Absolute Configuration of Brevetoxins

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The absolute configuration of the dinoflagellate toxins, brevetoxins, has been unequivocally determined by *X*-ray crystallography of a chiral dioxolane derivative.

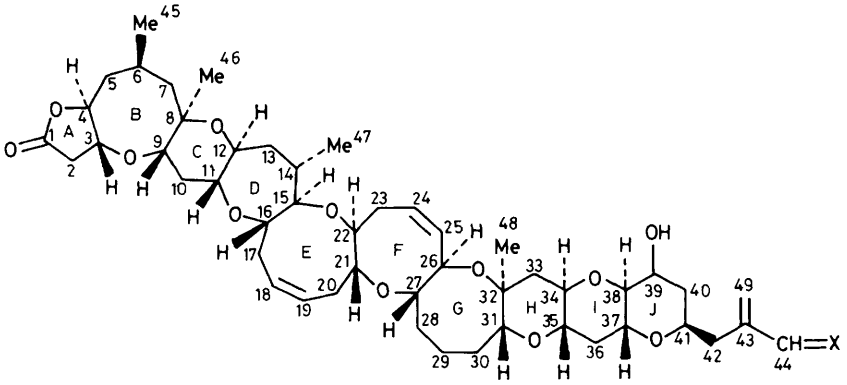
A group of polycyclic ether toxins found in the deleterious red tide organism, *Gymnodinium breve*, has been attracting much attention owing to the unique structures and pharmacological activity of the compounds.[1—3] The toxins can be classified into two groups according to the ring systems: decacyclic brevetoxin-A (**1**) and undecacyclic brevetoxin-B (**2**).

The structure of brevetoxin-B, (**2**) was established earlier by direct *X*-ray crystallography,[4] and the structure of brevetoxin-A by an *X*-ray study of its dimethyl acetal derivative.[5] In both cases, however, the crystallography did not afford the absolute configuration of the molecules, though a tentative assignment was made for (**2**) by the application of the dibenzoate chirality rule to the 27,28-dihydroxy derivative prepared by osmylation of the 27,28-double bond in (**2**).[4] However, the assignment was based upon two key assumptions: (i) the osmylation of the 27,28-double bond takes place on the β side of the molecule, and (ii) the benzoyloxylated 8-membered ring-H is in the crown form. Neither of the assumptions seems to have a solid basis, and the corresponding 8-membered ring-G of (**1**) in the crystal was shown to exist in the boat–chair form.[5] We have now unequivocally established the absolute configuration; an important finding since some groups are already engaged in the stereoselective total synthesis of these fascinating molecules.

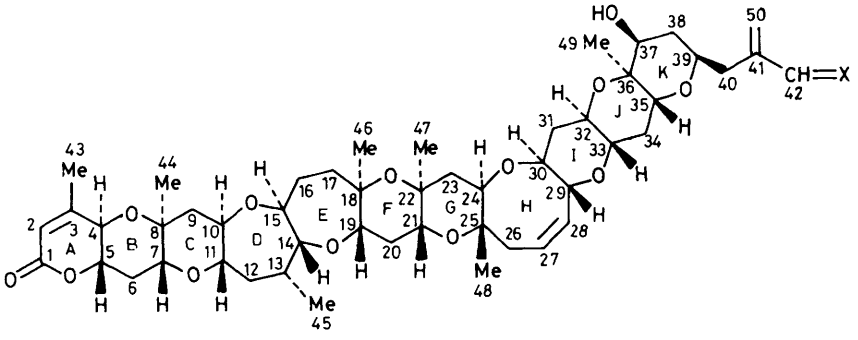
A number of approaches were examined, but finally we prepared the chiral crystalline 1,3-dioxolane derivative, (**3**) upon treatment of (**2**) with optically active (2*R*,3*R*)-(−)-butane-2,3-diol.†‡

† The compound (**3**) was prepared by treating brevetoxin-B (17 mg) with (2*R*,3*R*)-(−)-butane-2,3-diol {$[\alpha]^{22}$ −3.3° (*c* 1.15)} (55 mg) in the presence of Dowex 50W-X8, H^+ form, in benzene (2 ml) at 75 °C for 1 h. The product was purified by preparative t.l.c. with the system hexane–propan-2-ol (3 : 1) and then crystallized from a CH_2Cl_2–Et_2O solution as leaflets, m.p. 280—284 °C (decomp.).

