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THE STEREOCHEMISTRY AND BIOSYNTHESIS OF HYBRIDALACTONE, AN EICOSANOID FROM LAURENCIA HYBRIDA

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Summary: The stereochemistry of the marine eicosanoid, hybridalactone, has been determined experimentally to be as in 2, in accord with a proposed scheme of biosynthesis from eicosapentaenoic acid.

Recently a novel eicosanoid, designated hybridalactone, was isolated from the marine alga Laurencia hybrida and was assigned gross structure 1 on the basis of proton magnetic resonance (pmr) studies.[1] A partial assignment of stereochemistry was also made which included: (1) relative arrangement of substituents on the 5-membered ring, (2) cis relationship between carbons on the 3-membered ring, and (3) Z-arrangement of the 5,6- and 8,9- double bonds.[1] In this note we present evidence for the complete stereochemistry of hybridalactone (2) and also describe a possible pathway to biosynthesis, which correctly predicted absolute stereochemistry. Research on the total synthesis of hybridalactone, to be published separately, has completely confirmed the assignment of stereoformula 2 to hybridalactone.

The studies on stereochemistry and synthesis were initiated before a sample of natural hybridalactone was available to us and consisted of a combined analysis of molecular mechanics calculations, published[1] pmr data and biogenesis. The vicinal stereorelationship at C-14/15 was clarified first from pmr data and computer calculations performed on a simplified structure, a $\Delta^{11,12}$-olefin with an i-propyl group instead of ethylcyclopropyl at C-15. For clarity these results will be discussed relative to the finally determined R configuration at C-14. Random starting conformations were generated by a modified EMBED distance-geometry technique.[2] Energy minima were obtained for the starting conformations by the MM2 method of Allinger.[3] Sufficient calculations were done to allow essentially certain determination of the best minima in both the 15(S) and 15(R) series. Trial structures were produced and partially energy minimized until it became clear that no new macro-ring conformers were being obtained; approximately 400 such initial structures were generated. In the 15(S) series the minimum energy conformer (3) and three other conformers found at ca. 2.5 kcal/mol higher energy have H-(C14) antiperiplanar to H-(C15). The low energy 15(R) conformers have the ester oxygen anti to H-(C14).[4] Only the 15(S) configuration is consistent with the H-(C14)/H-(C15) coupling constant of J=10 Hz found for natural hybridalactone.[1] The best 15(R) conformer with H-(C14) constrained to be antiperiplanar to H-(C15) lies over 15 kcal/mol higher in energy than the best 15(S) conformer (3).

Since our biogenetic analysis suggested the absolute configuration 2 as discussed below, we were able to proceed with and complete the synthesis without further information. Subsequently, we obtained a

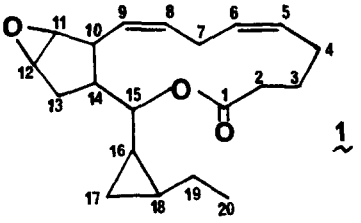
specimen of L. hybrida with the kind assistance of Drs. Peter R. Leeming (Chas. Pfizer, U.K.) and A. Pettet (U. of Khartoum), and were able to isolate ca. 50 mg of oily hybridalactone by extraction and chromatography starting from 140 g of dry L. hybrida.

A heavy-atom labeled, crystalline derivative of hybridalactone was prepared as follows. Hybridalactone (ir, pmr, and mass spectra identical to those reported[1,5]) was converted to a bromohydrin (11-hydroxy, 12-bromide) by reaction with dry hydrogen bromide in methylene chloride at 0° for 3 sec and then quenching with triethylamine. The oily bromohydrin obtained in 82% yield after chromatography on silica gel (tlc R_f 0.33 using 5 : 1 hexane-ethyl acetate as compared to R_f 0.52 for hybridalactone) was hydrogenated using Pd-C catalyst in ethyl acetate (5 min, 23°, 1 atm. H_2) to afford a saturated lactone bromohydrin which crystallized from hexane, mp 103-105°.

