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# STEREOCHEMISTRY OF THE HYGROLIDINS

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Summary: The stereochemistry shown in 6 has been determined by computer modelling for hygrolidin, prototypical member of a new class of macrolide antibiotics.

As a result of recent independent reports from four laboratories, the gross structures of a series of structurally related bioactive macrolides have been clarified on the basis principally of mass spectral and NMR data. This new family includes hygrolidin,[1] bafilomycin $C_1$,[2] and the $NaK^+$ ATP-ase inhibitor Merck L-681,110,[3] all of which share the common 16-membered macrocyclic nucleus 1, and differ in regard to the substituents at C-2 and C-18.[4] In no case has the full relative or absolute stereochemistry of the major subunit 1 been elucidated and no X-ray crystallographic data are reported.

We originally became interested in assigning complete stereochemistry to these macrolides because of the large amount of NMR data available and the prospect that there might be a clear preference for one stable conformation of the macrocycle 1. In this note we propose a complete stereochemical formulation of hygrolidin and some other members of the family. Our analysis to determine relative stereochemistry is based on extensive computer modelling coupled with published PMR data. Although these compounds do not correlate meaningfully with the Celmer model for macrolide absolute stereochemistry,[5] we have been able to assign absolute configuration from the observation that the chiral appendage of these macrolides is closely related to that of the 16-membered dilactone elaiophylin (azalomycin B) whose chirality is known from an X-ray crystallographic analysis.[6,7] The proposed structures for hygrolidin 2 and the bafilomycins 3 are as shown below. For convenience we use the term hygrolide to describe this new class of macrolides.

Conformational calculations were performed with a locally enhanced version of Allinger's MM2 molecular mechanics program.[8] Conjugated structures were handled by scaling pi-system torsional parameters on the basis of a VESCF-MO calculation as per the MMPI method.[9] Parameters for the conjugated ester moiety were interpolated from existing ester and enone values.[10] Initial modelling was done on the hygrolide macro-ring without any ring substituents. Random starting conformations were generated by a modified EMBED distance-geometry technique.[11] Mirror image conformations were removed by constraining one of the ring dihedral angles to positive values. Based on NOE and UV results[1] both diene regions were held s-transoid during the EMBED procedure. Energy minima were then obtained by the modified MM2 method described above. Trial structure generation was terminated when 10 low energy conformers (within approx. 5 kcal of the global energy minimum) had each been produced multiple times with no other low energy conformers having been found once. The large amount of unsaturation greatly reduces the flexibility of the

16-membered ring. The global energy minimum structure 4 lies slightly less than 1 kcal below the second best conformer.

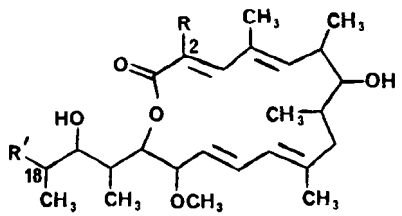
Each of the ten unsubstituted structures was examined for possible placements of the ring substituents consistent with reported PMR vicinal coupling constant data. Only four structures yield arrangements which avoid blatant inconsistencies. These were fully minimized (with methyl replacing the complex C-15 substituent) to a convergence of 0.001 kcal. The global minimum is a conformer derived from the original unsubstituted global minimum. It lies almost 2 kcal below the next best structure and fits the experimental PMR data better than any alternative structure. Thus, the lowest energy unsubstituted 16-membered ring skeleton leads unambiguously to the lowest energy hygrolide model structure consistent with published spectral information.

