Tetrahedron Letters No. 38, pp 3619 - 3622.

0040-4039/79/0915-3619$02.00/0

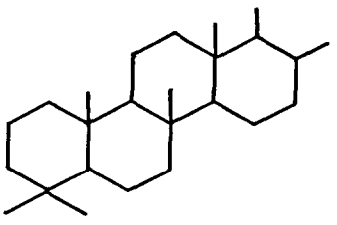
TWO NOVEL SESTERTERPENE HYDROXYQUINOLS FROM THE SPONGE MICROCIONA TOXISTYLA

G. Cimino, S. De Stefano, L. Minale* and R. Riccio
Laboratorio per la Chimica di Molecole di Interesse
del C.N.R. Via Toiano n.2, Arco Felice, Napoli, Italy

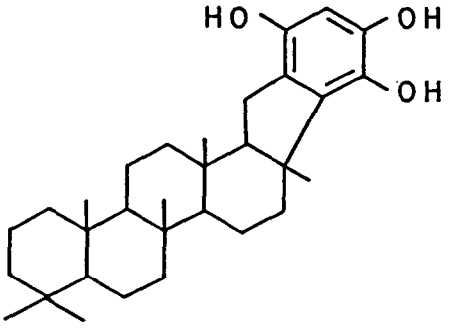
K. Hirtosu and J. Clardy*
Department of Chemistry - Baker Laboratory
Cornell University
Ithaca, NY 14853 U.S.A.

Summary: The structures of two unique sesterpenes, toxislylide A and B, have been deduced by chemical, spectral, and x-ray crystallographic studies. They are components of the sponge Microciona toxistyla.

Two different types of sesterterpenes, C_{25} terpenes rather uncommon in nature, have recently been reported from sponges.[1] One type is an essentially linear sesterterpene with a furan ring at one end and a tetronic acid moiety at the other. The other type has the general tetracyclic structure 1 which can be derived from a geranylfarnesyl precursor by a typical cyclization initiated at the isopropylidene end.[2] One member of this class, disidein (2) from Disidea pallescens, has an additional hydroxyquinol group, and occurs in the sponge as the mixed sodium-calcium salt of the disulfate.[3] We now wish to report the structures of two new sesterterpenoids, toxistylide A and B, from the sponge Microciona toxistyla. This sponge has previously been shown to contain a series of sesquiterpenes with rearranged skeletons.[4,5]

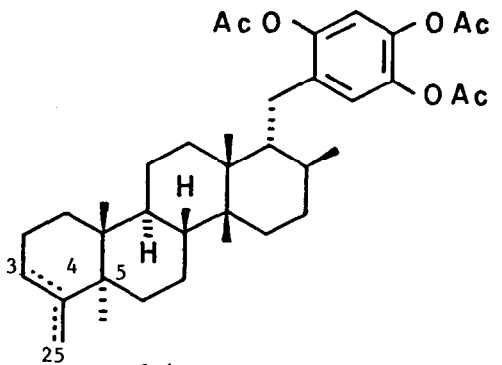


1



2

The acetone extract from the sponge was concentrated and extracted with ether and n-butanol, following the previously described procedure.[3,5] TLC (SiO_2; n-BuOH-AcOH-H_2O; 60:15:25) of the n-butanol extract revealed a substance resembling disidein disulfate in mobility and color reactions. Attempts to purify this material were unsuccessful and efforts to obtain free phenols by mild acid treatment gave a brown untractable material. When the crude material was acetylated (Ac_2O-pyridine, 90 min., reflux) it could be further separated (SiO_2-$AgNO_3$, benzene-ether, 93:7) into toxistylide A and B (3 and 4) triacetates.



