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The Crystal and Molecular Structure of Grayanotoxin XVIII. A New Minor Diterpene from *Leucothoe Grayana Max.*

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The molecular structure of grayanotoxin XVIII $C_{20}H_{28}O_4$, has been determined by means of X-ray crystal analysis. The crystals are monoclinic, with two molecules in a unit cell with dimensions of $a=9.592$, $b=11.414$, $c=8.180$ Å, and $\beta=93.21°$; the space group is $P2_1$. 1484 unique intensity data were collected on a four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation. The structure was solved by the Monte Carlo direct method, using the 20 strongest reflections as the starting set; the 25th random-phase set led to the correct solution. The R value reached 4.6% by block-diagonal least-squares refinements. The structure thus obtained corresponds to 3-dehydrograyanotoxin VII. The C-ring takes a boat conformation. The force-field calculations suggest that this energy loss is probably compensated for by the stabilization of the B-ring conformation. The crystal consists of hydrogen-bonded molecular layers parallel to the (100) plane.

A number of grayanane diterpenoids have been isolated from *Leucothoe grayana Max.*, *Pieris japonica* D. Don, *Rhododendron japonicum* Suringer, *etc.*, and their structures have been extensively investigated.[1—4] In this paper, we wish to report on the X-ray structure determination and molecular geometry of grayanotoxin (hereafter G) XVIII, a new constituent from *Leucothoe grayana Max.*

Experimental

Isolation of G XVIII. Grayathol A[5] was crystallized and removed from a diethyl ether solution of the unknown-compound-containing fraction (81 mg)[6] obtained from the crude extract of *Leucothoe grayana Max.* The chromatography of the filtrate on silica gel (1 g) afforded G XVIII (15 mg) in a 4×10^{-7}% yield from dried leaves; mp 204—210 °C (recrystallized from methanol), $[\alpha]_D$ −102° (*c* 1, MeOH); IR (Nujiol) 3400, 1725, 1655, 1628 cm^{-1}; ^{1}H-NMR (C_5D_5N) 1.35, 1.58 (each 3H, s), 1.70 (3H, d, $J=2$ Hz), 3.37 (1H, q, $J_{AX+BX}=6+10$ Hz), 4.70 (1H, s), 5.04, 5.11 (each 1H, s), 5.25 (1H, bs); MS *m/e* 332 (M$^+$). Found: C, 72.58; H, 8.98%. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%. The PMR spectrum was recorded on a Hitachi R-20B spectrometer by the use of TMS as the internal reference. The chemical shifts are given on the δ scale (s=singlet, d=doublet, q=quartet, bs=broad singlet). The IR spectrum was obtained on a JASCO Model IR-S spectrophotometer.

X-Ray Measurement. A colorless single crystal with dimensions of about $0.4\times0.5\times0.6$ mm^3 was used. The crystal data are summarized in Table 1. The cell dimensions and reflection intensities were measured on a Rigaku four-circle diffractometer using Ni-filtered Cu $K\alpha$ radiation (40 kV, 60 mA, $\lambda=1.5418$ Å). The θ-2θ continuous-scan technique was applied at a θ scan rate of 8° min^{-1}; the background was measured for 5 s at each end of the scan range. Three standard reflections, measured at intervals of every 60 reflections, showed no significant decrease in intensity during the course of data collection. The intensities were corrected for the Lorentz and polarization factors, but not for the absorption or the extinction effect. In the range of 2θ values up to 125°, 1484 unique structure-factor magnitudes above the $\sigma(F)$ level were selected for the structure determination.

Table 1. The crystal data

Molecular formula	$C_{20}H_{28}O_4$
Molecular weight	332.4
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	$a=9.592(1)$ Å $b=11.414(1)$ Å $c=8.180(1)$ Å $\beta=93.21(1)°$
V	894.2 Å^3
Z	2
D_x	1.235 g cm^{-3}
μ(Cu $K\alpha$)	6.43 cm^{-1}

Structure Determination

The structure was solved by the Monte Carlo direct method.[7] The 20 strongest reflections were chosen as the starting set. Tentative phase values for the starting reflections were derived from successively-generated random numbers. In order to extend this tentative phase set, 10 cycles of the tangent procedure were performed using 300 $|E|$ values above 1.30. Since the 25th phase set showed a low R_K value of 26.6% ($R_K=\Sigma||E_o|-k|E_c||/\Sigma|E_o|$), 6 additional cycles of the tangent procedure were carried out using 386 $|E|$ values above 1.20; the R_K value thereupon dropped to 22.2%. An E-map calculated with 375 phases clearly revealed the locations of all the 24 non-hydrogen atoms.