The analysis of absolute stereochemistry proceeded as follows. The C-15 to C-23 region of hygrolidin is very similar to the corresponding part of elaiophylin both in terms of structure and PMR spectrum. Molecular mechanics modelling of the elaiophylin aglycon gave a local minimum 5 very close to the reported[7,8] X-ray structure but with some lengthening of the hydrogen bonds.[12] The X-ray data and an earlier identification of 2-deoxy-L-fucose as the sugar component of elaiophylin[13] determine the absolute stereochemistry of this compound. The hydrogen bonding present in both the crystal and solution conformations of elaiophylin as well as the similarity of the hygrolidin and elaiophylin partial PMR data led us to propose the same hydrogen bonding network for hygrolidin. Molecular mechanics calculations were performed on an improved hygrolidin model with a C-15 to C-23 part structure replacing the earlier C-15 methyl group. The fully optimized structure 6 with "elaiophylin" absolute stereochemistry is shown below.[14]

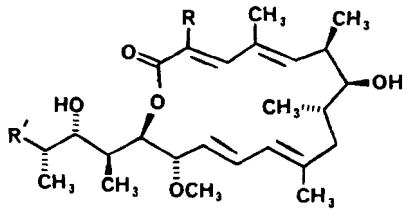
PMR coupling constants for 6 were calculated via a modified Karplus relation optimized for use with molecular mechanics structures.[15] The calculated and experimental values for key vicinal relationships are listed in the table below.

| Atoms | Dihedral Angle | Calc. J Value | Expt. J Value |
|---|---|---|---|
| H5-H6 | -174.9 | --- | 8.5 |
| H6-H7 | 64.3 | 1.2 | 2.0 |
| H7-H8 | -149.1 | 8.5 | 6.0 |
| H8-H9a | -170.3 | 12.0 | 11.0 |
| H8-H9b | 74.3 | 1.5 | 0.0 |
| H13-H14 | -171.7 | --- | 9.0 |
| H14-H15 | -164.0 | 7.8 | 8.5 |
| H15-H16 | 72.5 | 0.7 | 1.0 |
| H16-H17 | -175.7 | 9.5 | 10.5 |
| H17-H18 | -58.6 | 1.6 | 2.0 |

The calculations reported herein which lead to 6 as a preferred conformation also indicate that the ring substitutents serve to anchor that conformation.[16]

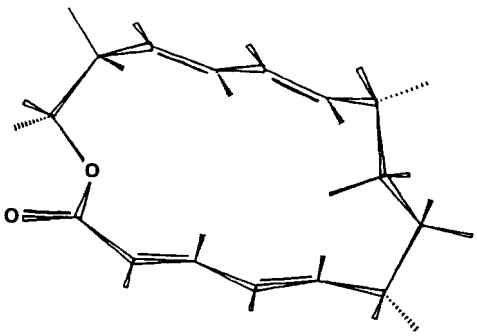


1



2 R = $CH_3$, R′ = $C_{12}H_{17}O_6$

3 R = $OCH_3$, R′ = $C_{13}H_{19}O_6$



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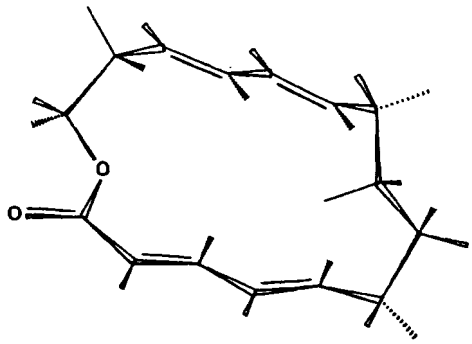
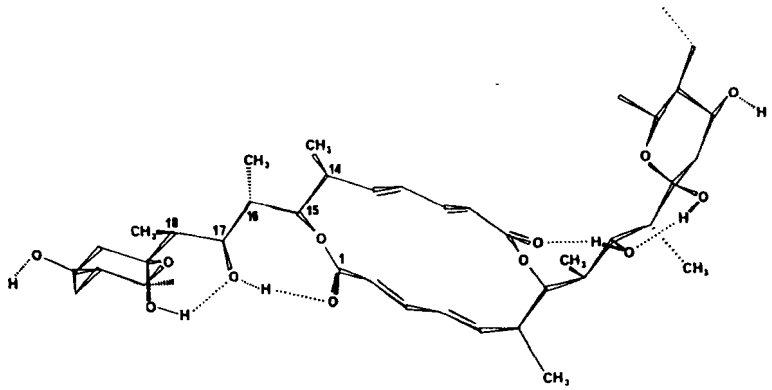


R

4 (stereo)



