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Crystal and Molecular Structure of (1*R*,6*S*)-3,6,14,16-Tetrahydroxyspiro[1,5]grayanotoxin-5-one

Mamoru SATO,* Yukiteru KATSUBE, Tadamasa TERAI,† Jun'ichi KATAKAWA,†† and Tadahiro TETSUMI††
Institute for Protein Research, Osaka University, 3-2 Yamada-oka, Suita, Osaka 565
† Department of Applied Chemistry, Osaka Institute of Technology, Omiya 5-16-1, Asahi-ku, Osaka 535
†† Faculty of Pharmaceutical Sciences, Setsunan University, Hirakata, Osaka 573-01

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Synopsis. The three-dimensional structure of a grayanotoxin II derivative, (1*R*,6*S*)-3,6,14,16-tetrahydroxyspiro[1,5]-grayanotoxin-5-one, has been determined by X-ray diffraction at room temperature. The structure was solved by direct methods and refined by the full matrix least-squares method to a final $R=0.043$ for 1436 independent reflections with $F_o \geqq 3\sigma(F_o)$. The molecule is based on a tetracyclic structure and consists of two six-membered and two five-membered rings. The absolute configuration at C(1) atom (spiro atom) was determined as *R* on the basis of internal comparison with the absolute structure of grayanotoxin II.

Grayanotoxins[1—3] are diterpenoids isolated from *Leucothoe grayana Max.* and show the physiological activities dependent on their ring conformations. The skeletal transformation of the grayanotoxins is of increasing importance of diterpenoids as bioactive substances and also of some value as a new route to cyclodecane derivatives. In this standpoint, we have studied *in vitro* conversions of the ring structure of grayanotoxin II 3,6,14,16-tetraacetate by $Pb(OAc)_4$ and $Tl(OAc)_3$[4,5] and showed the responsibility of C(1) position for the interaction with $Pb(OAc)_4$ and $Tl(OAc)_3$. Here, we report on the X-ray crystal-structure determination of the title compound, a ring-conversion product of grayanotoxin II and confirm the chemical evidences to establish the conversion mechanism of the ring structure.

Experimental

(1*R*,6*S*)-3,6,14,16-tetrahydroxyspiro[1,5]grayanotoxin-5-one was synthesized from grayanotoxin II. To a solution of grayanotoxin II (200 mg) in methanol (2 ml), $Pb(OAc)_4$ (500 mg) was added and the solution was stirred at room temperature for 3 h. The mixture was concentrated and extracted with ethyl acetate. The combined ethyl acetate layers were washed with an $Na_2S_2O_3$ aq solution and water, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure to give an oily product. The product was purified by silica-gel column chromatography and then subjected to crystallization for X-ray analysis.

Colorless, plate-like crystals were grown by slow evaporation from the mixture of ethyl acetate and hexane at room temperature. A crystal with approximate dimensions of 0.4×0.3×0.1 mm was selected for data collection on a Rigaku automated four-circle diffractometer equipped with a Rigaku RU200 rotating-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 $56.75° \leqq 2\theta \leqq 60.53°$. The crystal data are given in Table 1.

Table 1. Crystal Data

Mol. formula	$C_{20}H_{30}O_5$
Mol. weight	350.44
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	$a/\text{Å}=11.867(1)$ $b/\text{Å}=6.9005(4)$ $c/\text{Å}=11.0012(5)$ $\beta/°=98.376(5)$
$V/\text{Å}^3$	891.2(1)
Z	2
$D_c/\text{g cm}^{-3}$	1.306
$\mu(\text{Cu } K\alpha)/\text{cm}^{-1}$	7.59
$F(000)$	380

Integrated intensities were measured by the θ–2θ scan technique using Ni-filtered Cu $K\alpha$ radiation ($\lambda=1.5418$ Å) and a monitor count technique. The scan width was $\Delta\theta=(1.5+0.15 \tan\theta)°$ and scan speed 2° min^{-1}. Background intensities were measured for 7 s at both ends of a scan. Two sets of reflection data; *hkl* range, $-13 \leqq h \leqq 13$, $-7 \leqq k \leqq 7$, $0 \leqq l \leqq 12$, a total of 2820 reflections were collected up to $2\theta=120°$, and 20 reflections were considered as unobserved. Three standard reflections (622, 126, and 007) were measured every 150 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 over symmetry-related reflections to give 1457 independent reflections ($R_{\text{int}}=0.012$) after confirmation of no significant detection of Bijvoet differences.