3 $\Delta^{3,4}$

4 $\Delta^{4,25}$

The two compounds had the same molecular formula, $C_{37}H_{52}O_6$ (3, M^+ 592.3759; 4, M^+ 592.3761; required, M^+ 592.3764). The physical data for 3 and 4 are as follows: 3, m.p. 193-195° (from MeOH-H_2O); $[\alpha]_D$ + 9.4 (c, 1 in $CHCl_3$); λ_{max} 270 nm (ε, 708 in MeOH); ν_{max} ($CHCl_3$) 1760 cm^{-1}; H-NMR, δ(100 MHz-$CDCl_3$) 7.10 and 6.92 (each 1H, s, Ar-H's), 5.16 (1H, broad, C<u>H</u>=C), 2.22, 2.26 and 2.28 (9H, each s, C<u>H</u>$_3$-CO-), 1.60 (3H, bs, C<u>H</u>$_3$-C=CH-), 1.02 (3H, s, <u>tert</u>-CH_3), 0.93, 0.92 and 0.90 (9H, each s, <u>tert</u>-CH_3's), 0.65 (3H, d, J 6Hz, <u>sec</u>-CH_3); in C_6D_6 the benzylic methylene protons, which in $CDCl_3$ partially overlapped the acetate signals, separated out giving rise to an eight-line multiplet featuring the AB part of an ABX system (δ 2.7, dd, J 14,3 Hz; 2.4 dd, J 14,6 Hz); MS, m/e 592 (M^+, 60%), 550 (52), 508 (50), 466 (46), 327 (100, $C_{24}H_{39}$), 266 (10, $C_{13}H_{14}O_6$), 257 (10), 231 (16), 224 (28, $C_{11}H_{12}O_5$), 223 (16, $C_{11}H_{11}O_5$), 205 (24, $C_{15}H_{25}$), 203 (12), 182 (24; $C_9H_{10}O_4$), 181 (28, $C_9H_9O_4$), 163 (16), 147 ((12), 135 (36). 4, m.p. 226-228° (from EtOH); $[\alpha]_D$ + 25.0 (c, 0.5 in $CHCl_3$); λ_{max} 270 (ε, 908 in MeOH); ν_{max} ($CHCl_3$) 1760 and 1635, 895 (C=CH_2) cm^{-1}; δ (100 MHz-$CDCl_3$) 7.10 and 6.92 (each 1H, s, Ar-H's), 4.70 and 4.50 (each 1H, d, J 1.5 Hz, C=CH_2), 2.22, 2.26 and 2.28 (9H, each s, C<u>H</u>$_3$CO-), 1.08, 0.92, 0.88 and 0.82 (each 3H, s, <u>tert</u>-CH_3's) and 0.65 (3H, d, J 6 Hz, <u>sec</u>-CH_3); the MS was virtually identical to that of 3.

The above data suggested that toxistylide A and B were double bond isomers and this was confirmed by hydrogenation (Pd/C,r.t.) to a common product (m.p. 220-2°, m/e 594). The aromatic portion of the structure appeared to be a hydroxyquinol triacetate and the absence of coupling suggested a 1,2,4,5-substitution pattern. Since there was only one double bond apparent in the ^{13}C-NMR, the remainder ($C_{25}H_{41}$) of the molecule had to be tetracyclic.[6] The toxistylide structure

could certainly not be of the scalarin (1) type because the ^{1}H-NMR showed a secondary as well as a vinyl methyl. Since all possible structures consistent with the chemical and spectral data were new sesterterpene skeletons and it appeared that it would be difficult to assign stereochemistry, a single crystal x-ray diffraction study was carried out.

Crystals of toxistylide B (4) belonged to the monoclinic space group $P2_1$ with a = 9.520(7), b = 11.167(9), c = 16.380(6) Å and β = 105.02(5)°. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer controlled four-circle diffractometer with graphite monochromated CuKα radiation. After correction for Lorentz, polarization and background effects, 2085 (87%) of the reflections were judged observed ($|F_o| \geq 3\sigma(F_o)$). A phasing model was achieved using a magic integers implementation of a weighted tangent formula approach.[7] Full-matrix least-squares refinements with anisotropic nonhydrogen and isotropic hydrogen atoms have converged to the current crystallographic residual of 0.072 for the observed reflections.[8] A computer generated perspective drawing of toxistylide B is shown below with an arbitrary entantiomer choice. Bond distances and angles agree well with expected values.[9] The tetracyclic array has trans-anti-trans-syn-cis stereochemistry for the four cyclohexane rings. All of the cyclohexane rings have the chair conformation.

The structures of the toxistylides represent a new sesterterpene skeleton and a biogenesis is not readily apparent. If the basic carbon skeleton is assembled in head to tail fashion, then methyl migrations from C(4) to C(5) and from C(8) to C(21) have occurred but it is difficult to write a felicitous mechanism.