The structure thus obtained was refined by the block-diagonal-matrix least-squares method, first with isotropic and then with anisotropic temperature factors. After all the 28 hydrogen atoms had been located in a difference Fourier map, further least-squares refinement was repeated including these hydrogen atoms with isotropic temperature factors. For this refinement, the following weighting scheme was used:

$$W=1/\{\sigma(F)^2\exp(AX^2+BY^2+CXY+DX+EY)\},$$

where $X=|F_o|$ and $Y=\sin\theta/\lambda$. The A, B, C, D, and E coefficients are constants which were determined from the $(\Delta F)^2$ values. The final value of $R=\Sigma|$

Table 2. The final atomic parameters and estimated standard deviations

The coordinates of the non-hydrogen and hydrogen atoms are multiplied by 10^4 and 10^3 respectively.

(1) The non-hydrogen atoms

Atom	x	y	z	B_{eq}[a]/Å^2	Atom	x	y	z	B_{eq}[a]/Å^2
O(1)	6455(3)	1476(4)	−2110(3)	4.95	C(9)	1512(3)	2168(3)	2308(4)	2.22
O(2)	4746(2)	120(2)	1490(3)	2.50	C(10)	2292(3)	1578(3)	969(3)	2.12
O(3)	6055(2)	1108(2)	4342(3)	2.77	C(11)	961(3)	3370(3)	1679(4)	2.90
O(4)	3681(2)	3619(2)	5731(3)	2.92	C(12)	471(4)	4237(4)	2975(4)	3.14
C(1)	3737(3)	2012(3)	655(3)	2.12	C(13)	1293(4)	4092(3)	4638(4)	2.83
C(2)	4186(4)	1878(4)	−1116(4)	3.22	C(14)	2725(3)	3570(3)	4335(4)	2.25
C(3)	5726(4)	1645(4)	−975(4)	3.00	C(15)	1233(4)	2120(3)	5287(4)	2.87
C(4)	6269(3)	1662(3)	828(4)	2.47	C(16)	648(4)	3129(4)	5630(4)	3.26
C(5)	4915(3)	1358(3)	1700(3)	1.95	C(17)	−523(5)	3365(6)	6715(6)	5.97
C(6)	4900(3)	1703(3)	3508(3)	1.99	C(18)	7485(4)	828(4)	1129(5)	3.76
C(7)	3548(3)	1408(3)	4307(3)	2.17	C(19)	6768(4)	2917(4)	1194(5)	3.49
C(8)	2329(3)	2272(3)	4021(3)	2.03	C(20)	1664(4)	714(4)	102(4)	3.29

a) $B_{eq}=8\pi^2(u_1^2+u_2^2+u_3^2)/3$, where u_i is the root-mean-square deviation in the ith principal axis of the thermal ellipsoid.

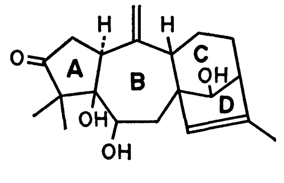
(2) The hydrogen atoms

Atom[a]	x	y	z	B/Å^2	Atom[a]	x	y	z	B/Å^2
H(1)	383(3)	284(4)	98(4)	2.6(7)	H(17a)	−60(5)	261(5)	716(6)	6.5(13)
H(2a)	390(3)	257(3)	−190(4)	2.6(7)	H(17b)	−132(5)	358(5)	611(6)	7.2(13)
H(2b)	370(4)	117(4)	−175(5)	4.3(9)	H(17c)	−31(6)	415(6)	763(7)	8.9(16)
H(6)	496(3)	259(3)	353(4)	2.8(7)	H(18a)	799(4)	108(4)	230(5)	4.5(9)
H(7a)	386(3)	137(3)	546(3)	1.0(5)	H(18b)	822(4)	100(4)	41(5)	5.0(10)
H(7b)	326(3)	60(3)	401(4)	2.6(7)	H(18c)	722(6)	15(6)	98(7)	8.6(16)
H(9)	67(3)	173(3)	251(4)	2.3(7)	H(19a)	740(4)	324(4)	57(5)	5.1(10)
H(11a)	169(4)	369(3)	119(4)	3.2(8)	H(19b)	708(4)	299(4)	234(5)	4.9(10)
H(11b)	28(4)	326(4)	93(4)	3.2(8)	H(19c)	611(5)	347(5)	91(5)	6.1(12)
H(12a)	59(3)	504(3)	258(4)	2.8(7)	H(20a)	80(3)	46(3)	35(4)	2.5(7)
H(12b)	−52(4)	411(3)	316(4)	2.7(7)	H(20b)	201(4)	29(4)	−74(5)	4.4(9)
H(13)	139(4)	496(4)	516(4)	4.0(9)	H(O2)	408(4)	−4(5)	182(5)	5.4(10)
H(14)	307(3)	394(3)	339(4)	1.7(6)	H(O3)	606(3)	132(3)	525(4)	2.5(7)
H(15)	101(4)	139(4)	574(5)	4.4(9)	H(O4)	377(4)	416(4)	597(5)	4.0(9)

