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TRANSFORMATION OF GRAYANOTOXIN II TETRAACETATE TO A 1,5-SECOGRAYANANE DERIVATIVE

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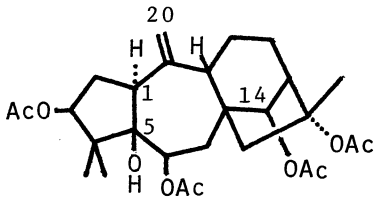
Irradiation of grayanotoxin II tetraacetate with UV light in the presence of lead tetraacetate in benzene afforded 1-epi-grayanol A pentaacetate in high yield.

As shown in previous papers, grayathol A[1] and leucothols[2], modified grayanoid diterpenes isolated from Leucothoe grayana Max., possess the C_1 atom antipodal to that of grayanotoxins. Occurrence of the 1,5-secograyanotoxins, grayanols A (2a) and B[3], in the same plant together with the above three kinds of diterpenes suggests that the 1,5-seco compounds are the possible biogenetic precursors for grayathol and leucothols, and even for grayanotoxins. In the present paper we report the in vitro conversion of a grayanotoxin derivative to a 1,5-secograyanane derivative.



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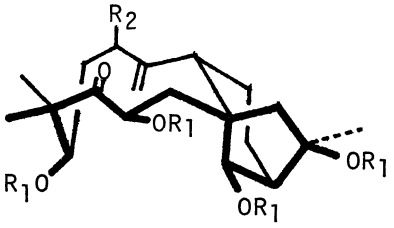
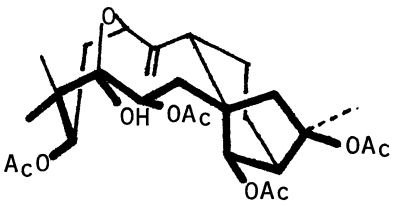


2 R_1= Ac, R_2= β-OAc

2a R_1= H, R_2= α-OH



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Irradiation of grayanotoxin II tetraacetate (1) in the presence of $Pb(OAc)_4$ (1.2 mol, rt, 3.5 h, benzene soln, high pressure Hg lamp) afforded, after usual workup, a pentaacetate 2,[4,5] $C_{30}H_{42}O_{11}$[6], mp 137 140 °C, in an 81% yield. The ^1H and ^{13}C nmr spectra[5] of 2 showed that an allylic secondary acetoxyl group

(δ_H 5.20, δ_C 71.1, d) and a carbonyl group (δ_C 212.1, s) were newly formed. Since it is already known[7] that similar treatment cleaves the C_5—C_{10} bond of 5α-hydroxy-steroids to give the corresponding 1(10)-cyclodecen-5-ones, the above findings were interpreted to indicate formation of a 1,5-secograyanotoxin derivative. Comparison of ^{1}H nmr data of 2 with those of grayanol pentaacetates[8], however, revealed that the product was neither pentaacetylgrayanol A nor B.

Mild alkaline alcoholysis (EtOH, $NaBH_4$ (6 mol, as a base), rt, 3 h) of 2 splits off a molecule of acetic acid to give hemiketal 3[9] (δ_C 100.5, s, no carbonyl carbon atom), $C_{28}H_{40}O_{10}$[6], mp 202—204 °C, in a 75% yield. The nmr spectrum of 3 in the presence of Eu(fod)$_3$ indicated that Eu^{3+} coordinated mainly around the O atom at C_3[10] and large induced shifts were observed for protons at C_3, C_6 and C_{20} [S($CDCl_3$): 7.20 (C_3-H), 3.94 (C_6-H), 4.22 (C_{20}-H), 2.72 (C_{20}-H), 1.96 (C_4-Me), 1.27 (C_4-Me), 1.80 (C_1-H), 0.96 (C_{14}-H), 0.92 (C_{16}-Me), 2.20 (Ac), 2.10 (Ac), 1.22 (Ac), 0.90 (Ac)]. These shift values as well as the observed J values[9] of 3 are compatible only with the stereostructure depicted above. Accordingly the parent compound 2 is formulated as 1-epi-grayanol A tetraacetate. Comparison of the J values of 2[5] and 3[9] shows that conformations of the two compounds are similar to each other. The ten-membered ring of 2 therefore adopts predominantly the BCC[11] conformation in the solution state, although it may be flexible to some extent.

