7.5 C(17)H 5.72; C(19)H 5.70; C(21)H 7.49, J_{21-22}=16.0; C(22)H 6.52; 16-CH_3 1.10; 18-CH_3 1.56; -OOCCH_3 2.19; C(2')H, C(3')H, C(4')H 7.1-7.4.

^{13}C NMR ($CDCl_3$) δ: C(1) 171.1; C(3) 54.4; C(4) 49.3[a]; C(5) 33.0[b]; C(6) 57.5; C(7) 60.4; C(8) 48.5[a]; C(9) 84.1; C(10) 44.0; C(11) 13.5[c]; C(12) 20.0[d]; C(13) 130.0[e]; C(14) 134.7[f]; C(15) 41.2; C(16) 35.7[b]; C(17) 136.8[f]; C(18) 127.1[e]; C(19) 84.9; C(20) 193.5; C(21) 142.7; C(22) 126.5; C(23) 164.0; 16-CH_3 11.5[c]; 18-CH_3 21.6[d]; -OO$\underline{C}CH_3$ 169.5; -OOC$\underline{C}H_3$ 20.6[d]; C(1') 136.8; C(2') 129.2; C(3') 128.9; C(4') 127.1[e]. (a-f: may be interchanged)

(Fig. 2) were compared with those of cytochalasin K (4), and resulted in structure 5 for cytochalasin L. The ^{13}C NMR shift for C_9 increases due to substitution with oxygen, while the shift for C_{23} decreases on going from a ketone to an ester.

Cytochalasin M (6) crystallized from MeOH/H_2O, mp. 161-162°C, $[\alpha]_D^{25}$ +18.7°(EtOH); mol. formula $C_{30}H_{37}NO_6$ (High res. MS: 507.2708; calcd. 507.2631); UV (abs. ethanol): 235 nm (11300); IR (KBr): 3380 (OH), 1750, 1705(broad) (C=O), 1670 (C=C). ^1H NMR and ^{13}C NMR of cytochalasin M (Fig. 3) revealed the disappearance of the fragment -OOC-CH=CH-CO-CHOAc- compared to cytochalasin L (5), but the existence of -OOC-, two $-CH_2-$ groups, -CHOH- and an α,β-unsaturated carbonyl group. These features,with the ester replaced by a ketone, are found in chaetoglobosin F (8)[7], and as a consequence cytochalasin M was assigned structure 6. The hydroxyl group was placed in the 20-position, as in chaetoglobosin F (8), to comply with the oxygenation pattern found in cytochalasin K (4) and L (5), and in the chaetoglobosins.

The structure for cytochalasin M (6) was verified by an X-ray analysis.[8] The relative configuration of the -CHOH- group was then disclosed, since it could not be determined from spectroscopic data.

Biogenetically, cytochalasin L (5) may be derived from cytochalasin K (4) by a Baeyer-Villiger type reaction, for which there is precedence among other cytochalasins.[9]

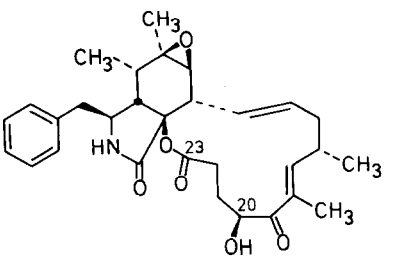
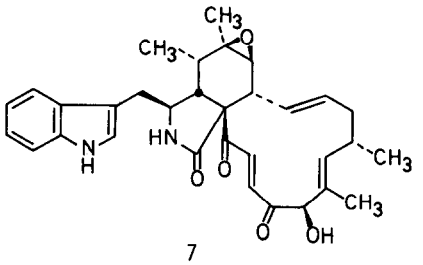