a) The hydrogen atoms are denoted by the number of the carbon atom to which they are attached, suffixed by a, b, or c where necessary.

$|F_o|-k|F_c||/\Sigma|F_o|$ was 4.6%. The atomic parameters are listed in Table 2. The tables of the anisotropic thermal parameters and of the observed and calculated structure factors are kept at the Chemical Society of Japan (Document No. 8102).

The calculations were performed on an ACOS 700 computer at the Institute for Protein Research, Osaka University, and on a FACOM 230-75 computer at the Hokkaido University Computing Center. The atomic scattering factors were taken from the International Tables.[8]



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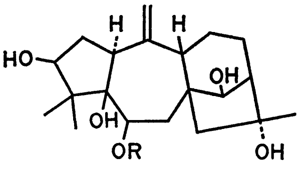
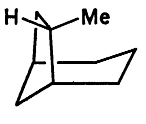


2: R=H 3: R=Ac



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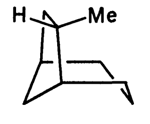

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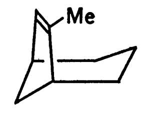

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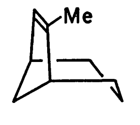

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Results and Discussion

Molecular Structure. The molecular structure of G XVIII is illustrated in Fig. 1, where each atom is represented as a thermal ellipsoid enclosing a 50% probability. As can be seen in Fig. 1, the molecular framework obtained corresponds to **1**. The bond distances and angles are listed in Table 3; all these

Table 3. The bond distances (l/Å) and angles (ϕ/°), with their standard deviations
The standard deviations given in parentheses refer to the last decimal position.

C(1)-C(2)	1.542(4)	C(15)-C(16)	1.318(5)	C(7)-C(8)-C(9)	115.1(2)
C(1)-C(5)	1.567(4)	C(16)-C(17)	1.494(6)	C(7)-C(8)-C(14)	114.3(2)
C(1)-C(10)	1.508(4)	C(2)-C(1)-C(5)	103.6(2)	C(7)-C(8)-C(15)	111.8(3)
C(1)-C(3)	1.499(5)	C(2)-C(1)-C(10)	115.8(2)	C(9)-C(8)-C(14)	109.1(2)
C(3)-C(4)	1.536(4)	C(5)-C(1)-C(10)	113.1(3)	C(9)-C(8)-C(15)	105.6(2)
C(3)-O(1)	1.209(4)	C(1)-C(2)-C(3)	105.7(2)	C(14)-C(8)-C(15)	99.7(3)
C(4)-C(5)	1.556(4)	C(2)-C(3)-C(4)	110.6(3)	C(8)-C(9)-C(10)	115.8(2)
C(4)-C(18)	1.515(5)	C(2)-C(3)-O(1)	125.4(3)	C(8)-C(9)-C(11)	111.9(3)
C(4)-C(19)	1.535(5)	C(4)-C(3)-O(1)	124.0(3)	C(10)-C(9)-C(11)	109.0(3)
C(5)-C(6)	1.531(4)	C(3)-C(4)-C(5)	101.0(2)	C(1)-C(10)-C(9)	118.2(3)
C(5)-O(2)	1.432(4)	C(3)-C(4)-C(18)	111.4(3)	C(1)-C(10)-C(20)	122.9(3)
C(6)-C(7)	1.522(4)	C(3)-C(4)-C(19)	106.5(3)	C(9)-C(10)-C(20)	118.9(3)
C(6)-O(3)	1.438(4)	C(5)-C(4)-C(18)	116.1(3)	C(9)-C(11)-C(12)	116.9(3)
C(7)-C(8)	1.538(4)	C(5)-C(4)-C(19)	112.2(3)	C(11)-C(12)-C(13)	112.2(3)
C(8)-C(9)	1.572(4)	C(18)-C(4)-C(19)	109.0(3)	C(12)-C(13)-C(14)	108.5(3)
C(8)-C(14)	1.548(4)	C(1)-C(5)-C(4)	103.8(2)	C(12)-C(13)-C(16)	110.2(3)
C(8)-C(15)	1.526(4)	C(1)-C(5)-C(6)	111.0(2)	C(14)-C(13)-C(16)	101.6(3)
C(9)-C(10)	1.519(4)	C(1)-C(5)-O(2)	109.4(2)	C(8)-C(14)-C(13)	100.7(3)
C(9)-C(11)	1.548(5)	C(4)-C(5)-C(6)	116.1(2)	C(8)-C(14)-O(4)	108.1(2)
C(10)-C(20)	1.338(5)	C(4)-C(5)-O(2)	104.9(2)	C(13)-C(14)-O(4)	113.4(3)
C(11)-C(12)	1.543(5)	C(6)-C(5)-O(2)	111.2(2)	C(8)-C(15)-C(16)	111.3(3)
C(12)-C(13)	1.543(5)	C(5)-C(6)-C(7)	114.4(2)	C(13)-C(16)-C(15)	109.1(3)
C(13)-C(14)	1.530(5)	C(5)-C(6)-O(3)	106.7(2)	C(13)-C(16)-C(17)	122.0(4)
C(13)-C(16)	1.518(5)	C(7)-C(6)-O(3)	110.1(2)	C(15)-C(16)-C(17)	128.8(4)
C(14)-O(4)	1.425(4)	C(6)-C(7)-C(8)	116.8(3)		