Unambiguous proof for the proposed structure 2 was provided by X-ray analysis of a single crystal of 2. The crystal data for the chloroform-d solvate of 2 are as follows: tetragonal, space group $P4_32_12$, a=11.012(2), c=56.154(6) Å, Z=8, D_c=1.246 gcm^{-3}. 3173 unique intensity data for 2θ<140° were collected on an automatic, four-circle diffractometer with Ni-filtered Cu Kα radiation. The structure was solved by the Monte Carlo direct method[12], using the 40 strongest reflections as the starting set. The 189th random phase set led to the correct solution; an E-map based on 825 phases afforded 38 out of the 45 independent non-hydrogen atoms. A difference Fourier map yielded all the remaining non-hydrogen atoms except the chloroform carbon atom, and revealed that the chloroform molecule is statistically distributed between two positions related by the two-fold rotation axis. After 24 hydrogen atoms had been located in a second difference Fourier map, several cycles of the block-diagonal least-squares refinement were carried out including these hydrogen atoms; the final R value was 8.4%. A perspective view of the molecule and the atomic coordinates are given in the Figure and in the Table respectively. It may be of interest that the conformation of 2 in the crystalline state is quite different from the main conformation in the solution state[13].

In view of increasing importance of ten-membered terpenoids as bioactive substances, the above $Pb(OAc)_4$ induced skeletal transformation may be of some value as a new route to cyclodecane derivatives.

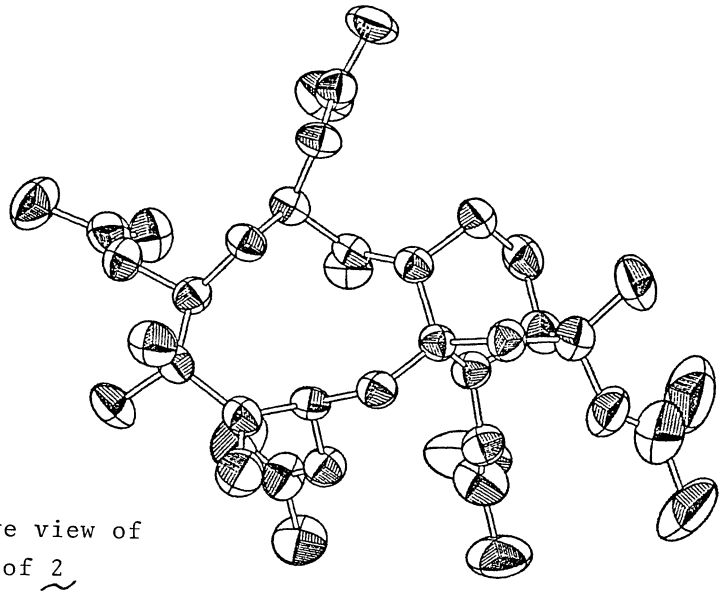

Fig. A perspective view of the molecule of 2

Table The atomic coordinates

Atom	x	y	z				
O(1)	0.7808	0.4979	-0.10657	C(12)	0.9486	0.6494	-0.17793
O(2)	0.8428	0.6773	-0.09210	C(13)	0.8938	0.6135	-0.20209
O(3)	0.3945	0.5150	-0.09951	C(14)	0.7549	0.6132	-0.19831
O(4)	0.4454	0.7090	-0.09457	C(15)	0.8252	0.4079	-0.19560
O(5)	0.3471	0.3739	-0.17913	C(16)	0.9215	0.4809	-0.20880
O(6)	0.4516	0.5876	-0.19534	C(17)	1.0538	0.4383	-0.20521
O(7)	0.3519	0.7065	-0.17078	C(18)	0.2361	0.4816	-0.13721
O(8)	0.6931	0.5961	-0.22125	C(19)	0.3680	0.2968	-0.13063
O(9)	0.6603	0.7923	-0.22426	C(20)	0.6932	0.7270	-0.14461
O(10)	0.8912	0.4597	-0.23424	C(21)	0.8592	0.5699	-0.09494
O(11)	1.0301	0.5866	-0.24826	C(22)	0.9686	0.4979	-0.08639
C(1)	0.6754	0.5558	-0.11767	C(23)	0.3952	0.6201	-0.08745
C(2)	0.5791	0.4586	-0.12014	C(24)	0.3238	0.6103	-0.06455
C(3)	0.4519	0.5092	-0.12301	C(25)	0.3774	0.6800	-0.19031
C(4)	0.3659	0.4317	-0.13862	C(26)	0.3264	0.7410	-0.21213
C(5)	0.4014	0.4374	-0.16513	C(27)	0.6523	0.6938	-0.23239
C(6)	0.5008	0.5222	-0.17490	C(28)	0.5985	0.6599	-0.25650
C(7)	0.6058	0.4460	-0.18384	C(29)	0.9432	0.5120	-0.25087
C(8)	0.7339	0.4989	-0.18335	C(30)	0.8995	0.4726	-0.27552
C(9)	0.7824	0.5245	-0.15794	Cl(1)	0.5093	0.3998	-0.00782
C(10)	0.7141	0.6095	-0.14147	Cl(2)	0.6279	0.5038	-0.04763
C(11)	0.9187	0.5603	-0.15789	Cl(3)	0.5967	0.6314	-0.00263