Fig. 3 Cytochalasin M 6

^1H NMR ($CDCl_3$) δ, J (Hz): NH 5.63; C(3)H 3.63, J_{3-10a}=10, J_{3-10b}=4, J_{3-4}=4; C(4)H 2.53 J_{4-5}=4; C(5)H 2.07, J_{5-11}=7; C(7)H 2.70, J_{7-8}=5.5; C(8)H 2.49, J_{8-13}=9.5; C(10)H_a 3.17 $J_{10a-10b}$=13.5; C(10)H_b 2.88; C(11)H_3 1.08; C(12)H_3 1.32; C(13)H 5.89, J_{13-14}=15.0, J_{13-15}=1.5; C(14)H 5.46, J_{14-15}=10.0 and 3.5; C(15)H_2 2.2-2.5; C(16)H 2.85, $J_{16-16CH_3}$=7.0, J_{16-17}=9.5; C(17)H 6.55, $J_{17-18CH_3}$=1.3; C(20)H 4.98, J_{20-21}=4 and 6, J_{20-OH}=5.8; C(21)H_2 =1.95; C(22)H_2 =2.45; 16-CH_3 1.13; 18-CH_3 1.88; 20-OH 3.67; C(2')H, C(3')H, C(4')H 7.2-7.45.

^{13}C NMR ($CDCl_3$) δ: C(1) 171.3[a]; C(3) 54.5; C(4) 49.2[b]; C(5) 33.6[c]; C(6) 57.5; C(7) 59.7; C(8) 50.8[b]; C(9) 82.7; C(10) 43.0; C(11) 13.8[d]; C(12) 20.3[e]; C(13) 127.6[f]; C(14) 132.5; C(15) 39.8; C(16) 35.9[c]; C(17) 150.2; C(18) 132.5; C(19) 203.2; C(20) 70.9; C(21) 30.5[g]; C(22) 33.1[g]; C(23) 171.9[a]; 16-CH_3 12.0[d]; 18-CH_3 19.6[e]; C(1') 137.8; C(2') 128.9; C(3') 128.9; C(4') 126.9[f]. (a-g: may be interchanged)



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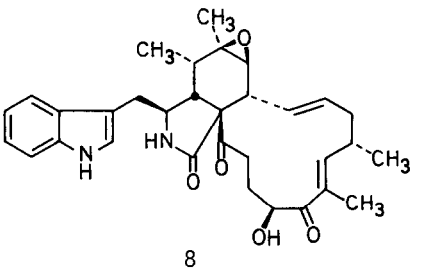

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Acknowledgements - I wish to thank Prof. B. Wickberg for his encouragement and for valuable suggestions during this work. I am also indebted to Prof. M. Johansson and Dr. A. Hyppel (Department of Forest Mycology and Pathology, Swedish University of Agricultural Sciences, Uppsala), for providing the fungus, and for pointing out its antibiotic properties. Mr. R. Torberntsson (Chalmers Institute of Technology, Göteborg) very kindly recorded the 270 MHz ^{1}H NMR spectra.

This work was supported by the Swedish Natural Science Research Council.

References:

1. T. Fex, J. Trofast and B. Wickberg, Acta Chem. Scand., B 35 (1981). To be published.
2. T. Fex and B. Wickberg, Acta Chem. Scand., B 35 (1981). To be published.
3. T. Fex. Submitted for publication in Tetrahedron Lett.
4. T. Fex. Submitted for publication in Phytochemistry.
5. S. Sekita, K. Yoshihira, S. Natori and H. Kuwano. Tetrahedron Lett., 2109 (1973).
6. ^{13}C NMR for cytochalasin B and D: W. Graf, J.-L. Robert, J. C. Vederas, Ch. Tamm, P. H. Solomon, I. Miura and K. Nakanishi, Helv. Chim. Acta, 57, 1801 (1974).
7. S. Sekita, K. Yoshihira and S. Natori, Tetrahedron Lett., 1351 (1976).
8. The X-ray analysis was completed during the preparation of this manuscript, and will be published elsewhere by J. Albertsson, T. Fex and C. Svensson.
9. J.-L. Robert and Ch. Tamm, Helv.Chim. Acta, 58, 2501 (1975).

(Received in UK 28 April 1981)