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THE RELATIVE AND ABSOLUTE CONFIGURATION OF CLEROCIDIN AND ITS COMETABOLITES

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Abstract The structures of clerocidin and five cometabolites have been established by chemical interconversion, spectral, and X-ray crystallographic methods.

Fermentation of the fungus, Oidiodendron truncatum, produces clerocidin (PR 1350)[1] and five cometabolites:

PR 1389, m.p. 140-142°C, $[\alpha]_D$ + 40.6° (c, 0.23, MeOH)
PR 1383, colourless oil, (ref. 1)
PR 1421, m.p. 157-159°C, $[\alpha]_D$ + 69.8° (c, 0.53, MeOH)
PR 1387, m.p. 214-216°C, $[\alpha]_D$ - 193.5° (c, 0.25, $CHCl_3$)
PR 1388, m.p. 232-233°C, $[\alpha]_D$ + 84.0°, (c, 0.3, MeOH)

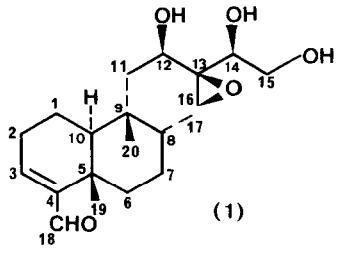
The molecular formulae of PR 1389 ($C_{20}H_{34}O_5$), PR 1383 ($C_{20}H_{34}O_5$) and PR 1421 ($C_{20}H_{32}O_5$) suggested that these cometabolites were structurally related to the monomeric equivalent ($C_{20}H_{28}O_5$) of the dimeric constitutional formula put forward for the antibiotic, clerocidin ($C_{40}H_{56}O_{10}$).[2] These structural relationships were supported by the correspondence of functional groups assigned on the basis of their ^{1}H-n.m.r. and ^{13}C-n.m.r. spectra (Tables 1, 2) and were established by two chemical transformations. Reduction (sodium borohydride in ethanol) of clerocidin gave PR 1389 and PR 1383[1] (product ratio ~ 1:9). Similar reduction of PR 1421 gave PR 1389 exclusively. These observations identified PR 1389 as hexahydroclerocidin (diastereoisomer-X), PR 1383 as hexahydroclerocidin (diastereoisomer-Y) and PR 1421 as tetrahydroclerocidin. The constitution and relative configuration of PR 1421 (1) has been firmly established by X-ray crystallography (C.P.F. and T.J.K.).

Tetrahydroclerocidin (PR 1421) crystal data: $C_{20}H_{32}O_5$, M = 352.456, orthorhombic, a = 7.6482 (11), b = 10.2807 (9), c = 24.0175 Å (14), U = 1888.4 Å^3, D_c = 1.24, Z = 4, space group $P2_12_12_1$. Cu-K_α radiation = 1.5418 Å.

† Deceased 12th April, 1983.

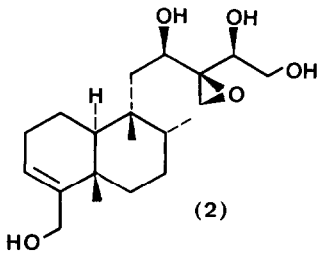
The structure of tetrahydroclerocidin was solved by direct methods using the MULTAN-78 programme with 1908 independent reflections. The co-ordinates of all the carbon and oxygen atoms were determined but it was not possible to make a distinction between C(16) of the clerodane skeleton and the epoxide oxygen atom to which C(16) was attached. The trial structure was refined using the CRYSTALS package and the relative positions of C(16) and its attached oxygen atom were settled by examination of their isotropic temperature factors.

Refinement proceeded normally using isotropic and then anisotropic temperature factors. The R value converged at 8.22% when Fourier difference synthesis detected 20 out of the 32 hydrogen atoms of the tetrahydroclerocidin molecule. The hydrogen atoms of the three hydroxyl groups were included in these found positions, but the remaining hydrogen atoms were placed in the calculated positions. Refinement was then continued giving a final R value of 3.35% giving the relative stereochemistry (1) for tetrahydroclerocidin (PR 1421). Attempts to determine the absolute configuration of tetrahydroclerocidin based upon the anomalous dispersion of its five oxygen atoms were not successful.



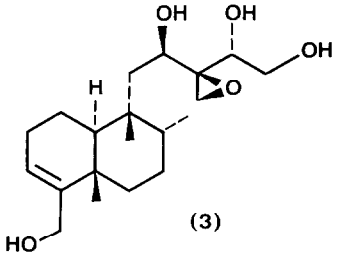
(1)

(PR 1421)



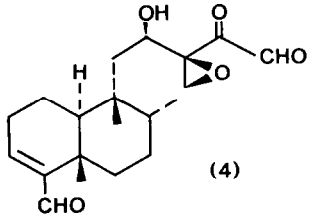
(2)

(PR 1389)

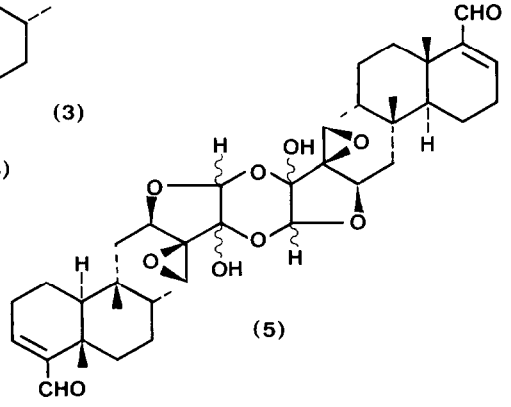


(3)

(PR 1383)



(4)



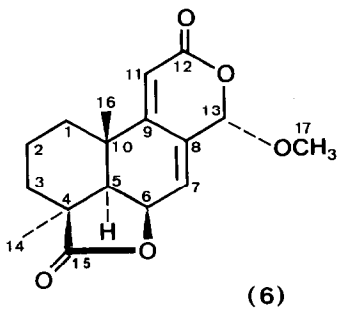
(5)

Sodium borohydride reduction of tetrahydroclerocidin (1) gave one product; hexahydroclerocidin (diastereoisomer-X). This reduction product was identical with the mould metabolite, PR 1389, so this establishes the relative stereochemistry (2).