References and Notes

1) A. Furusaki, S. Gasa, N. Hamanaka, R. Ikeda, and T. Matsumoto, Chem. Lett., 1979, 665.
2) A. Furusaki, N. Hamanaka, H. Miyakoshi, T. Okuno, and T. Matsumoto, Chem. Lett., 1972, 783.
3) S. Fushiya, H. Hikino, and T. Takemoto, Tetrahedron Lett., 1974, 183.
4) Compound 2 is obtained also by non-photochemical version[7] of $Pb(OAc)_4$ oxidation (rt, 24 h, 50% conversion, 40% yield).
5) m/e 578 (M^+). ^1H nmr (200 MHz, $CDCl_3$): δ 1.07, 1.13, 1.67 (each 3H, s), 1.96, 1.97, 1.99, 2.08, 2.13 (each 3H, s), 2.46 (1H, dd, J=16.0, 7.0 Hz, C_7-H), 2.67 (1H, d, J=16.0 Hz, C_7-H), 2.74 (1H, s, W_h=8 Hz, C_9-H), 5.33 (1H, s, C_{14}-H), 5.36 (1H, dd, J=11.0, 4.0 Hz, C_3-H), 5.62, 5.68 (each 1H, s, C_{20}-H), 5.65 (1H, d, J=6 Hz, C_1-H), 5.83 (1H, d, J=7.0 Hz, C_6-H). CD: (c=0.199, EtOH) $[\theta]_{299}^{25}$=−5,112 . ^{13}C nmr ($CDCl_3$): δ 18.5 (q), 20.2 (q), 20.4 (q), 20.7 (q), 21.1 (q), 21.5 (q), 22.6 (q), 24.1 (t), 24.5 (q), 27.3 (t), 36.8 (t×2), 44.7 (d), 49.6 (d), 50.3 (s), 52.5 (s), 53.7 (t), 70.1 (d), 71.1 (d), 79.0 (d), 79.8 (d), 88.8 (s), 120.0 (t), 148.2 (s), 169.0 (s), 169.7 (s), 169.8 (s), 169.9 (s), 170.3 (s), 212.1 (s).
6) Satisfactory elemental analytical values were obtained for this compound.
7) H. Fuhrer, L. Lorenc, V. Palrović, G. Rihs, G. Rist, J. Kalvoda, and M. Lj. Mihailović, Helv. Chim. Acta, 62, 1770 (1979) and references cited therein.
8) We thank Dr. S. Fusiya, Tohoku University, for providing us with nmr data of grayanol derivatives.
9) m/e 536 (M^+). ^1H nmr (100 MHz, $CDCl_3$): δ 0.83, 1.13, 1.61 (each 3H, s), 1.90, 1.92, 1.97, 2.05 (each 3H, s), 4.40 (1H, br.d, J=6 Hz, C_1-H), 4.80 (1H, dd, J=4.0, 12.0 Hz, C_3-H), 5.21 (1H, s, C_{14}-H), 5.42 (1H, d, J=7.5 Hz, C_6-H), 5.58, 5.72 (each 1H, br.s, C_{20}-H). ^{13}C nmr ($CDCl_3$): δ 16.7 (q), 20.5 (q), 20.9 (q×2), 21.1 (q), 21.4 (q), 22.6 (q), 25.8 (t), 26.1 (t), 27.3 (t), 38.9 (t), 43.1 (s), 49.0 (d), 50.1 (s), 50.2 (d), 53.3 (t), 69.1 (d), 72.5 (d), 74.9 (d), 79.6 (d), 89.2 (s), 100.5 (s), 114.6 (t), 153.0 (s), 168.6 (s), 169.7 (s), 169.8 (s), 170.3 (s).
10) The small S values for the Me groups at C_4 may be explained by the steric hindrance due to these groups to the coordination of Eu^{3+}. Similar small relative S values for gem-diMe groups were observed also in model compounds 2,2-dimethyl-1-cyclohexanol [S($CDCl_3$): 23.5 (C_1-H), ~18.1 (C_2-HX2), 11.5 (Me), 9.9 (Me)] and its acetate [S($CDCl_3$): 24.3 (C_1-H), 12.1 (C_{2eq}-H), 10.6 (C_{2ax}-H), 6.20 (Me), 5.60 (Me)]. S=Δδ(ppm)/Δ[Eu^{3+}(mol)/Substrate(mol)].
11) J.B. Hendrickson, J. Am. Chem. Soc., 89, 7037 (1967).
12) A. Furusaki, Acta Crystalogr., Sect. A, 35, 220 (1979).
13) The conformer in the crystalline state [θ(dihedral angle): C_1–C_2 −81.0 (5)°, C_2–C_3 147.7 (4)°, C_6–C_7 151.2 (4)°] will not exhibit the observed splitting pattern in the nmr spectrum.

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