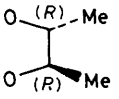
‡ *Crystal data:* (**3**), $C_{54}H_{78}O_{15}$, monoclinic, space group $P2_1$, a = 11.379(8), b = 13.320(3), c = 17.876(5) Å, β = 100.50(5)°, U = 2664.2 Å^3, D = 1.20 g cm^{-3}, Z = 2. All unique diffraction maxima with 2θ<114° were collected using graphite monochromated Cu-$K_{\bar{\alpha}}$ radiation (1.54178 Å) and variable speed, 1° ω-scans. Of the 2879 reflections examined in this way, 2062 (72%) were judged observed [$F_o > 3\sigma(F_o)$].[6] This structure was not isostructural with the previously determined brevetoxins, and a phasing model was found *de novo* using the RANTAN approach. The initial phasing model was extended with weighted Fourier refinements and hydrogens were included from a difference synthesis. Anisotropic least squares refinement was carried out. The *R*-factor based on non-hydrogen atom refinement only is 0.073 for the observed data. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.



(1) X = O



(2) X = O

(3) X = 

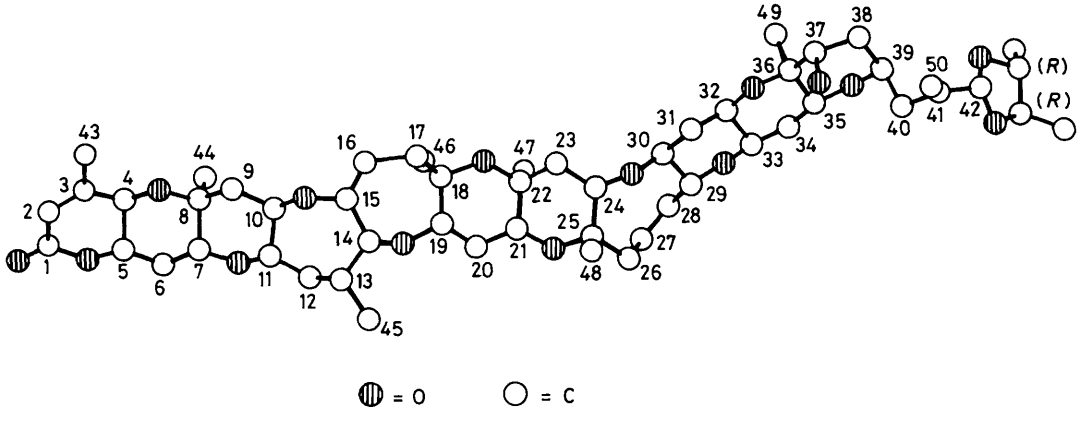


Figure 1. Computer generated perspective drawing of brevetoxin-B-1,3-dioxolane (**3**). Hydrogens are omitted for clarity.

A computer generated perspective drawing of the final *X*-ray model of (**3**) is shown in Figure 1. The important point is the configuration at the acetal end of the molecule. Since (2*R*,3*R*)-(−)-butane-2,3-diol was used to prepare the derivative, the known configuration at these centres determines the absolute configuration of all stereocentres, which is in agreement with the previously proposed configuration. Regarding the absolute stereochemistry of brevetoxin-A, the close structural resemblance of rings G—J in (**1**) to rings H—K in (**2**) suggests that it has the absolute configuration of stereocentres as shown in the structure (**1**). Since all the other toxins isolated from *G. breve* have been correlated with brevetoxin-A and brevetoxin-B, their absolute configuration is also clarified.

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6 All crystallographic calculations were done on a PRIME 9950 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: M. E. Leonowicz, 'REDUCE' and 'UNIQUE,' (data reduction programs) Cornell University, 1978; P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, 'MULTAN 80' and 'RANTAN 80,' (systems of computer programs for the automatic solution of crystal structures from *X*-ray diffraction data, locally modified to perform all Fourier calculations including Patterson syntheses) University of York, England, 1980; K. Hirotsu and E. Arnold, 'BLS78A,' (an anisotropic block diagonal least squares refinement) Cornell University, 1980; W. D. S. Motherwell, 'PLUTO78,' (a locally modified crystallographic illustration program) Cambridge Crystallographic Data Centre, 1978; K. Hirotsu and G. Van Duyne, 'BOND,' (a program to calculate molecular parameters and prepare tables) Cornell University, 1985.