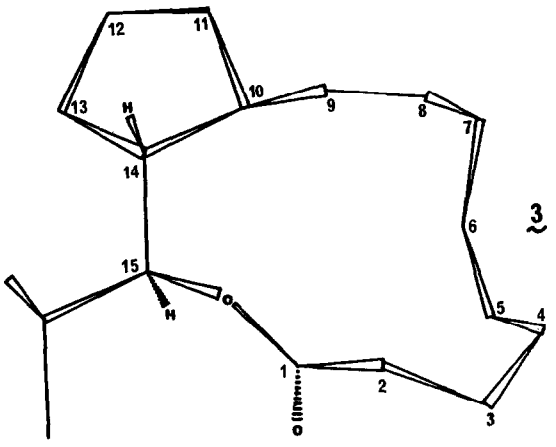
The structure of this bromohydrin was determined by X-ray crystallography.[6-8] The crystals, $C_{20}H_{33}O_3Br$, are orthorhombic, space group $P2_12_12_1$ with a = 9.8199, b = 10.1375, c = 20.4027 A. Reflections of the form h,k,l were collected for $3° < 2\theta < 25°$ while those of the form h,k,l were collected for $25° < 2\theta < 40°$. Data were corrected for decay based on three standard reflections monitored every 60 reflections and for absorption. A total of 928 reflections with $F^2 > 3\sigma(F^2)$ were used in the final refinement. The structure was solved by Patterson methods and refined to give $R_w = 0.0707$ with an anisotropic temperature factor for the bromine and isotropic temperature factors for all other non-hydrogen atoms. Hydrogen atoms were included in calculated positions. The absolute configuration was ascertained by inverting the coordinates and refining to yield $R_w = 0.0862$.[9] Inspection of the Friedel pairs provided further assurance. The structure thus obtained for the bromohydrin of tetrahydro hybridalactone ($\underset{\sim}{4}$) establishes hybridalactone itself as possessing formula $\underset{\sim}{2}$.

Molecular mechanics calculations using the MM2 program found a local minimum almost identical to the X-ray structure. This minimum falls 0.9 kcal below any other found by means of the distance-geometry technique outlined above.

The biosynthesis of hybridalactone was of considerable interest since this eicosanoid embodies structural features which are quite different from those contained in other known members of this family. We propose that the biosynthesis proceeds starting with eicosapentaenoic acid along the lines indicated in the accompanying chart. The first step is a 12-lipoxygenation (LO) reaction which according to the general rule[10] for LO stereochemistry would be expected to afford the 12(S)-hydroperoxide. Cationic oxirane formation and further carbo cyclization generate an allyl carbinyl cation which after a 180° rotation to relieve internal non-bonded repulsions can enter a cyclopropylcarbinyl ⟶ cyclobutyl ⟶ cyclopropyl carbinyl cation rearrangement manifold. After nucleophilic attack by carboxylate the final carbocation is neutralized and a macro lactone structure is generated which corresponds exactly to hybridalactone, including absolute configuration. Although free radical pathways seem likely for prostaglandin[11] and clavulone[12] biosynthesis, cationic intermediates seem more reasonable mechanistically for the biogenesis of hybridalactone. The cationic pathway can lead to the correct carbon skeleton and stereochemistry in a straightforward way, but such is not the case for radical intermediates.[13]



1



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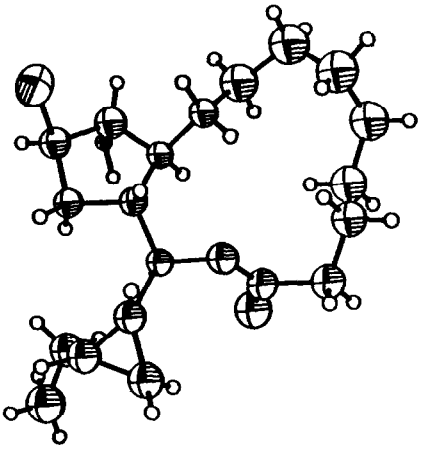

