Tetrahedron Letters No. 47, pp 4219 - 4222, 1976. Pergamon Press. Printed in Great Britain.

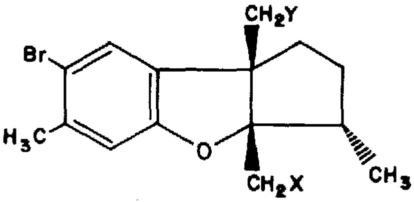
APLYSINOL FROM LAURENCIA DECIDUA: CRYSTAL STRUCTURE AND ABSOLUTE STEREOCHEMISTRY

Joyce A. McMillan, Iain C. Paul,*
Salvatore Caccamese, and Kenneth L. Rinehart, Jr.*

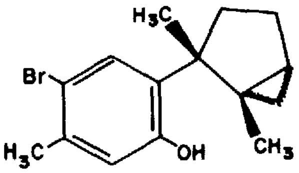
School of Chemical Sciences, University of Illinois, Urbana, Ill. 61801, U.S.A.

(Received in USA 11 August 1976; received in UK for publication 4 October 1976)

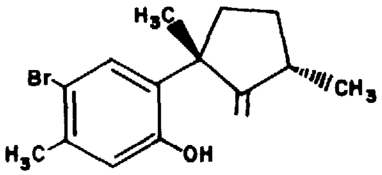
During the course of our extensive search for antibacterial substances[1] and halometabolites[2] among the samples collected on the 1974 Alpha Helix Baja Expedition[1-4] we have investigated by gas chromatography-mass spectrometry (gc-ms) the constituents of several species of the Laurencia genus.[5] Laurencia decidua (AHBE-18-III-74-2-106)[6] proved to be of special interest, since it contained a number of brominated sesquiterpenes other than the usual laurinterol (1), isolaurinterol (2), and aplysin (3).[3,5]



1



2



3: X=Y=H
4: X=OH;Y=H
5: X=H;Y=OH

One of the compounds tentatively identified by gc-ms appeared to be aplysinol. The gc-mass spectrum contained a molecular ion at m/e 310 ($C_{15}H_{19}{}^{79}BrO$) and fragment ions at m/e 277 (M - CH_3 - H_2O) and m/e 279 (M - CH_2OH), but no fragment ion due to loss of isoprene (or hydroxyisoprene) characteristic of laurinterol.[3] Aplysinol was previously isolated from Aplysia kurodai[7] and from Laurencia okamurai,[8] supporting ingestion of red algae of this genus by the Aplysia sea hare. Stimulated by the tentative gc-ms identification, we elected to attempt to isolate the compound, and to establish its structure and absolute stereochemistry by X-ray crystallography, for two reasons. First, of the numerous brominated aromatic sesquiterpenes isolated from the genus Laurencia, the complete stereochemistry has been rigorously established by X-ray crystallography for only laurinterol (1),[9] although chemical arguments have been advanced for the stereochemistry of aplysin (3) based on its formation from 1 in acid.[9] Second, aplysinol had been isolated earlier and the tentative structure 4 assigned, based on biogenetic considerations, although the isomeric structure 5 could not be ruled out.[7] These alternative structures were also pointed out in recent reviews.[10,11]

L. decidua was extracted as previously described[2] and the toluene layer was chromatographed over silica gel, with fractions characterized by gc-ms. From a benzene eluate a semisolid material was recovered and partially dissolved in acetonitrile, while undissolved material was dissolved in chloroform; on standing overnight the chloroform solution deposited a few crystals due to evaporation. The crystals were identified as aplysinol by m.p. as well as gas chromatographic coinjection and mixture m.p. with an authentic sample.[1 2]

