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# Ring Transformation of a Diterpenoid Grayanol Derivative into 1-*epi*-Leucothol

JINSAKU SAKAKIBARA,*,[a] TOYO KAIYA,[a] and YOICHI IITAKA[b]

*Faculty of Pharmaceutical Sciences, Nagoya City University,[a] 3–1 Tanabe-dori,
Mizuho-ku, Nagoya 467, Japan and Faculty of Pharmaceutical Sciences,
University of Tokyo,[b] 7–3–1 Hongo, Bunkyo-ku,
Tokyo 113, Japan*

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Acidic treatment of a grayanol derivative (**3**), easily formed from grayanotoxin-II (**1**), afforded a novel cyclization product (**7**), whose structure was elucidated as 3(*S*),20 : 5(*R*),10(*R*)-diepoxy-14(*R*),16(*R*)-dihydroxy-1-*epi*-leucothane by direct X-ray crystallographic analysis.

**Keywords**——grayanotoxin; grayanol; leucothol; grayanotoxin-II; *Leucothoe grayana*; 3(*S*),20 : 5(*R*),10(*R*)-diepoxy-14(*R*),16(*R*)-dihydroxy-1-*epi*-leucothane; X-ray analysis; acid-catalyzed reaction

Various diterpenoids have been isolated from *Leucothoe grayana* MAX. (*Ericaceae*), and classified into three structural groups: grayanotoxins (**1**), leucothols (**2**), and grayanolds (**3**).[1] We have been studying the interconversion of these skeletons by using metallic salts, and succeeded in the transformation of grayanotoxin-II(G-II) (**1**) into leucothol D (**2**)[1] and grayanol B (**3**).[2] During the study, we obtained an epoxy compound (**4**), a grayanol derivative, from **1** by the reaction with thallium (III) nitrate.[3] The structure of **4** was finally established by X-ray diffraction analysis of its reduction product (**5**). However, in the course of the structure determination, compound **5** was treated with *p*-toluenesulfonic acid in acetone in order to synthesize an acetonide, and two products **6** and **7** were obtained in 48 and 32% yields, respectively.

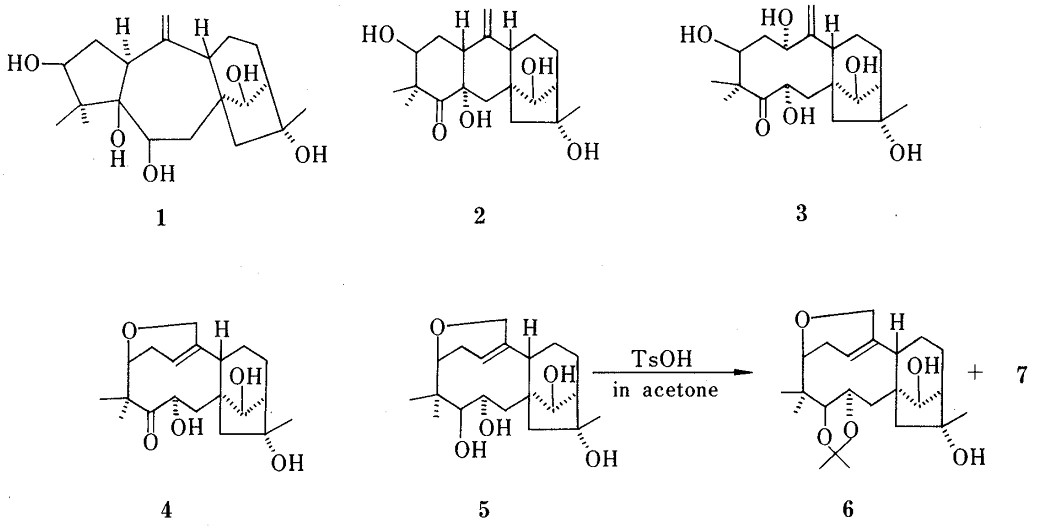
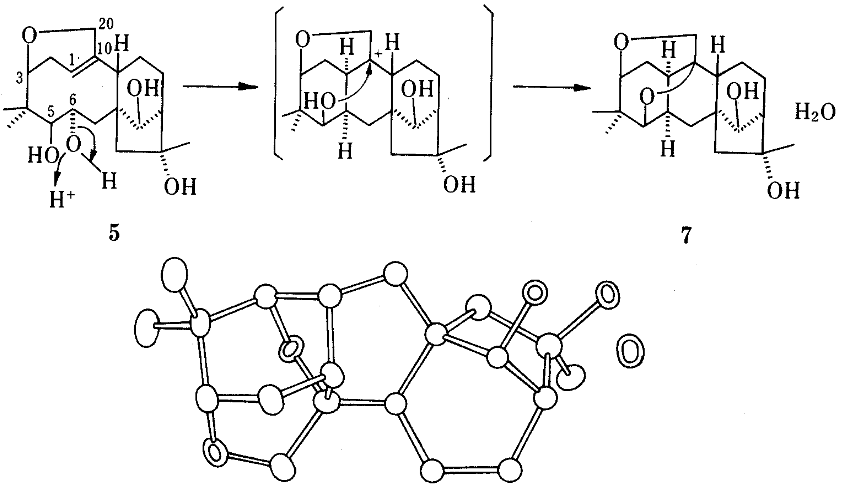