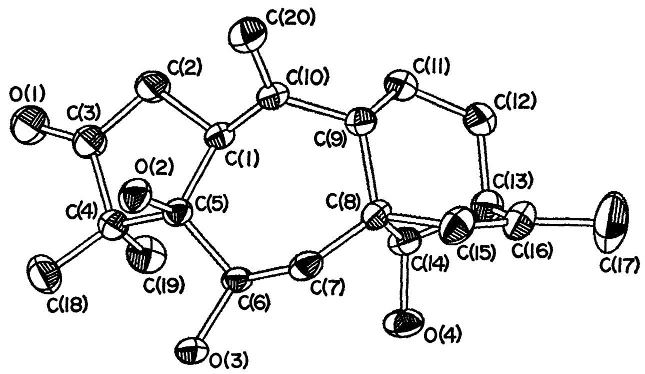

Fig. 1. A perspective view of the G XVIII molecule.

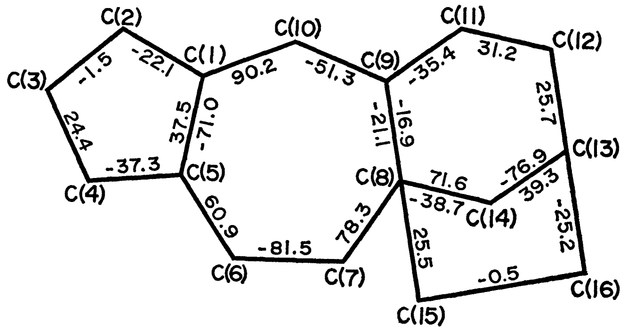

Fig. 2. The torsion angles (ϕ/°) of the A-, B-, C-, and D-rings. Only the torsion angles relevant to atoms which form the same ring are given in the ring.

values are normal. The torsion angles for the tetracyclic system are given in Fig. 2.

The five-membered A-ring takes an envelope form different from those of the A-rings in G II (**2**)[9] and G XVI (**3**):[10] In the former an approximate mirror plane runs through the C(5) atom, while in the latter two it goes through the C(4) atom. The conformation of the latter type is probably unfavorable to the present A-ring, because it makes the O(1) carbonyl oxygen atom almost eclipse the C(18)H$_3$ methyl group around the C(3)–C(4) bond.

The C(5)–C(4)–C(18) and C(5)–C(4)–C(19) bond angles, 116.1 and 112.2°, are somewhat larger than the C(3)–C(4)–C(18) and C(3)–C(4)–C(19) angles, 111.4 and 106.5°, respectively. This distortion of the C(4)–C(18) and C(4)–C(19) bonds may be caused by the steric repulsions between the C(18)H$_3$ and O(2)H groups and between the C(19)H$_3$ and C(6)H groups; C(18)···O(2), 2.780(4) Å; C(19)···C(6), 3.016(5) Å. As is found also in **2** and **3**, these steric repulsions further result in a small lengthening of the C(4)–C(5) bond.

