Crystal and Molecular Structure of 1,5-Seco-grayanotoxin-1,3,6,14,16-pentaacetate

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Synopsis. The three-dimensional structure of 1,5-seco-grayanotoxin-1,3,6,14,16-pentaacetate has been determined by X-ray diffraction at room temperature. The monoclinic structure was refined by the full matrix least-squares method to a final R=0.037 for 2269 independent reflections. The molecule has a tricyclic structure that consists of ten-, six-, and five-membered rings. The absolute configuration at C1 atom was determined as S on the basis of internal comparison with the absolute structure of 1,5-seco-grayanotoxin-1(R),3,6,14,16-pentaacetate.

The skeletal transformation of grayanotoxins[1—3] is of increasing importance of ten-membered terpenoids as bioactive substances and also of some value as a new route to cyclodecane derivatives. In this standpoint, we have so far studied in vitro conversion of the ring structure of grayanotoxin II-3,6,14,16-tetraacetate by $Pb(OAc)_4$ and $Tl(OAc)_3$ and showed the responsibility of C1 atom for the interaction with $Pb(OAc)_4$ and $Tl(OAc)_3$. In fact, the three-dimensional structure analysis of a ten-membered terpenoid transformed from the grayanotoxin II tetraacetate by $Pb(OAc)_4$, showed occurrence of 1,5-seco-grayanotoxin-1(R),3,6,14,16-pentaacetate with R configuration at C1 atom.[4] In this paper, we report on the X-ray crystal structure determination of the other 1,5-seco-grayanotoxin-1,3,6,14,16-pentaacetate, transformed by $Tl(OAc)_3$ from the grayanotoxin II tetraacetate, to elucidate the ring structure around C1 atom.

Experimental

Grayanotoxin II-3,6,14,16-tetraacetate was prepared by acetylation of grayanotoxin II, which was isolated from the leaves of *Leucothoe grayana* Max., with acetic anhydride. It was then converted to 1,5-seco-grayanotoxin-1,3,6,14,16-pentaacetate by $Tl(OAc)_3$ at 80 °C in benzene.

Table 1. Crystal Data

Mol. formula	$C_{30}H_{42}O_{11}$
Mol. weight	578.64
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	a/Å=18.947(2)
	b/Å= 7.744(1)
	c/Å=10.207(2)
	β/°=94.47(2)
V/Å^3	1493.1(3)
Z	2
D_c/g cm^{-3}	1.288
μ(Cu $K\alpha$)/cm^{-1}	8.22
F(000)	620

Colorless, plate-like crystals of the 1,5-seco-grayanotoxin-1,3,6,14,16-pentaacetate were grown by slow evaporation from a mixture solution of ethyl acetate and hexane at room temperature. A crystal with approximate dimensions of 0.1×0.1×0.03 mm was selected for data collection on a Rigaku automated four-circle diffractometer equipped with a rotating-

Table 2. Final Atomic Coordinates and Their Equivalent Isotropic Thermal Parameters[a)]