Chart 1

Compound **6**, viscous syrup, had a molecular formula of $C_{23}H_{36}O_5$ as determined from the mass spectrum (MS). Its proton nuclear magnetic resonance ($^1$H-NMR) spectrum showed the presence of five tertiary methyls (δ 1.01, 1.07, 1.27, 1.37 and 1.40), a one-proton singlet at δ 4.52 characteristic of the C-14 proton, and a one-proton multiplet at δ 5.64 assignable to the C-1 proton. Thus the structure of **6** was concluded to be the desired acetonide of **5**.

Compound **7**, $C_{20}H_{30}O_4 \cdot H_2O$ mp 204—206 °C, was also obtained by treatment of **5** ($C_{20}H_{32}O_5$) with *p*-toluenesulfonic acid in methanol instead of acetone in 86% yield. Therefore **7** must be an acid-catalyzed reaction product of **5**. The $^{13}$C-NMR spectrum of **7**



**5** **7**

Chart 2

TABLE I. Atomic Parameters for the Crystal of 7

| Atom | *x* | *y* | *z* | B11 | B22 | B33 | B12 | B13 | B23 |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 7716 (4) | 8727 (2) | 6115 (6) | 61 (3) | 13 (1) | 117 (7) | 3 (1) | −5 (4) | 0 (2) |
| C(2) | 8507 (4) | 8502 (2) | 4447 (6) | 74 (3) | 20 (1) | 141 (9) | 5 (1) | 16 (5) | −2 (2) |
| C(3) | 9396 (4) | 8125 (2) | 5522 (8) | 68 (3) | 16 (1) | 223 (12) | 4 (1) | 31 (6) | −10 (2) |
| C(4) | 10040 (4) | 8443 (2) | 7224 (8) | 49 (3) | 15 (1) | 210 (11) | 5 (1) | 15 (5) | 1 (2) |
| C(5) | 9144 (4) | 8751 (2) | 8585 (6) | 51 (3) | 14 (1) | 156 (9) | 2 (1) | 0 (5) | −4 (2) |
| C(6) | 8300 (3) | 9141 (1) | 7515 (7) | 52 (3) | 11 (1) | 186 (9) | −1 (1) | 5 (5) | 1 (2) |
| C(7) | 7399 (3) | 9365 (2) | 9072 (7) | 44 (3) | 13 (1) | 214 (10) | −1 (1) | 3 (5) | −12 (2) |
| C(8) | 6203 (3) | 9048 (2) | 9243 (6) | 42 (3) | 13 (1) | 151 (8) | 0 (1) | −10 (4) | −8 (2) |
| C(9) | 6294 (3) | 8400 (1) | 8768 (6) | 45 (2) | 12 (1) | 155 (8) | 1 (1) | 0 (4) | −4 (2) |
| C(10) | 7445 (3) | 8272 (1) | 7733 (6) | 53 (3) | 11 (1) | 135 (8) | −1 (1) | −8 (4) | −3 (2) |
| C(11) | 5267 (4) | 8182 (2) | 7513 (8) | 53 (3) | 14 (1) | 210 (10) | −2 (1) | −14 (5) | −13 (2) |
| C(12) | 4085 (4) | 8396 (2) | 8287 (8) | 50 (3) | 16 (1) | 230 (11) | −2 (1) | −6 (6) | −8 (2) |
| C(13) | 4137 (3) | 9032 (2) | 8824 (6) | 45 (3) | 14 (1) | 155 (8) | 4 (1) | −8 (5) | −2 (2) |
| C(14) | 5234 (3) | 9296 (1) | 7894 (6) | 49 (3) | 12 (1) | 147 (9) | 4 (1) | −7 (5) | −2 (2) |
| C(15) | 5667 (4) | 9135 (2) | 11396 (7) | 53 (3) | 17 (1) | 138 (8) | 3 (1) | −7 (5) | −11 (2) |
| C(16) | 4325 (4) | 9151 (2) | 11138 (7) | 58 (3) | 13 (1) | 150 (9) | 2 (1) | −2 (5) | 0 (2) |
| C(17) | 10734 (4) | 8031 (2) | 8559 (10) | 66 (4) | 22 (1) | 357 (18) | 13 (2) | 7 (8) | 28 (4) |
| C(18) | 10910 (5) | 8862 (2) | 6246 (9) | 66 (3) | 20 (1) | 284 (14) | 1 (1) | 37 (7) | 6 (3) |
| C(19) | 3653 (4) | 8786 (2) | 12599 (8) | 76 (4) | 20 (1) | 183 (10) | −6 (2) | 10 (6) | 9 (3) |
| C(20) | 7625 (4) | 7695 (2) | 6867 (10) | 71 (4) | 13 (1) | 329 (15) | 3 (1) | 22 (7) | −10 (3) |
| O(1) | 8820 (3) | 7630 (1) | 6228 (6) | 74 (3) | 12 (0) | 353 (11) | 5 (1) | 42 (5) | −5 (2) |
| O(2) | 8320 (2) | 8335 (1) | 9312 (4) | 48 (2) | 16 (0) | 144 (6) | 1 (1) | −7 (3) | 9 (1) |
| O(3) | 5202 (3) | 9892 (1) | 8147 (5) | 71 (2) | 11 (0) | 180 (7) | 2 (1) | 0 (4) | 2 (1) |
| O(4) | 3907 (3) | 9717 (1) | 11515 (5) | 69 (2) | 15 (0) | 190 (7) | 7 (1) | 10 (4) | −4 (2) |
| O(W) | 3541 (3) | 10182 (2) | 5419 (6) | 84 (3) | 27 (1) | 214 (9) | 15 (1) | −22 (5) | 1 (2) |

