PHOTOCHEMICAL SYNTHESIS OF COMPOUNDS WITH GRAYANOTOXIN SKELETON[*]

M. Shiozaki[**], K. Mori, M. Matsui, and T. Hiraoka[**]

Department of Agricultural Chemistry, The University of Tokyo

Bunkyo-ku, Tokyo, 113, Japan

The Grayanotoxins[1] which are tetracyclic diterpenoids with the per-hydroazulene skeleton are well known as the toxic substances obtained from Leucothoe grayana Max. and up until now many related compounds have been iso-lated[2]. Solvolysis of a steroidal compound was attempted for the synthesis of this hydroazulene skeleton by Okuno and Matsumoto[3]. In the present study we adapted the photochemical rearrangement which was found in Santonin by Barton[4] to the 2-formyldienones 12 and 12' to obtain the grayanotoxin skeleton, (e.g., A→B).
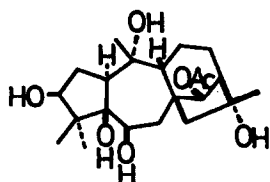
grayanotoxin-I   A   B
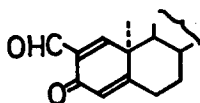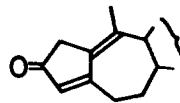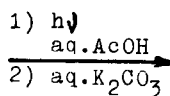

The racemic diketone $\underline{2}$, mp 146-148°, ν_{max}^{nujol} 1770, 1730 cm^{-1}, having

an oxygen function in the A ring of the kaurene skeleton, was newly synthe-

sized through an ordinary route in 13 steps in ca 7% overall yield from the

racemic ketone $\underline{1}$[5]. Grignard reaction of this diketone $\underline{2}$ using MeMgI yielded

a β-hydroxy ketone ($\underline{3}$) and its C-16 epimer ($\underline{4}$) in 79% and 8% yield, respective-

ly, which were separated by recrystallization and chromatography on alumina.

By hydrolysis with AcOH-H$_2$O(2:1) $\underline{3}$ afforded the diol $\underline{5}$, mp 215-216°, in 98%

yield. Oxidation of $\underline{5}$ using Jones reagent gave the diketone $\underline{6}$, mp 189-190°, in

90% yield. After reduction of $\underline{4}$ using Li-NH$_3$/NH$_4$Cl, the resulting oily diol was

treated with MeCHO-anhydrous ZnCl$_2$ at 5° for 15 hr to yield both the THP ether

$\underline{7}$, mp 162-165°, with no absorption band for hydroxyl group, and the alcohol $\underline{8}$,

mp 157-159°, which was easily converted to $\underline{7}$ and revealed NOE between the C-10

methyl group and C-14 hydrogen, and no coupling between the hydrogens at C-14

and C-13.

The diketone $\underline{6}$ was dehydrogenated using 2,3-dichloro-5,6-dicyano-

benzoquinone(DDQ)[6] in dioxane to produce the dienone $\underline{9}$, mp 175-176°, λ_{max}^{EtOH}

239.5 nm(ε=15500), ν_{max}^{nujol} 3420, 1740, 1660, 1630, 1604 cm^{-1}, $\delta_{ppm}^{CDCl_3}$ 1.21

(CH$_3$, s), 1.29(CH$_3$, s), 6.08 (1H, m), 6.17(1H, dd, J=2, 10 Hz), 7.05 (1H, d,

J=10 Hz), in 53% yield. The dienone $\underline{9}$ was treated with Li-NH$_3$/NH$_4$Cl to give

the enone $\underline{10}$ and C-14 epimer $\underline{10}$' (ca 1:2) in 79% yield[7], which did not afford

an ethylidene compound corresponding to $\underline{7}$. A mixture of $\underline{10}$ and $\underline{10}$' was con-

verted to formyl enones with HCO$_2$Et-NaOMe in 87% yield. A small part of this

mixture was separated by chromatography on silica gel to give $\underline{11}$, mp 217-222°,

$\delta_{ppm}^{d_6-DMSO}$ 3.62(C-14 H, d, J=4 Hz, coupling with C-13 H), and $\underline{11}$', mp 208-211°,

$\delta_{ppm}^{d_6-DMSO}$ 4.12(C-14 H, s, no coupling with C-13 H). Treatment of the mixture

of $\underline{11}$ and $\underline{11}$' with DDQ as described by Edwards et al. (method A)[8] afforded a

mixture of the 2-formyl dienones $\underline{12}$ and $\underline{12}$' in 32% yield. The ratio of $\underline{12}$ to

$\underline{12}$' is about 3:1, which reveals that the yield of dehydrogenation of $\underline{11}$ is

high, but that of $\underline{11}$' is very low.