Structure Analysis and Refinement

The structure was solved by direct methods with the SHELX86 program.[6] The atomic positions obtained from the direct method were automatically assessed and confirmed by alternatively applying Fourier syntheses and diagonal approximation least-squares that refine the atomic positions and their occupancies, instead of isotropic temperature factors.[7] The structure was then refined by the full-matrix least-squares procedure using the FMLS program:[8] the function minimized being $\Sigma w(F_o-F_c)^2$ with $w=1.0$. Non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were determined from difference Fourier maps and refined isotropically. The final stage of the refinement that has 346 variables yields $R(R_w)=$

0.043 (0.052), goodness-of-fit $S=0.537$, and ratio of maximum least-squares shift to error $(\Delta/\sigma)_{\max}=0.119$ $((\Delta/\sigma)_{\text{mean}}=0.014)$ for 1436 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 $+0.25$ e Å^{-3} and -0.15 e Å^{-3}, respectively. The atomic scattering factors used for non-hydrogen atoms were taken from International Tables[9] and for hydrogen atoms form Stewart et al.[10] The absolute configuration of the molecule was assigned on the basis of internal comparison with the absolute structure of grayanotoxin II.[2] The final atomic parameters are listed in Table 2.[#] All computations were carried out on an NEC PC-9801 personal computer.

Results and Discussion

Figure 1 shows a chemical structure of the molecule with atom-numbering scheme. Figure 2 represents an ORTEP-II[11] 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.

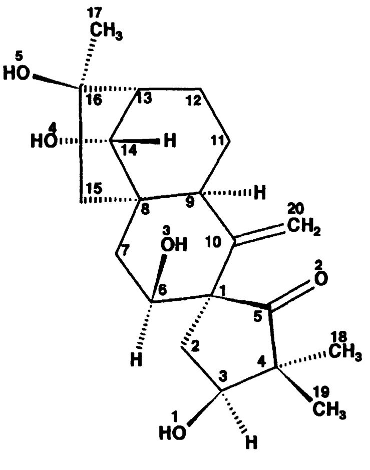

Fig. 1. A chemical structure of the molecule with the atom-numbering scheme.

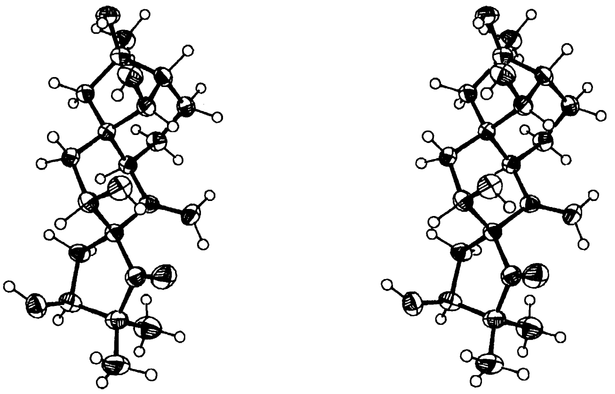

Fig. 2. A stereoscopic view of an ORTEP drawing of the molecule. The thermal ellipsoids correspond to 50% probability level.

The molecule is based on a tetracyclic structure with two six- and two five-membered rings, with *R* configuration at C(1) position. The six-membered ring consisting of C(8), C(9), C(11), C(12), C(13), and C(14) atoms takes a conformation with typical chair form and has a cis-junction with the other six-membered ring, which has a chair conformation deformed slightly due to the double bond between C(10) and C(20) atoms. The two five-membered ring, composed of C(1), C(2), C(3), C(4), and C(5) atoms and of C(8), C(15), C(16), C(13), and C(14) atoms, takes envelope conformations, with respective C(3) and C(14) atoms deviating significantly from the mean planes formed by the remaining four atoms.