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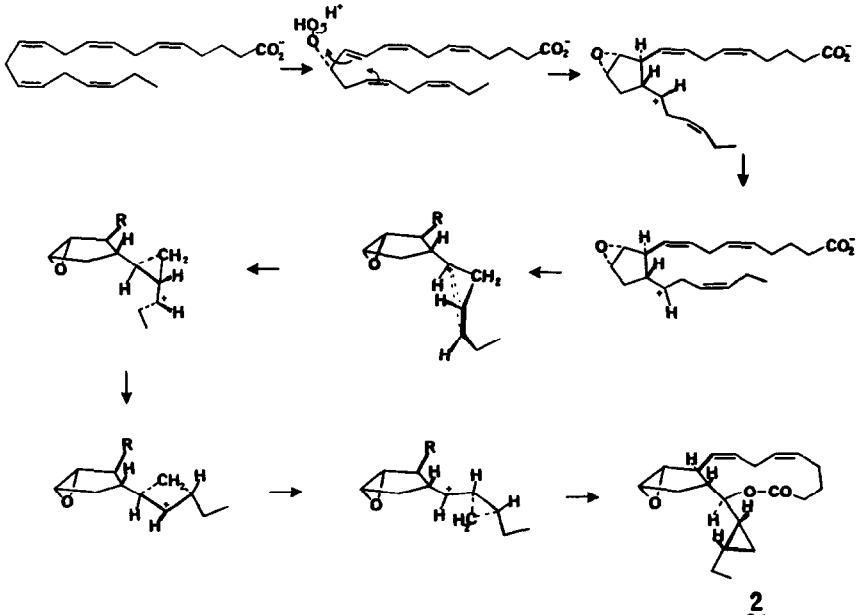

2

PROPOSED BIOSYNTHESIS OF HYBRIDALACTONE

References and Notes

1. M. D. Higgs and L. J. Mulheirn, Tetrahedron, 37, 4259 (1981).

2. 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 alkenes from cis planarity and the ester from trans planarity was added along with chirality constraints to the overall error function. A preliminary minimization cycle was performed on the torsional and chirality constraints to the overall error function. A preliminary minimization cycle was performed on the torsional and chirality constraints followed by minimization of the entire error function. Only non-hydrogen atoms were included in the embedding. Cf. P. K. Weiner, S. Profeta, Jr., G. Wipff, T. Havel, I. D. Kuntz, R. Langridge and P. A. Kollman, Tetrahedron, 39, 1113 (1983).

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

4. The global minimum MM2 strain energy for the 15(S) epimer is 27.59 kcal; three other conformations of the macrocyclic ring yield minima under 30 kcal. For 15(R) the MM2 global minimum is 27.62 kcal with two other macro-ring conformations yielding structures under 30 kcal.

5. We are indebted to Dr. M. D. Higgs for providing copies of the spectra.

6. Structure determined on a Nicolet R3 Diffractometer using Mo K_α radiation. Calculations were performed using the SHELXTL series of programs. Instrument purchased with funds provided by NSF Grant CHE 8000670.

7. The atomic coordinates for this work are available from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K. Any request should be accompanied by the full literature citation for this communication.

8. Supplementary data available: coordinates, bond distances and angles, structure factors. See Announcement to Authors, Tetrahedron Letters, 24, 5154 (1983).

9. W. C. Hamilton, Acta Cryst., 18, 502 (1965).

10. For the generality of this stereochemical pattern see E. J. Corey, J. O. Albright, A. E. Barton, and S. Hashimoto, J. Am. Chem. Soc., 102, 1435 (1980).

11. B. Samuelsson, Progr. Biochem. Pharmacol., 5, 109 (1969).

12. E. J. Corey, Experientia, 39, 1084 (1983).

13. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

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