An X-ray structure determination was undertaken. The crystals were found to be monoclinic, $\underline{a}$ = 13.753(5), $\underline{b}$ = 7.319(4), $\underline{c}$ = 13.746(4) Å, $\underline{\beta}$ = 90.27(4)°, space group, $\underline{P2_1}$ with four molecules per unit cell. A small, colorless crystal approximately 0.3 x 0.1 x 0.05 mm was used to collect data on a Syntex $\underline{P2_1}$ diffractometer (CuK_α, λ = 1.54178 Å). Heavy atom methods were used to solve the structure; the Patterson map revealed that four bromine atoms in the unit cell were related by near-perfect 4_2 symmetry. Anomalous dispersion corrections were applied to the scattering due to the bromine atoms and all non-hydrogen atoms were refined by full-matrix least squares methods incorporating anisotropic temperature factors. The hydrogen atoms were given isotropic temperature factors. The final $\underline{R}$-factors on 1503 observed reflections were $\underline{R}_1$ (unweighted) = 0.076, $\underline{R}_2$ (weighted) = 0.055 for the enantiomer shown below. The other possible enantiomer refined to $\underline{R}$-factors of $\underline{R}_1$ = 0.080, and $\underline{R}_2$ = 0.059. The atomic co-ordinates are listed in Table I. A stereoscopic drawing of the two molecules in the asymmetric unit is shown in Figure 1. The hydroxyl oxygen atoms form hydrogen bonds which join the [illegible] molecules together into a spiral column around the 2_1 axis in the $\underline{y}$-direction. The molecules in this column have no close contacts in the $\underline{x}$- or $\underline{z}$-direction. The closest Br---Br distance is 4.27 Å. A stereoscopic diagram showing the packing is given in Figure 2.

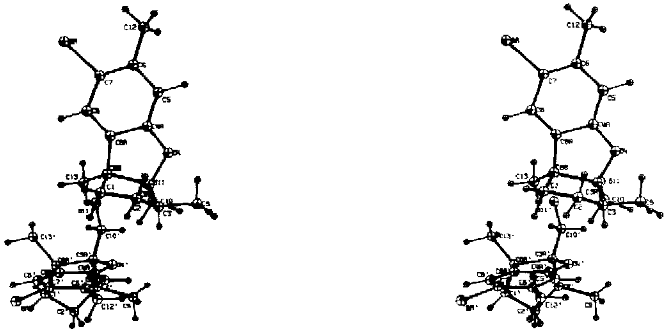


Figure 1. Stereoscopic drawing of the two molecules in the asymmetric unit.

Table I: Final Atomic Coordinates (Standard Deviations in Parentheses)

ATOM	x	y	z	ATOM	x	y	z
Br	0.8350(2)	0.50000(0)[a]	0.8886(2)	Br'	0.1107(2)	0.7490(5)	0.8351(2)
O(4)	0.5345(9)	-0.0565(15)	0.7858(9)	O(4')	0.2156(8)	0.2012(16)	0.5366(8)
O(11)	0.4573(9)	0.0160(19)	0.5927(8)	O(11')	0.4083(8)	0.2716(21)	0.4607(8)
C(1)	0.417(1)	0.321(3)	0.876(1)	C(1')	0.124(1)	0.569(2)	0.413(1)
C(2)	0.399(2)	0.144(3)	0.934(1)	C(2')	0.065(1)	0.396(2)	0.397(1)
C(3)	0.376(1)	0.013(3)	0.859(1)	C(3')	0.145(1)	0.255(3)	0.379(1)
C(3a)	0.447(1)	0.041(2)	0.768(1)	C(3a')	0.228(1)	0.294(3)	0.446(1)
C(4a)	0.607(1)	0.057(3)	0.810(1)	C(4a')	0.188(1)	0.308(2)	0.609(1)
C(5)	0.701(1)	-0.001(3)	0.835(1)	C(5')	0.169(1)	0.268(3)	0.703(1)
C(6)	0.773(2)	0.138(3)	0.859(1)	C(6')	0.144(1)	0.381(3)	0.770(1)
C(7)	0.745(2)	0.318(3)	0.859(1)	C(7')	0.149(1)	0.568(3)	0.744(1)
C(8)	0.648(2)	0.377(3)	0.831(1)	C(8')	0.167(1)	0.627(3)	0.648(1)
C(8a)	0.580(1)	0.251(4)	0.808(1)	C(8a')	0.193(1)	0.503(3)	0.582(1)
C(8b)	0.474(1)	0.265(3)	0.783(1)	C(8b')	0.213(1)	0.513(3)	0.474(1)
C(9)	0.382(2)	-0.188(4)	0.889(2)	C(9')	0.105(2)	0.046(3)	0.378(1)
C(10)	0.402(1)	-0.000(3)	0.677(1)	C(10')	0.325(1)	0.237(3)	0.403(1)
C(12)	0.881(2)	0.090(3)	0.875(1)	C(12')	0.124(1)	0.331(3)	0.873(1)
C(13)	0.457(2)	0.381(3)	0.699(1)	C(13')	0.299(1)	0.641(3)	0.457(1)

[a] This coordinate was held constant to define the origin.