Atom	x	y	z	B_{eq}/Å^2
O1	0.7897(2)	0.6815(0)	−0.3346(3)	3.82(8)
O2	0.8068(3)	0.9671(7)	−0.3157(5)	6.9(2)
O3	0.5428(2)	0.7141(6)	−0.2677(3)	4.24(9)
O4	0.5437(2)	0.4295(7)	−0.3100(4)	5.8(2)
O5	0.7125(2)	0.9943(6)	0.0066(3)	4.26(9)
O6	0.6667(2)	0.7186(6)	0.1985(3)	3.66(8)
O7	0.6213(2)	0.4502(7)	0.1713(4)	5.3(1)
O8	0.7835(2)	0.4071(6)	0.2747(3)	3.07(7)
O9	0.7466(3)	0.1323(7)	0.2930(4)	6.1(2)
O10	0.9297(2)	0.3909(6)	0.3430(3)	3.80(8)
O11	0.9587(3)	0.1089(7)	0.3703(4)	5.9(2)
C1	0.7448(3)	0.6814(8)	−0.2224(4)	3.3(1)
C2	0.6689(3)	0.7026(9)	−0.2829(5)	3.9(2)
C3	0.6102(3)	0.7022(8)	−0.1876(5)	3.5(2)
C4	0.6088(3)	0.8567(8)	−0.0915(5)	3.6(2)
C5	0.6783(3)	0.8633(8)	−0.0023(4)	3.3(1)
C6	0.7037(3)	0.7031(8)	0.0785(4)	3.2(1)
C7	0.7842(3)	0.7065(8)	0.1165(5)	3.4(1)
C8	0.8277(3)	0.5460(7)	0.0851(4)	3.0(1)
C9	0.8339(3)	0.5219(8)	−0.0668(4)	3.4(1)
C10	0.7641(3)	0.5140(8)	−0.1520(4)	3.2(1)
C11	0.8843(3)	0.3700(9)	−0.0932(5)	4.3(2)
C12	0.8785(3)	0.2128(8)	−0.0036(5)	4.2(2)
C13	0.8703(3)	0.2620(8)	0.1404(4)	3.3(1)
C14	0.8032(2)	0.3732(7)	0.1406(4)	2.9(1)
C15	0.9043(3)	0.5653(8)	0.1538(5)	3.4(2)
C16	0.9297(3)	0.3832(8)	0.1976(4)	3.6(2)
C17	1.0058(3)	0.343(1)	0.1652(6)	4.7(2)
C18	0.5463(3)	0.831(2)	−0.0043(6)	4.9(2)
C19	0.5997(4)	1.0290(9)	−0.1647(6)	5.0(2)
C20	0.7255(3)	0.3726(8)	−0.1728(5)	3.9(2)
C21	0.8152(3)	0.8351(9)	−0.3729(5)	4.4(2)
C22	0.8537(5)	0.810(2)	−0.4953(7)	6.3(3)
C23	0.5149(3)	0.5676(9)	−0.3207(5)	4.7(2)
C24	0.4445(4)	0.603(2)	−0.3939(9)	6.8(3)
C25	0.6278(3)	0.5809(9)	0.2319(5)	4.1(2)
C26	0.5923(4)	0.621(2)	0.3561(6)	5.5(2)
C27	0.7557(3)	0.2723(8)	0.3382(5)	3.8(2)
C28	0.7387(4)	0.325(1)	0.4740(5)	4.6(2)
C29	0.9443(3)	0.2461(9)	0.4147(5)	4.6(2)
C30	0.9381(4)	0.282(2)	0.5588(6)	6.1(2)

a) Equivalent isotropic B_{eq} defined as $B_{eq}=(4/3)\sum\sum B_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$.

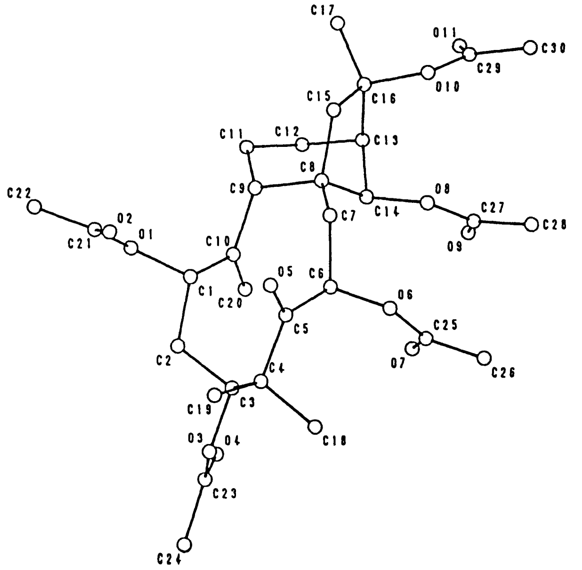

Fig. 1. A perspective view of the molecule with the atom-numbering scheme. Hydrogen atoms are omitted for clarity.

anode X-ray generator operated at 40 kV, 200 mA. Unit-cell parameters were accurately determined by the least-squares method from 25 reflections in the range $42.71^\circ \leqq 2\theta \leqq 45.73^\circ$. The crystal data are shown in Table 1.

Integrated intensities were measured by the θ-2θ scan technique using Ni-filtered Cu $K\alpha$ radiation (λ=1.5418 Å) and a monitor count technique. The scan width was $\Delta\theta=(1.2+0.15\tan\theta)^\circ$ and scan speed 2° min^{-1}. Background intensities were measured for 7 s at both ends of a scan. Two sets of reflections; $h\ k\ l$ range, $-21 \leqq h \leqq 21$, $-8 \leqq k \leqq 8$, $0 \leqq l \leqq 11$, a total of 4707 reflections were collected up to $2\theta=120^\circ$, and 93 reflections were considered as unobserved. Three standard reflections (8 1 2, 0 0 6, and 0 3 3) were measured every 100 reflections to monitor crystal stability and orientation. No intensity decrease was observed during the data collection. Corrections were made for usual Lorentz and polarization effect but not for absorption nor extinction. The two sets of reflection data were averaged for symmetry-related reflections to give 2400 independent reflections (R_{int}=0.024) after confirmation of no significant detection of Bijvoet differences.