Fractional coordinates of atoms, *x*, *y* and *z* are multiplied by $10^4$.
The temperature factors are of the form:
$T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$, where $\beta_{ij}$'s are multiplied by $10^4$.

disclosed the presence of the following groups: three methyls, five methylenes, four methines, two quaternary carbons, a methylene adjacent to oxygen, three methines adjacent to oxygen, and two tertiary carbinyl carbons. These data indicate that dehydration of **5** and saturation of its double bond had occurred, followed by C–C and C–O bond formations. However, as no carbon framework of **7** could be deduced from the above spectral evidence, a direct X-ray crystallographic analysis was carried out in order to determine the structure of **7**. A drawing of the stereostructure is shown in Chart 2. Thus, **7** was established as 3(*S*),20;5(*R*),10(*R*)-diepoxy-14(*R*),16(*R*)-dihydroxy-1-*epi*-leucothane, that is, a novel hexacyclic compound possessing two ether rings. A possible reaction mechanism is as follows: initially the C-6 hydroxyl group is removed by acid, followed by C–C bond formation between C-1 and C-6, when the C-1 proton is α-oriented because of the presence of the 3$\beta$,20-epoxy ring. Then an ether linkage is formed by attack of the C-5 hydroxyl gorup on C-10.

Thus, the linkage between C-1 and C-5 of G-II (**1**) was cleaved by thallium (III) nitrate, giving a compound with a ten-membered ring (**4**). Then ring closure occurred again between C-1 and C-6 in the presence of an acid to afford **7**, with a different ring structure from the starting material.

## Experimental

Melting points were measured with a micro melting point apparatus (Yanaco) and are uncorrected. Infrared (IR)

TABLE II. Bond Lengths in Å

| Atom 1 | | Atom 2 | Length | (Std) |
|---|---|---|---|---|
| C(1) | – | C(2) | 1.523 | (6) |
| C(1) | – | C(6) | 1.512 | (6) |
| C(1) | – | C(10) | 1.555 | (5) |
| C(2) | – | C(3) | 1.538 | (7) |
| C(3) | – | C(4) | 1.544 | (7) |
| C(3) | – | O(1) | 1.436 | (6) |
| C(4) | – | C(5) | 1.553 | (6) |
| C(4) | – | C(17) | 1.545 | (7) |
| C(4) | – | C(18) | 1.557 | (7) |
| C(5) | – | C(6) | 1.520 | (6) |
| C(5) | – | O(2) | 1.457 | (5) |
| C(6) | – | C(7) | 1.552 | (6) |
| C(7) | – | C(8) | 1.576 | (5) |
| C(8) | – | C(9) | 1.590 | (5) |
| C(8) | – | C(14) | 1.543 | (5) |
| C(8) | – | C(15) | 1.558 | (6) |
| C(9) | – | C(10) | 1.519 | (6) |
| C(9) | – | C(11) | 1.532 | (6) |
| C(10) | – | C(20) | 1.513 | (6) |
| C(10) | – | O(2) | 1.453 | (5) |
| C(11) | – | C(12) | 1.538 | (6) |
| C(12) | – | C(13) | 1.570 | (6) |
| C(13) | – | C(14) | 1.536 | (5) |
| C(13) | – | C(16) | 1.563 | (6) |
| C(14) | – | O(3) | 1.443 | (4) |
| C(15) | – | C(16) | 1.552 | (6) |
| C(16) | – | C(19) | 1.512 | (6) |
| C(16) | – | O(4) | 1.463 | (5) |
| C(20) | – | O(1) | 1.444 | (6) |