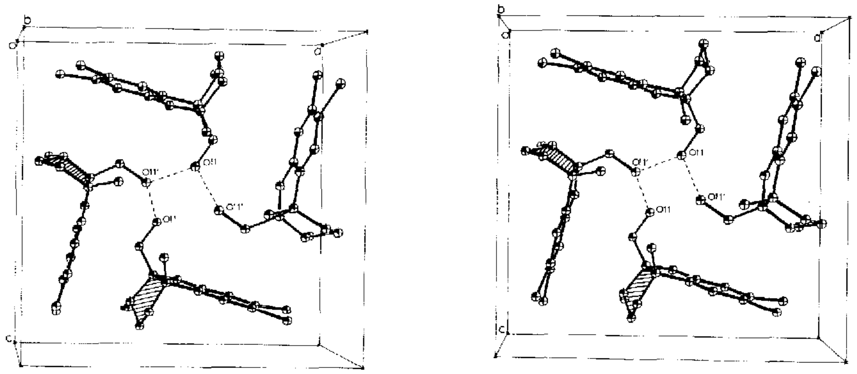


Figure 2. Stereoscopic view of the packing looking along the b-axis. Parts of the two reference molecules have been shaded. The dashed lines indicate hydrogen bonding.

The bond lengths and angles are not unusual except for the C(8b)-C(3a) bond (1.69(3) Å) and the C(8b')-C(3a') bond (1.66(3) Å). There is severe steric hindrance around these two quaternary substituted atoms; in fact, the C(13)---C(10) distance measured by Dreiding models, using the normal bond lengths, would be 2.85 Å, well below the outer limit calculated using pair-wise Lennard-Jones potential interactions and the coefficients from Scott and Scheraga.[13] The observed lengthening of the C(8b)-C(3a) bond partly releases this energy strain and the actual C(13)---C(10) non bonded distance is 3.45(3) Å.

These results confirm the structure 4 and the absolute stereochemistry of aplysinol is seen to be the same as that of laurinterol, in keeping with a related biosynthetic pathway.

Acknowledgement: One of us (S.C.), on leave of absence from the University of Catania, Italy, thanks the National Research Council of Italy for a fellowship (1974-1975). Support is also acknowledged from NIH Research Grants GM 19336, AI 04769, the fellowship CA 00467, and from the DuPont Company.

References and Footnotes

1. P. D. Shaw, W. O. McClure, G. Van Blaricom, J. Sims, W. Fenical, and J. Rude, "Food-Drugs from the Sea", Proceedings 1974, Marine Technology Society, Washington, D.C., 1976, p. 429.
2. L. P. Hager, R. H. White, P. F. Hollenberg, D. L. Doubek, R. C. Brusca, and R. Guerrero, *ibid.*, p. 421.
3. K. L. Rinehart, Jr., R. D. Johnson, I. C. Paul, J. A. McMillan, J. F. Siuda, and G. E. Krejcarek, *ibid.*, p. 434.
4. K. L. Rinehart, Jr., R. D. Johnson, J. F. Siuda, G. E. Krejcarek, P. D. Shaw, J. A. McMillan, and I. C. Paul in "The Nature of Seawater", E. D. Goldberg, Ed., Physical and Chemical Sciences Research Report 1, Abahon Verlagsgesellschaft, Berlin, 1975, p. 623.
5. S. Caccamese, K. L. Rinehart, Jr., P. D. Shaw, and R. D. Johnson, 170th National Meeting of the American Chemical Society, Chicago, Ill., August 1975, Abstracts, ORGN 19.
6. The alga was identified by Mr. Robert B. Setzer, Allan Hancock Foundation, University of Southern California, Los Angeles, from a sample preserved in 70% ethyl alcohol.
7. S. Yamamura and Y. Hirata, *Tetrahedron*, **49**, 1485 (1963).
8. T. Irie, M. Susuki, and Y. Hayakawa, *Bull. Chem. Soc. Japan*, **42**, 843 (1969).
9. A. F. Cameron, G. Ferguson, and J. M. Robertson, *Chem. Commun.*, 271 (1967); *J. Chem. Soc. B*, 692 (1969).
10. P. J. Scheuer, "Chemistry of Marine Natural Products", Academic Press, New York, 1973, p.12.
11. E. Premuzic, *Fortschr. Chem. Org. Naturstffe.*, **29**, 417 (1972).
12. Obtained from Profs. Y. Hirata and K. Yamada, Nagoya University, whom the authors gratefully thank.
13. R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, **45**, 2091 (1966); *ibid.*, **46**, 4410 (1967).