Structure Analysis and Refinement

The structure was solved by direct methods with the SHELX86 program.[5] The locations of all the non-hydrogen

Table 3. Bond Lengths (l/Å) and Bond Angles (ϕ/°)

Bond lengths (l/Å)					
O1-C1	1.480(6)	O11-C29	1.195(9)	C9-C10	1.526(8)
O1-C21	1.352(7)	C1-C2	1.530(9)	C9-C11	1.552(9)
O2-C21	1.193(8)	C1-C10	1.513(8)	C10-C20	1.324(8)
O3-C3	1.465(7)	C2-C3	1.533(9)	C11-C12	1.532(9)
O3-C23	1.347(8)	C3-C4	1.549(8)	C12-C13	1.537(8)
O4-C23	1.202(8)	C4-C5	1.543(8)	C13-C14	1.536(7)
O5-C5	1.204(7)	C4-C18	1.55(1)	C13-C16	1.545(8)
O6-C6	1.463(7)	C4-C19	1.532(9)	C15-C16	1.545(8)
O6-C25	1.355(8)	C5-C6	1.545(8)	C16-C17	1.535(9)
O7-C25	1.188(8)	C6-C7	1.546(8)	C21-C22	1.51(2)
O8-C14	1.471(6)	C7-C8	1.538(8)	C23-C24	1.50(2)
O8-C27	1.356(7)	C8-C9	1.576(8)	C25-C26	1.51(1)
O9-C27	1.185(8)	C8-C14	1.538(7)	C27-C28	1.51(1)
O10-C16	1.485(7)	C8-C15	1.570(8)	C29-C30	1.51(2)
O10-C29	1.355(8)				
Bond angles (ϕ/°)					
C1-O1-C21	117.6(4)	C5-C6-C7	112.3(5)	C8-C15-C16	107.4(5)
C3-O3-C23	118.0(5)	C6-C7-C8	117.9(5)	O10-C16-C13	110.2(5)
C6-O6-C25	116.8(5)	C7-C8-C9	112.5(5)	O10-C16-C15	103.2(5)
C14-O8-C27	116.3(5)	C7-C8-C14	116.4(5)	O10-C16-C17	107.2(5)
C16-O10-C29	119.4(5)	C7-C8-C15	108.8(5)	C13-C16-C15	104.1(5)
O1-C1-C2	105.5(5)	C9-C8-C14	107.9(5)	C13-C16-C17	117.7(5)
O1-C1-C10	103.7(5)	C9-C8-C15	108.2(5)	C15-C16-C17	113.5(5)
C2-C1-C10	117.9(5)	C14-C8-C15	102.3(5)	O1-C21-O2	123.2(6)
C1-C2-C3	116.7(6)	C8-C9-C10	115.9(5)	O1-C21-C22	109.5(6)
O3-C3-C2	106.8(5)	C8-C9-C11	110.8(5)	O2-C21-C22	127.2(7)
O3-C3-C4	104.3(5)	C10-C9-C11	112.9(5)	O3-C23-O4	123.4(6)
C2-C3-C4	116.7(5)	C1-C10-C9	113.7(5)	O3-C23-C24	110.6(6)
C3-C4-C5	110.1(5)	C1-C10-C20	121.5(6)	O4-C23-C24	125.9(7)
C3-C4-C18	108.3(5)	C9-C10-C20	124.6(6)	O6-C25-O7	125.2(6)
C3-C4-C19	111.8(5)	C9-C11-C12	115.1(6)	O6-C25-C26	109.7(6)
C5-C4-C18	108.7(5)	C11-C12-C13	113.0(5)	O7-C25-C26	125.1(7)
C5-C4-C19	108.5(5)	C12-C13-C14	106.6(5)	O8-C27-O9	124.7(6)
C18-C4-C19	109.4(6)	C12-C13-C16	112.8(5)	O8-C27-C28	110.5(6)
O5-C5-C4	120.1(6)	C14-C13-C16	103.7(5)	O9-C27-C28	124.9(7)
O5-C5-C6	119.6(5)	O8-C14-C8	107.0(4)	O10-C29-O11	125.0(7)
C4-C5-C6	120.3(5)	O8-C14-C13	111.8(5)	O10-C29-C30	110.2(6)
O6-C6-C5	103.4(5)	C8-C14-C13	102.4(5)	O11-C29-C30	124.8(7)
O6-C6-C7	108.4(5)				