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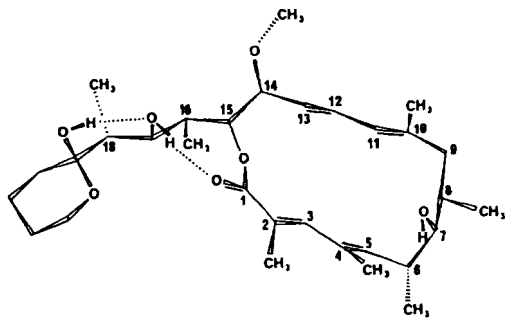

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References and Notes


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2. G. Werner, H. Hagenmaier, K. Albert and H. Kohlshorn, Tetrahedron Lett., 24, 5193 (1983).

3. (a) O. D. Hensens, R. L. Monaghan, L. Huang and G. Albers-Schonberg, J. Am. Chem. Soc., 105, 3672 (1983); (b) The 4,5-double bond in L-681,110 has E geometry, see: G. Werner, H. Hagenmaier, H. Drautz, A. Baumgartner and H. Zahner, J. Antibiotics, 37, 110 (1984).

4. For a related series of 18-membered lactones, the concanamycins, see: H. Kinashi, K. Sakaguchi, T. Higashijima and T. Miyazawa, J. Antibiotics, 35, 1619 (1982).

5. W. D. Celmer, Pure Appl. Chem., 28, 413 (1971). See also: S. Masamune, G. S. Bates and J. W. Corcoran, Angew. Chem. Int. Ed., 16, 585 (1977).

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7. K. Neupert-Laves and M. Dobler, Helv. Chim. Acta, 65, 262 (1982).

8. N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977).

9. See: N. L. Allinger and J. T. Sprague, J. Am. Chem. Soc., 95, 3893 (1973). Our program implemented on a VAX 11/750 incorporates MMPI-type torsional parameter scaling for conjugated systems, full namelist input and several changes to increase speed and flexibility. A binary version of Prof. Allinger's extension of MM2 to conjugated systems, MMP2, is available from Molecular Design Ltd., Hayward, CA.

10. Previously reported parameters of W. C. Still and I. Galynker, Tetrahedron, 37, 3981 (1981) are not appropriate for use with VESCF-MO scaling. We used usual MM2 values plus the following enone parameters:

| | | | |
|---|---|---|---|
| 1 - 2 - 3 - 6 | 0.000 | 11.100 | 0.000 |
| 2 - 2 - 3 - 6 | 0.000 | 11.100 | 0.000 |
| 5 - 2 - 3 - 6 | 0.000 | 11.100 | 0.000 |
| 2 - 3 - 6 - 1 | -2.500 | 1.390 | 0.000 |
| 2 - 3 - 6 -20 | 0.000 | 0.000 | 0.000 |
| 2 - 3 - 6 | 0.500 | 120.000 | |

11. G. M. Crippen, J. Comput. Phys., 24, 96 (1977). Our version of the program allows the user interactively to alter and smooth the bounds matrix as well as freeze or heavily weight chiral centers and specific torsional angles. In particular, a quadratic term representing deviation of the pi-system and ester from planarity was added along with chirality constraints to the overall error function. Only non-hydrogens were included. For a similar program see: P. K. Weiner, S. Profeta, Jr., G. Wipff, T. Havel, I. D. Kuntz, R. Langridge and P. A. Kollman, Tetrahedron, 39, 1113 (1983).

12. For a recent method to improve MM2 hydrogen bonding see: L. M. J. Kroon-Batenburg and J. A. Kanters, J. Molecular. Structure, 105, 417 (1983).

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14. C. A. G. Haasnoot, F. A. A. M. DeLeeuw and C. Altona, Tetrahedron, 36, 2783 (1980).

15. As a further indication of the correctness of our model, we note that except for the C-2 substituent the C-1 to C-8 portion of tirandamycin is identical to the C-1 to C-8 region we propose for the hygrolides. Streptomyces griseus produces both tirandamycin and the bafilomycins. See reference 3b above and: A. R. Branfman, A. C. Button, K. L. Rinehart and D. J. Duchamp, J. Am. Chem. Soc., 95, 4077 (1973).

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