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

Atom	x	y	z	B_{eq}/Å^2
O(1)	−0.6252(4)	0.482(0)	0.5575(4)	3.4(1)
O(2)	−0.4433(4)	0.782(1)	0.8030(4)	3.9(2)
O(3)	−0.2884(4)	0.729(1)	0.6450(5)	3.1(1)
O(4)	−0.0340(4)	0.602(1)	0.6339(4)	3.2(1)
O(5)	0.1055(4)	0.299(1)	0.6056(4)	3.5(2)
C(1)	−0.3956(5)	0.462(2)	0.7292(5)	2.3(2)
C(2)	−0.4799(5)	0.293(2)	0.6875(6)	2.8(2)
C(3)	−0.6002(5)	0.386(2)	0.6724(6)	3.1(2)
C(4)	−0.5930(5)	0.539(2)	0.7751(5)	3.0(2)
C(5)	−0.4732(5)	0.618(2)	0.7758(5)	2.8(2)
C(6)	−0.3458(5)	0.547(2)	0.6165(5)	2.6(2)
C(7)	−0.2607(5)	0.410(2)	0.5716(5)	2.4(2)
C(8)	−0.1660(4)	0.338(2)	0.6720(5)	2.3(2)
C(9)	−0.2215(5)	0.250(2)	0.7786(5)	2.4(2)
C(10)	−0.2983(5)	0.398(2)	0.8278(5)	2.5(2)
C(11)	−0.1314(5)	0.155(2)	0.8760(6)	3.0(2)
C(12)	−0.0212(5)	0.275(2)	0.9050(5)	3.0(2)
C(13)	0.0178(5)	0.363(2)	0.7898(5)	2.7(2)
C(14)	−0.0785(5)	0.492(2)	0.7263(5)	2.5(2)
C(15)	−0.0895(5)	0.184(2)	0.6197(6)	2.7(2)
C(16)	0.0339(5)	0.215(2)	0.6878(5)	3.0(2)
C(17)	0.0952(6)	0.028(2)	0.7321(7)	3.7(2)
C(18)	−0.5967(7)	0.440(2)	0.9007(7)	4.5(3)
C(19)	−0.6806(7)	0.701(2)	0.7560(8)	4.2(3)
C(20)	−0.2846(6)	0.464(2)	0.9417(5)	3.6(2)

a) Equivalent isotropic B_{eq} defined as $B_{\text{eq}}=(4/3)\Sigma\Sigma B_{ij}\,a_i\cdot a_j$.

Intramolecular hydrogen bonds are formed between O(2) and O(3) atoms, with the O(3) atom as a hydrogen (H(2)) donor, and between O(4) and O(5) atoms, with the O(5) atom as a hydrogen (H(4)) donor. H-(3) atom that binds to O(4) atom participates in the formation of the intermolecular hydrogen bond to O-(5) atom of the molecule at $(-x,\ 0.5+y,\ 1-z)$. The geometrical parameters of the intramolecular and intermolecular hydrogen bonds are given in Table 4. All the

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[#] List of observed and calculated structure factors, anisotropic thermal parameters and hydrogen atom parameters have been deposited as Document No. 66045 at the Office of the Editor of Bull. Chem. Soc. Jpn..

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

Bond lengths (l/Å)					
O(1)-C(3)	1.421(9)	C(3)-C(4)	1.54(2)	C(9)-C(10)	1.52(2)
O(2)-C(5)	1.21(2)	C(4)-C(5)	1.52(2)	C(9)-C(11)	1.55(2)
O(3)-C(6)	1.44(1)	C(4)-C(18)	1.55(2)	C(10)-C(20)	1.32(2)
O(4)-C(14)	1.43(1)	C(4)-C(19)	1.52(2)	C(11)-C(12)	1.54(2)
O(5)-C(16)	1.45(1)	C(6)-C(7)	1.52(2)	C(12)-C(13)	1.54(2)
C(1)-C(2)	1.56(2)	C(7)-C(8)	1.54(1)	C(13)-C(14)	1.53(2)
C(1)-C(5)	1.55(2)	C(8)-C(9)	1.55(1)	C(13)-C(16)	1.55(2)
C(1)-C(6)	1.56(2)	C(8)-C(14)	1.55(2)	C(15)-C(16)	1.56(2)
C(1)-C(10)	1.53(2)	C(8)-C(15)	1.56(2)	C(16)-C(17)	1.52(2)
C(2)-C(3)	1.55(2)				