Sodium borohydride reduction of clerocidin gave a mixture of diastereoisomers-X and -Y of hexahydroclerocidin. These two diastereoisomers must have identical configurations at C(5), C(8), C(9), C(10), C(12), and C(13) so clearly they must be epimeric at C(14). The structure (2) of hexahydroclerocidin (diastereoisomer-X) (PR 1389) is established so it follows that the diastereoisomer-Y (PR 1383) must have the structure (3). These results also established that the monomeric equivalent of clerocidin has the structure (4), thus giving the structure (5) for dimeric clerocidin[2]. In view of the equilibration (4⇄5) which has been discussed[2], it is not possible to specify the configurations at the four centres of chirality which are generated in the formation of the 2,5-dihydroxy-1,4-dioxan system in the dimer (5).

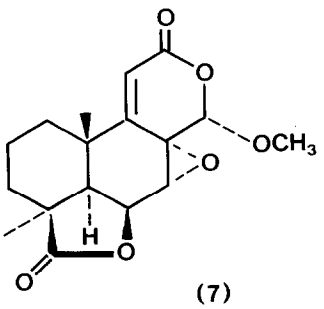
Although the relative configurations are certainly established, iron-clad evidence for the absolute configurations of clerocidin and its cometabolites (PR 1389, PR 1383, and PR 1421) is not yet available. However, in view of the incredible variety of relative and absolute configurations exhibited by naturally occurring clerodane derivatives[3], the absolute configurations of PR 1350, PR 1389, PR 1383, and PR 1421 need to be settled. A pointer is now considered which seems to favour the indicated absolute configurations (1-5) for these mould metabolites.

Comparison of the spectral characteristics (Tables 3, 4) and physical data of PR 1387 and those of the mould metabolite, LL-Z 1271α[4], (6) clearly established their identity. PR 1388 was new and was shown to be the corresponding epoxide (7). The absolute configuration of LL-Z 1271α (6)[4] and its biosynthesis from geranylgeranyl pyrophosphate has been established[5]. The operation of common biosynthetic pathways from geranylgeranyl pyrophosphate leading to the labdane derivative, PR 1387 (6) and PR 1388 (7), and the clerodane derivatives PR 1350, PR 1389, PR 1383, and PR 1421 favours the absolute stereochemistries shown in the formulae (1-5).



(6)

(PR 1387)



(7)

(PR 1388)

Table 1
^{1}H NMR data*

	& PR 1383	& PR 1389	&& PR 1421
3	5.49	5.50 bt	6.68 bt
12	3.80 m	3.85 dd	3.75
14	3.95 m	4.02 m	m
15	3.58 m	3.66 m	3.42 m
16	ABq {2.74 d, 2.88 d}	ABq {2.76 d, 2.94 d}	ABq {2.57 d, 2.75 d}
17	1.07 d	1.06 d	0.98 d
18	4.03 bs	4.04 bs	9.25 s
19	1.17 s$^\Delta$	1.15 s$^\Delta$	1.15 s$^\Delta$
20	1.04 s$^\Delta$	1.03 s$^\Delta$	0.95 s$^\Delta$

Table 2
^{13}C NMR data*

	& PR 1383	& PR 1389	&& PR 1421
3	120.1 d	120.5 d	152.1 d
4	148.7 s	149.1 s	150.8 s
12	68.9 d	69.3 d	67.2 d
13	63.1 s	62.8 s	62.5 s
14	72.3 d	70.6 d	68.7 d
15	63.8 t	64.4 t	62.5 t
16	48.7 t	49.3 t	47.5 t
18	62.1 t	62.4 t	193.4 d

Table 3
^{1}H NMR data*

Proton No.	PR 1387**	PR 1388**
5	1.92 d	1.90 d
6	5.02 m	4.95 dd
7	6.52 m	4.01 d
11	5.75 m	6.03 s
13	5.75 m	5.47 s
14	1.33 s	1.30 s
16	1.17 s	1.14 s
17	3.71 s	3.37 s

Table 4
^{13}C NMR data*

Carbon No.	PR 1387**	PR 1388**
1	27.9 t	28.3 t
2	17.4 t	17.6 t
3	30.0 t	29.4 t
4	42.8 s	35.8 s
5	48.2 d	43.7 d
6	71.3 d	71.7 d
7	123.8 d	52.9 d
8	133.0 s	56.1 s
9	156.0 s	156.7 s
10	35.1 s	41.7 s
11	111.6 d	118.1 d
12	weak	161.7 s
13	101.0 d	99.2 d
14	24.8 q	24.0 q
15	weak	179.7 s
16	24.2 q	25.2 q
17	57.1 q	57.5 q

* Chemical shift in ppm δ scale. TMS as internal reference. Instrument JEOL FX 100

& Solvent $(CD_3)_2CO$ (Uvasol ® Merck)

&& Solvent $(CD_3)_2SO$ (Uvasol ® Merck)

$^\Delta$ Interchangeable

** Solvent $CDCl_3$ (Uvasol ® Merck)

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The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

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