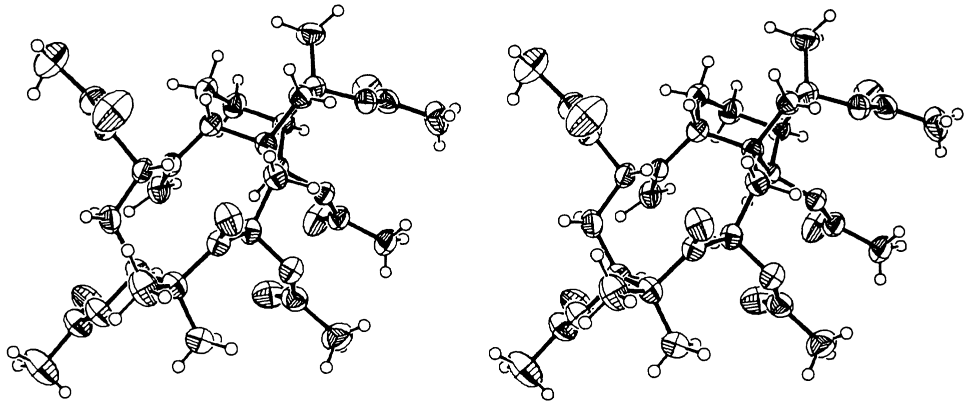

Fig. 2. A stereoscopic view of an ORTEP drawing of the molecule. The thermal ellipsoids correspond to 50% probability level.

atoms were performed by alternatively applying Fourier syntheses and diagonal approximation least-squares.[6] The structure was further refined by the full-matrix least-squares procedure using the FMLS program:[7] the function minimized being $\sum w(F_o-F_c)^2$ with $w=1.0$. Non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were determined from difference Fourier maps and refined isotropically in the subsequent refinements. The final stage of the refinement that has 390 variables yields $R(R_w)=0.037$ (0.035), goodness-of-fit $S=0.379$, and ratio of maximum least-squares shift to error $(\Delta/\sigma)=0.006$ $((\Delta/\sigma)_{mean}=0.001)$ for 2269 non-zero independent reflections with $F_o \geqq 3\sigma(F_o)$. Maximum positive and negative electron densities in the final difference Fourier map were $+0.20$ eÅ^{-3} and -0.10 eÅ^{-3}, respectively. The atomic scattering factors used for non-hydrogen atoms were taken from International Tables[8] and for hydrogen atoms from Stewart et al.[9] The absolute configuration of the molecule was assigned on the basis of internal comparison with the absolute structure of 1,5-seco-grayanotoxin-1(*R*), 3,6,14,16-pentaacetate,[4] except at C1 position. The final atomic parameters are listed in Table 2.[#]

All computations were carried out on an NEC PC-9801 personal computer and an ACOS-S830 computer at the Institute for Protein Research, Osaka University.

Results and Discussion

Figure 1 shows a perspective view of the molecule with atom-numbering scheme. Figure 2 represents an ORTEP-II[10] drawing of the molecule with thermal ellipsoids enclosing 50% probability level. Bond lengths and bond angles, along with their estimated standard deviations, are given in Table 3.

The molecule is based on tricyclic structure with ten-, six-, and five-membered rings. The absolute configuration at C1 atom is S, which is the only difference from 1,5-seco-grayanotoxin-1(*R*),3,6,14,16-penntaacetate in absolute structure and makes a slight alteration to the conformation of about half the ten-membered ring. The ring conformations of the six- and five-membered rings are almost the same as those of 1,5-seco-grayanotoxin-1(*R*),3,6,14,16-pentaacetate. The six-membered ring has a conformation with typical chair form and has a *cis*-junction with the ten-membered ring. The five-membered ring, comprising C8, C15, C16, C13, and C14 atoms, takes an envelope conformation, with C14 atom deviating significantly from the mean plane formed by the remaining four atoms. There are no conspicuous hydrogen bonds within the molecule.

A close intermolecular contact for non-hydrogen atoms is present between O11 and C30 atoms (O11–C30 distance=3.24(1) Å) in the molecule at $(2-x, -1/2+y, 1-z)$. All the other intermolecular atomic distances for non-hydrogen atoms are larger than 3.48 Å and are usual van der Waals distances.

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[#] List of observed and calculated structure factors, anisotropic thermal parameters, and H-atom parameters have been deposited as Document No. 9051 at the Office of the Editor of Bull. Chem. Soc. Jpn.