Bond angles (ϕ/°)			
C(2)-C(1)-C(5)	103.2(6)	C(7)-C(8)-C(15)	111.1(6)
C(2)-C(1)-C(6)	110.3(6)	C(9)-C(8)-C(14)	108.3(6)
C(2)-C(1)-C(10)	112.0(7)	C(9)-C(8)-C(15)	110.3(6)
C(5)-C(1)-C(6)	108.4(6)	C(14)-C(8)-C(15)	102.5(6)
C(5)-C(1)-C(10)	113.0(7)	C(8)-C(9)-C(10)	110.4(6)
C(6)-C(1)-C(10)	109.7(6)	C(8)-C(9)-C(11)	111.3(6)
C(1)-C(2)-C(3)	105.3(7)	C(10)-C(9)-C(11)	115.4(7)
O(1)-C(3)-C(2)	110.9(7)	C(1)-C(10)-C(9)	111.9(7)
O(1)-C(3)-C(4)	108.3(7)	C(1)-C(10)-C(20)	123.2(8)
C(2)-C(3)-C(4)	104.6(7)	C(9)-C(10)-C(20)	124.9(8)
C(3)-C(4)-C(5)	101.6(7)	C(9)-C(11)-C(12)	113.3(7)
C(3)-C(4)-C(18)	110.4(7)	C(11)-C(12)-C(13)	113.0(7)
C(3)-C(4)-C(19)	116.0(8)	C(12)-C(13)-C(14)	108.2(7)
C(5)-C(4)-C(18)	107.5(7)	C(12)-C(13)-C(16)	114.6(7)
C(5)-C(4)-C(19)	111.0(8)	C(14)-C(13)-C(16)	102.5(7)
C(18)-C(4)-C(19)	109.8(8)	O(4)-C(14)-C(8)	112.8(7)
O(2)-C(5)-C(1)	124.2(8)	O(4)-C(14)-C(13)	107.6(7)
O(2)-C(5)-C(4)	125.2(8)	C(8)-C(14)-C(13)	101.0(6)
C(1)-C(5)-C(4)	110.6(7)	O(8)-C(15)-C(16)	106.8(7)
O(3)-C(6)-C(1)	112.0(6)	O(5)-C(16)-C(13)	109.3(7)
O(3)-C(6)-C(7)	107.3(6)	O(5)-C(16)-C(15)	110.4(7)
C(1)-C(6)-C(7)	111.9(6)	O(5)-C(16)-C(17)	104.0(7)
C(6)-C(7)-C(8)	114.9(7)	C(13)C(16)-C(15)	103.3(7)
C(7)-C(8)-C(9)	108.9(6)	C(13)-C(16)-C(17)	115.5(7)
C(7)-C(8)-C(14)	115.6(6)	C(15)-C(16)-C(17)	114.4(7)

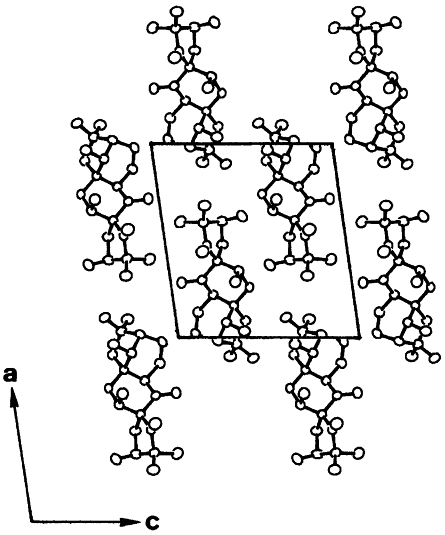

Fig. 3. Crystal structure of the molecules viewed along the *b* axis. Hydrogen atoms are omitted for clarity.

Table 4. Summary of Intramolecular and Intermolecular Hydrogen Bonds, X–H···Y

X	H	Y	X···Y (l/Å)	H···Y (l/Å)	X–H···Y (ϕ/°)
Intramolecular hydrogen bonds					
O(3)	H(2)	O(2)	2.732(9)	2.1(1)	140(10)
O(5)	H(4)	O(4)	2.712(9)	2.0(1)	132(9)
Intermolecular hydrogen bond					
O(4)	H(3)	O(5)$^{a)}$	2.977(5)	2.2(1)	126(8)

a) Atom with an equivalent position of ($-x$, $0.5+y$, $1-z$).

other intermolecular atomic distances for non-hydrogen atoms are usual van der Waals distances. The crystal structure viewed along the *b* axis is shown in Fig. 3.

References

1) P. Narayanan, M. Rohrl, K. Zechmeister, and W. Hoppe, *Tetrahedron Lett.*, **1970**, 3943.

2) A. Furusaki, N. Hamanaka, and T. Matsumoto, *Bull. Chem. Soc. Jpn.*, **53**, 1956 (1980), see also references cited

therein.

3) P. W. Codding, *J. Am. Chem. Soc.*, **106**, 7905 (1984).

4) T. Terai, H. Meguri, N. Hamanaka, T. Matsuzaki, A. Furusaki, T. Kato, and T. Matsumoto, *Chem. Lett.*, **1980**, 1111.

5) M. Sato, Y. Katsube, T. Terai, J. Katakawa, and T. Tetsumi, *Bull. Chem. Soc. Jpn.*, **65**, 3482 (1992).

6) G. M. Sheldrick, "Program for the Solution of Crystal Structuers," University of Göttingen, Germany (1986).

7) N. Tanaka, K. Yamanouchi, Y. Katsube, and T. Ashida, *J. Crystallogr. Soc. Jpn.*, **31**, 27 (1989).

8) T. Ashida, "The Universal Crystallographic Computing System-Osaka," The Computing Center, Osaka University, Japan (1979), p. 60.

9) "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham (1974), Vol. IV.

10) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

11) C. K. Johnson, "ORTEP-II, Report ORLN-5138," Oak Ridge National Laboratory, Tennessee, U.S.A. (1976).