Std: standard deviation.

Table III. Valency Angles in Degrees

| Atom 1 | | Atom 2 | | Atom 3 | Angle | (Std) |
|---|---|---|---|---|---|---|
| C(2) | – | C(1) | – | C(6) | 114.0 | (3) |
| C(2) | – | C(1) | – | C(10) | 111.3 | (3) |
| C(6) | – | C(1) | – | C(10) | 97.7 | (3) |
| C(3) | – | C(2) | – | C(1) | 105.9 | (4) |
| C(4) | – | C(3) | – | C(2) | 111.1 | (4) |
| C(4) | – | C(3) | – | O(1) | 113.3 | (4) |
| C(2) | – | C(3) | – | O(1) | 109.2 | (4) |
| C(5) | – | C(4) | – | C(3) | 109.6 | (4) |
| C(5) | – | C(4) | – | C(17) | 108.7 | (4) |
| C(5) | – | C(4) | – | C(18) | 110.8 | (4) |
| C(3) | – | C(4) | – | C(17) | 110.0 | (4) |
| C(3) | – | C(4) | – | C(18) | 109.1 | (4) |
| C(17) | – | C(4) | – | C(18) | 108.5 | (4) |
| C(6) | – | C(5) | – | C(4) | 116.8 | (3) |
| C(6) | – | C(5) | – | O(2) | 99.2 | (3) |
| C(4) | – | C(5) | – | O(2) | 107.0 | (3) |
| C(7) | – | C(6) | – | C(1) | 109.5 | (3) |
| C(7) | – | C(6) | – | C(5) | 109.5 | (3) |
| C(1) | – | C(6) | – | C(5) | 99.2 | (3) |
| C(8) | – | C(7) | – | C(6) | 117.4 | (3) |
| C(9) | – | C(8) | – | C(7) | 113.7 | (3) |
| C(9) | – | C(8) | – | C(14) | 108.2 | (3) |
| C(9) | – | C(8) | – | C(15) | 109.6 | (3) |
| C(7) | – | C(8) | – | C(14) | 113.7 | (3) |
| C(7) | – | C(8) | – | C(15) | 110.2 | (3) |
| C(14) | – | C(8) | – | C(15) | 100.7 | (3) |
| C(10) | – | C(9) | – | C(8) | 110.1 | (3) |
| C(10) | – | C(9) | – | C(11) | 111.1 | (3) |
| C(8) | – | C(9) | – | C(11) | 112.9 | (3) |
| C(20) | – | C(10) | – | C(1) | 111.0 | (3) |
| C(20) | – | C(10) | – | C(9) | 118.2 | (4) |
| C(20) | – | C(10) | – | O(2) | 105.6 | (3) |
| C(1) | – | C(10) | – | C(9) | 109.8 | (3) |
| C(1) | – | C(10) | – | O(2) | 106.2 | (3) |
| C(9) | – | C(10) | – | O(2) | 105.1 | (3) |
| C(12) | – | C(11) | – | C(9) | 112.8 | (4) |
| C(13) | – | C(12) | – | C(11) | 111.4 | (4) |
| C(14) | – | C(13) | – | C(12) | 110.0 | (3) |
| C(14) | – | C(13) | – | C(16) | 101.5 | (3) |
| C(12) | – | C(13) | – | C(16) | 113.7 | (3) |
| O(3) | – | C(14) | – | C(8) | 109.5 | (3) |
| O(3) | – | C(14) | – | C(13) | 110.0 | (3) |
| C(8) | – | C(14) | – | C(13) | 101.8 | (3) |
| C(16) | – | C(15) | – | C(8) | 107.2 | (3) |
| C(19) | – | C(16) | – | C(13) | 116.3 | (4) |
| C(19) | – | C(16) | – | C(15) | 115.0 | (4) |
| C(19) | – | C(16) | – | O(4) | 105.2 | (3) |
| C(13) | – | C(16) | – | C(15) | 103.9 | (3) |
| C(13) | – | C(16) | – | O(4) | 106.8 | (3) |
| C(15) | – | C(16) | – | O(4) | 109.3 | (3) |
| O(1) | – | C(20) | – | C(10) | 109.7 | (4) |
| C(3) | – | O(1) | – | C(20) | 116.4 | (4) |
| C(5) | – | O(2) | – | C(10) | 106.6 | (3) |