The conformation adopted by the seven-membered B-ring is intermediate between the chair form with the mirror plane through the C(5) atom and the twist-chair form with the two-fold rotation axis through the C(9) atom. In this conformation, the severe 3a-3′a or 2a-3′a repulsion characteristic of the chair and twist-chair cycloheptane rings[11] is much relieved, since the exocyclic methylene group, C(20)H$_2$, occupies exactly the 3a or 2a position. This suggests that the present B-ring conformation may contain less strain than the twist-chair form in **2** and the twist-chair and chair forms** in **3**. This tentative conclusion is supported by a comparison of the values of

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**The G XVI hemihydrate crystal contains two conformers with regard to the B-ring conformation: (a) the twist-chair form and (b) the chair form.

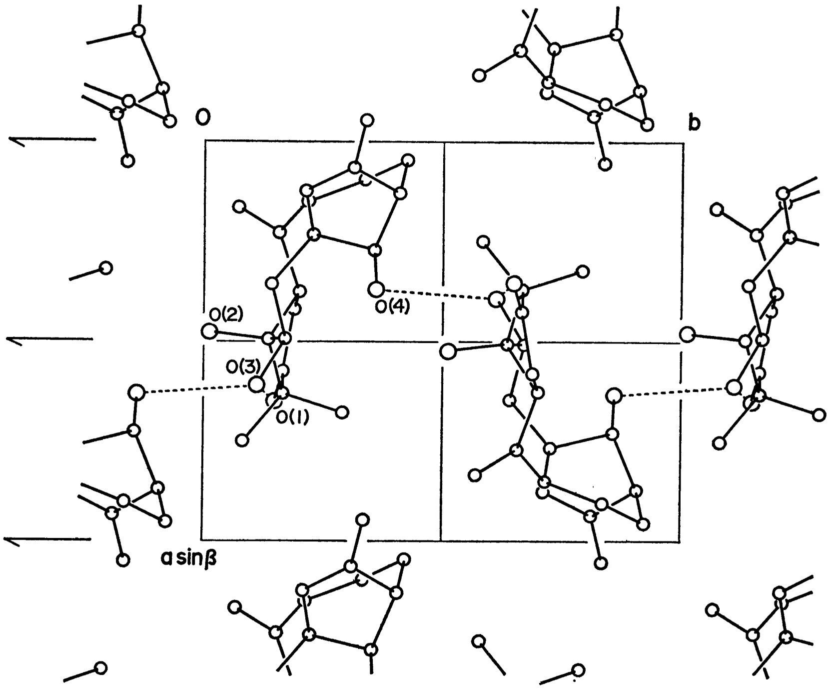

Fig. 3. The crystal structure viewed along the c axis.

$EB=(\theta_i-\theta^0_i)^2$, where the θ_i's ($i=1, 2, \cdots, 7$) are the observed bond angles in the B-ring and where the θ^0_i's are 109.5 and 116.6° for the sp^3 and sp^2 bond angles respectively. The calculated values of EB are as follows: G II, 438; G XVI (a), 345; G XVI (b), 288; G XVIII, 166 $(°)^2$.

The possibility exists that the O(2)H hydroxyl group may form an intramolecular hydrogen bond of the O–H⋯π type:12) O(2)⋯C(10), 2.895(4) Å; H(O2)⋯C(10), 2.59(5) Å; H(O2)⋯C(20), 2.78(4) Å. This weak interaction may also contribute to the stability of the present B-ring conformation.

It should be noted that the six-membered C-ring adopts the unstable boat conformation, while it takes the chair conformation in both **2** and **3**. In order to clarify the cause of this boat conformation, we performed force-field calculations for **4**—**7**, using the MMI program.13) The calculated heats of formation are as follows: **4**, −28.8; **5**, −22.4; **6**, −4.7; **7**, −0.1 kcal/mol. These results show that the transformation of the C(15)–C(16) single bond into the double bond reduces the chair-boat enthalpy difference of the C-ring from 6.4 to 4.6 kcal/mol. Therefore, if one assumes that the present B-ring conformation is more stable than those in **2** and **3** by more than 4.6 kcal/mol and by less than 6.4 kcal/mol, the conformational behavior of the C-ring can be easily understood.

Crystal Structure. The crystal structure viewed along the c axis is shown in Fig. 3. There are two kinds of intermolecular hydrogen bonds, O(3)–H⋯O(1′) and O(4)–H⋯O(3″); their O⋯O distances are 2.937(3) and 2.854(4) Å respectively. Through these hydrogen bonds, the molecules form a molecular layer parallel to the (100) plane. These molecular layers are further held together mainly by the van der Waals interactions.

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