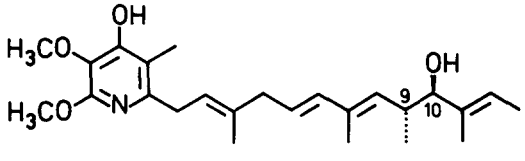
Tetrahedron Letters,Vol.24,No.49,pp 5485-5486,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

REVISED STEREOCHEMISTRY OF PIERICIDIN A_1

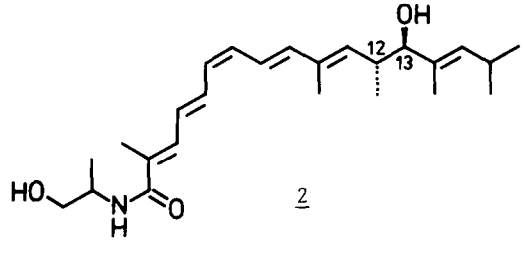
Rolf Jansen* and Gerhard Höfle
GBF, Gesellschaft für Biotechnologische Forschung mbH, Abteilung Naturstoffchemie
Mascheroder Weg 1, D-3300 Braunschweig, West-Germany

On the basis of unequivocal optical rotation data for the 3,5-dinitrobenzoate of (S)-2-methyl-3-pentanol (5a) the configuration of piericidin A_1 must be revised to 9R,10R as depicted in 1.

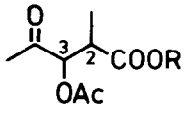
The piericidins (e.g. piericidin A_1 (1)) are well studied antibiotics and highly effective inhibitors of mitochondrial electron transport[1]. Recently we isolated the myxalamides (e.g. myxalamide B (2)), which exhibit striking similarities to the piericidins regarding not only the nature of their biological activity[2] but also a considerable part of their constitution[3]. Although the details of the side chain may be not so important for the inhibitory action of piericidins[1], it seems strange, that the myxalamides should possess the reverse configuration in the otherwise analogous structural element[4].



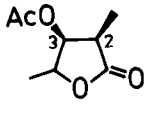
1



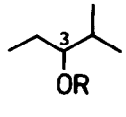
2



3a R = H
3a R = p-bromophenacyl-



4



5a R = H
5b R = 3,5-DNBz

The (12R,13R)-configuration in the myxalamides was unambigously deduced from X-ray structural analysis of the p-bromophenacyl ester 3b, obtained from acetylated myxalamide B (2) by ozonolysis and esterification of the intermediate γ-keto acid 3a[4].
The structure elucidation of the seventeen piericidins[5], isolated from several *streptomyces* species, is based on extensive spectroscopic, chemical[6] and biosynthetic[7] studies resulting in the constitution of piericidin A_1. The stereochemistry of both chiral centres, common to all structural varieties, was determined by ozone degradation of acetylated piericidin A_1 (1),

which afforded the key intermediate 3a. On catalytic hydrogenation the γ-keto acid 3a readily cyclised to the γ-lactone 4. Comparison of the piericidin derived lactone 4 with synthetic diastereomers allowed the assignment of the 2,3-cis-configuration in lactone 4[8]. The absolute configuration of C-3 was deduced from stepwise reduction of the γ-keto acid 3a to 2-methyl-3-pentanol (5a), eventually characterised as the dextro rotatory (+)-3,5-dinitrobenzoate (5b) ($[\alpha]_D^{15}$ = + 7.7°, c = 2.9 in $CHCl_3$). This was correlated with the known (-)-3,5-dinitrobenzoate of (S)-2-methyl-3-pentanol (5a)[9], thus identifying the degradation product 5a as R-alcohol and attributing (2R,3S)-configuration to the γ-keto acid 3a. Consequently (9S,10S)-configuration was assigned to piericidin A_1 (1)[6].

Examination of the literature cited[9] for this correlation revealed a serious ambiguity concerning the direction of the optical rotation ascribed to the 3,5-dinitrobenzoate of (S)-2-methyl-3-pentanol (5a) (pages 2844 and 2853 in lit.[9]).

In order to resolve this ambiguity we prepared the acidic phthalate of racemic 2-methyl-3-pentanol (5a), recrystalised its brucine salt several times from acetone and regenerated the acidic phthalate[10] ($[\alpha]_D^{22}$ = + 1.6°, c = 2.8 in CH_2Cl_2). Basic hydrolysis and distillation yielded (-)-2-methyl-3-pentanol (5a) of 48 % optical purity ($[\alpha]_D^{22}$ = - 4.1°, c = 2.0 in $CHCl_3$; lit.[9] $[\alpha]_D^{27}$ = - 8.5°, c = 3.3 in ethanol). Upon addition of $Eu(hfbc)_3$ a resolution of the methyl signals in the ^{1}H-nmr spectrum of alcohol 5a is observed with the expected ratio of intensities 72:28. The 3,5-dinitrobenzoate of the S-enriched alkohol (5a) exhibits a positive optical rotation ($[\alpha]_D^{22}$ = + 2.5°, c = 2.9 in $CHCl_3$; lit.[9] $[\alpha]_D^{26}$ = + 4.9°, c = 1.1 in $CHCl_3$). This result proves: The dextro rotatory 3,5-dinitrobenzoate 5b obtained from piericidin A_1 (1) indicates S-configuration for the alcohol 5a and it implies (2S,3R)-configuration for the keto acid 3a. Accordingly (R,R)-configuration results for piericidin A_1 (1), as for myxalamide B (2).

Aknowledgment: We thank *Dr. L. Ernst* for ^{1}H-nmr spectra.

References and notes

1) S. Yoshida, Y. Nagao, A. Watanabe and N. Takahashi, *Agric. Biol. Chem.* 44, 2921 (1980).

2) K. Gerth, R. Jansen, G. Reifenstahl, G. Höfle, H. Irschik, B. Kunze, H. Reichenbach and G. Thierbach, *J. Antibiotics*, in press.

3) R. Jansen, G. Reifenstahl, K. Gerth and G. Höfle, *Liebigs Ann. Chem.* 1983, 1083.

4) R. Jansen and G. Höfle, *Liebigs Ann. Chem.*, in press.

5) a: S. Yoshida, K. Yoneyama, S. Shiraishi, A. Watanabe and N. Takahashi, *Agric. Biol. Chem.* 41, 855 (1977); b: C.Y. Chen, W.C. Huang, K.J. Lin, Y.Y. Quian, L.Y. Wang and W.Q. Zhou, *Wei Sheng Wu Hsueh Pao* 21, 192 (1981), *Chem. Abstr.* 95, 148643 (1981).

6) N. Takahashi, S. Yoshida, A. Suzuki and S. Tamura, *Agric. Biol. Chem.* 32, 1008 (1968) and lit. cited.

7) S. Yoshida, S. Shiraishi and N. Takahashi, *Agric. Biol. Chem.* 41, 587 (1977) and lit. cited.

8) Since the ^{1}H-nmr spetra of the methyl esters of 3a derived from piericidin A_1 and myxalamide B are identical, this relative configuration is confirmed[4].

9) G. Büchi, L. Crombie, P.J. Godin, J.S. Kaltenbronn, K.S. Siddalingaiah and D.A. Whiting, *J. Chem. Soc.* 1961, 2843.

10) P.A. Levene and R.E. Marker, *J. Biol. Chem.* 99, 321 (1932/33) and 97, 379 (1932).

(Received in Germany 26 August 1983)