spectra were recorded on an EPI-G3 spectrometer (Hitachi). $^1$H- and $^{13}$C-NMR spectra were taken on JNM-MH 100 (JEOL) and JNM-FX 100 (JEOL) spectrometers at 100 and 25.1 MHz, respectively, with tetramethylsilane as an internal standard ($\delta$ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were measured with an M-52 spectrometer (Hitachi) at 20 eV. Column chromatography and preparative thin-layer chromatography (PTLC) were carried out with Silica gel 60 (70—230 mesh, Merck) and Silica gel 60 $PF_{254}$ (Merck), respectively.

**Reaction of 5 with *p*-Toluenesulfonic Acid (TsOH) in Acetone**——TsOH (40 mg) was added to a suspension of **5** (40 mg) in acetone (2 ml). The reaction mixture was kept at 5 °C overnight, then diluted with $H_2O$, neutralized with 10% $K_2Co_3$ solution, and extracted with AcOEt. The AcOEt extract was subjected to PTLC (eluent: $C_6H_6$–AcOEt (1 : 1)) to afford **6** (21 mg, 48%) and **7** (13 mg, 32%).

**Acetonide of 5 (6)**——Viscous syrup. MS *m/z*: 392 ($M^+$, $C_{23}H_{36}O_5$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.01, 1.07, 1.27, 1.37, 1.40 (each 3H, s), 3.62—4.10 (4H, m), 4.32 (1H, m), 4.52 (1H, s, $C_{14}$–H), 5.64 (1H, m, $C_1$–H).

**Reaction of 5 with TsOH in MeOH**——TsOH (30 mg) was added to a solution of **5** (33 mg) in MeOH (3 ml). The reaction mixture was kept for 3 h at room temperature, then diluted with $H_2O$, neutralized with 10% KOH solution, and extracted with AcOEt. The AcOEt extract was purified by PTLC (eluent: $CHCl_3$–MeOH (9 : 1)) and recrystallized from AcOEt to give 28 mg (86%) of **7**.

**3(*S*),20;5(*R*),10(*R*)-Diepoxy-14(*R*),16(*R*)-dihydroxy-1-*epi*-leucothane (7)**——Colorless needles, mp 204—206 °C. *Anal.* Calcd for $C_{20}H_{30}O_4 \cdot H_2O$; C, 68.15; H, 9.15. Found: C, 68.16; H, 9.38. MS *m/z*: 334 ($M^+$). IR $\nu_{max}$ cm$^{-1}$: 3315, 3.72 (2H, s), 4.18 (1H, s). $^{13}$C-NMR ($C_5D_5N$) $\delta$: 21.7, 24.9, 26.7 (each q), 20.1, 23.3, 25.9, 34.8, 61.3 (each t), 33.0, 40.0, 53.5, 55.7 (each d), 40.8, 48.1 (each s), 65.4 (–$CH_2$ –O–), 77.0, 79.6, 88.7 (each >CH–O–), 80.5, 84.0 (each $-\overset{|}{\underset{|}{C}}-O-$).
O–).

**X-Ray Analysis of 7**——The crystals, grown from an AcOEt solution, were colorless bisphenoidal ones. A sample with approximate dimensions of 0.5 × 0.4 × 0.3 mm was chosen for the X-ray diffraction study. The lattice parameters and intensities were measured on a Philips PW 1100 diffractometer using Cu$K\alpha$ radiation monochromated by means of a graphite plate. The intensities of 2165 reflections were measured within a $2\Theta$ range of 156° as being above the $2\sigma$ (I) level out of 2218 theoretical ones in the same angular range.

Crystal data for **5**: $C_{20}H_{30}O_4 \cdot H_2O$, MW = 352.5, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 11.489$ (11), $b = 24.010$ (20), $c = 6.577$ (7) Å.

The crystal structure was solved by the direct method using MULTAN[5] and refined by the block-diagonal least-squares method. The final *R* value was 0.08, including anisotropic temperature factors. No hydrogen atom contributions were taken into account. The final atomic parameters are listed in Table I and the bond lengths and valency angles in Tables II and III, respectively.

## References and Notes

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