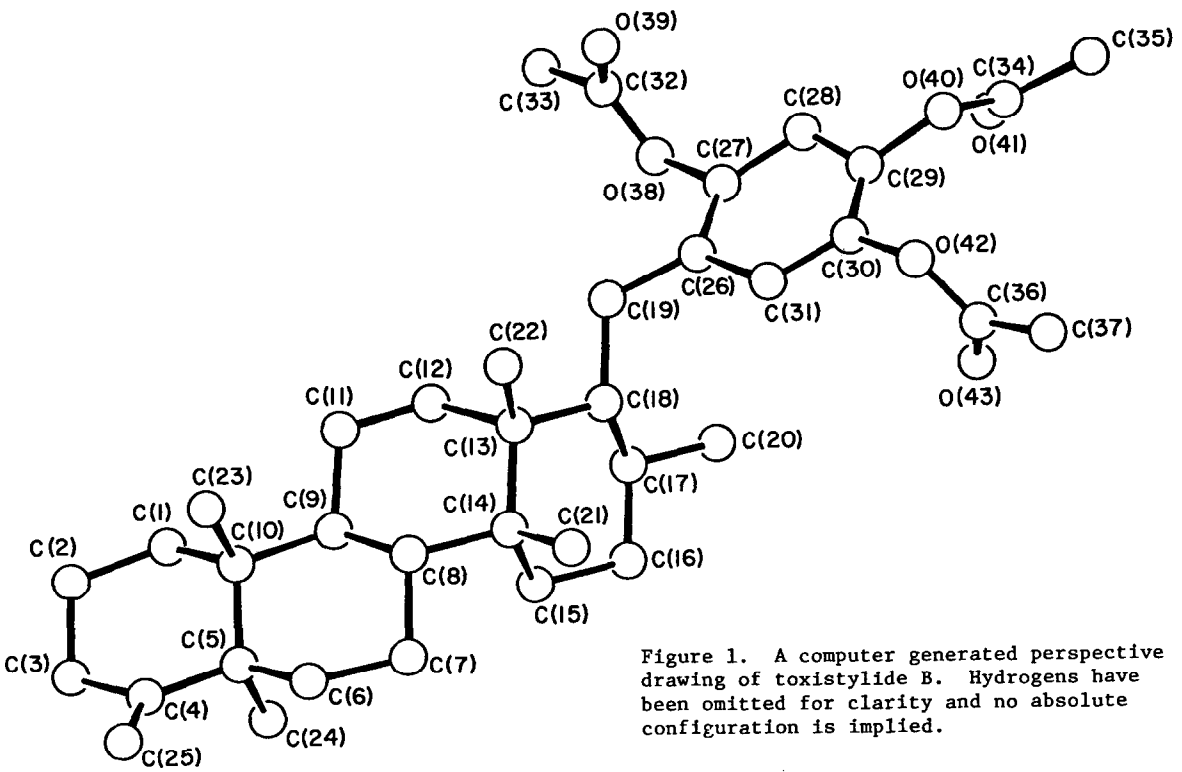


Figure 1. A computer generated perspective drawing of toxistylide B. Hydrogens have been omitted for clarity and no absolute configuration is implied.

ACKNOWLEDGEMENTS

The authors wish to gratefully acknowledge support for this research from NATO and NIH. The diffractometer used in the study was funded by NSF.

REFERENCES

1. D.J. Faulkner, Tetrahedron Report No. 28, Tetrahedron, 33 (1977).

2. L. Minale, G. Cimino, S. De Stefano and G. Sodano, Fortschritte d. Chem. Org. Naturst. 33, 1, 1976; L. Minale in "Marine Natural Products: New Prospectives" (P.J. Scheuer, ed.) Academic Press, 1977 (in the press).

3. G.Cimino, P. De Luca, S. De Stefano and L. Minale, Tetrahedron 31, 271 (1975).

4. Different collections of the sponge have been extracted; all of them contained the sesquiterpenes[5], but only some of them contained the sesterterpenoid hydroxyquinols.

5. G. Cimino, S. De Stefano, A. Guerriero and L. Minale, Tetrahedron Letters, 3723, (1975).

6. ^{13}C-NMR data: 3, CH_3: 15.1, 19.3, 19.8, 20.2, 20.6, 20.8, 21.2, 21.6, 21.8; CH_2: 31.8, 29.1 (x2), 28.3,2]7.9, 22.5 - three CH_2 carbons are not visible as separated signals; CH: 49.9, 40.9, 38.2, 34.5; C: 40.0, 39.2, 37.7; CH=C< : 119.5 and 141.9; ArCH: 117.2 and 123.2; ArC: 135.1, 139.4, 145.3 - two signals being degenerate; C=O: 168.6, 168.0, 167.8 p.p.m. 4, CH_3: 15.7, 19.8, 20.4, 20.7, 20.9, 21.2, 21.7, 21.9; CH_2: 31.9 (x2), 31.5, 31.0, 29.2, 28.4, 27.7, 22.3 - two CH_2 carbons are not visible as separated signals; CH: 49.9, 41.0, 38.4, 34.6, C: 42.4, 40.1, 39.4, 39.3; CH_2=C : 105.6, 155.2 p.p.m., the remainder of the spectrum was identical to that of 3; spectra were taken in $CDCl_3$; 25.20 MHz; Varian XL-100 Fourier Transform (3) and Camega 250 Fourier Transform (4) spectrometers; we thank Mr. C. Di Pinto for the 100 MHz spectrum and Dr. G. Lukacs who provided the 250 MHz spectrum.

7. J.P. Declercq, G. Germain and M.M. Woolfson, Acta Cryst., A31, 367 (1975).

8. All crystallographic calculations were done on a Prime 400 computer, operated by the Materials Science Center, Cornell University. The principal programs used were: REDUCE and UNIQUE, data reduction programs, M.E. Leonowicz, Cornell University, 1978; BLS, block diagonal least squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full matrix least squares, W.R. Busing, K.O. Martin, and H.S. Levy, Oak Ridge, ORNL-TM305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge,ORNL-3794, BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.

9. Refined fractional coordinates have been deposited with the Cambridge Crystallographic Data Centre and are also available from J.C.

(Received in USA 6 June 1979)