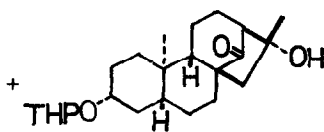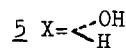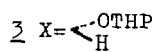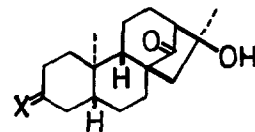A mixture of $\underline{12}$ and $\underline{12}$' in aqueous acetic acid (45%) was irradiated

with an ultraviolet lamp (Hanovia, 450 W), and the crude photo-products were

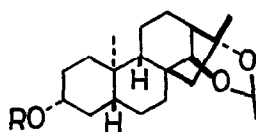treated with aq. K$_2$CO$_3$ according to Caine's method[9] to furnish crystalline
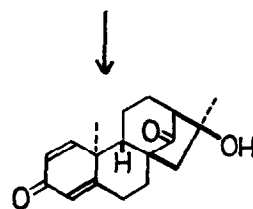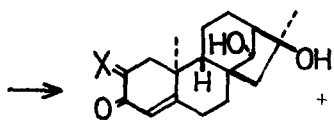
1

2

3 X=<OTHP, H

5 X=<OH, H

6 X= O

+
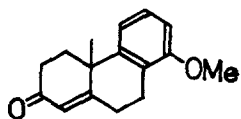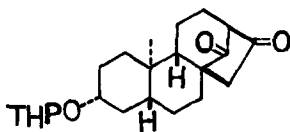
4

7 R= THP

8 R= H
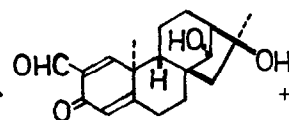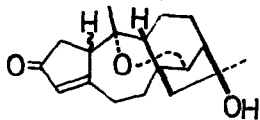
9

10 X= H₂

11 X= CHOH

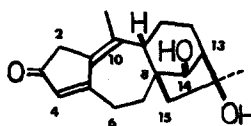10' X= H₂

11' X= CHOH

+ C-14 epimer →

12

+ C-14 epimer

12

13

14

compounds which were separated by thick layer chromatography and fractional crystallization to give two crystalline products $\underline{13}$, and $\underline{14}$ (ca 3:1) in 12% yield; the ether $\underline{13}$, mp 225-226°, ν_{max}^{KBr} 3380, 1690, 1618 cm^{-1}, λ_{max}^{EtOH} 232 nm (ε=14100), M$^+$ 288, $\delta_{ppm}^{d_5\text{-pyridine}}$ 1.45(CH$_3$, s), 1.48 (CH$_3$, s), 2.06(C-2 H, dd, J=4.8, 18 Hz), 2.59(C-2 H, dd, J=6, 18 Hz), 3.01(C-1 H, ddd, J=6, 4.8, 1.8 Hz), 4.42(C-14 H, d, J=5 Hz, coupling with C-13 H at δ 2.05), 5.94(C-4 H, d, J=1.8 Hz), and the diol $\underline{14}$, mp 250-252.5°(decomp), ν_{max}^{KBr} 3380, 3320, 1656, 1623, 1564 cm^{-1}, M$^+$ 288, λ_{max}^{EtOH} 306.5 nm(ε=17900), $\delta_{ppm}^{d_5\text{-pyridine}}$ 1.80(CH$_3$, s), 2.07(CH$_3$, s), 3.90(C-14 H, d, J=3 Hz, coupling with C-14 OH, this changes to a singlet on addition of D$_2$O), 5.56(C-16 OH, bs), 5.94(C-14 OH, d, J=3 Hz), 6.02(C-4 H, J$\lesssim$ 1, coupling with C-6 H at δ ca 2.64). These data indicate that the compounds $\underline{13}$ and $\underline{14}$ have the hydroazulene skeleton.

References

1) S. Takei and S. Miyazima, J. Agr. Chem. Japan, $\underline{10}$, 1093 (1934).

2) H. Hikino, T. Ohta, S. Koriyama, Y. Hikino, and T. Takemoto, Chem. Pharm. Bull., $\underline{19}$, (6) 1289 (1971).

3) T. Okuno and T. Matsumoto, Tetrahedron Letters, 4077 (1969).

4) D. H. R. Barton, Helv. Chim. Acta, $\underline{42}$, 2604 (1959).

5) J. W. Cornforth and Sir R. Robinson, J. Chem. Soc., 1855 (1949).

6) D. Walker and J. D. Hiebert, Chem. Rev., $\underline{67}$, 153 (1967).

7) R. E. Schaub and M. J. Weis, Chem. & Ind., 2003 (1961).

8) J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. Cabezas Rivera, R. Urquiza, L. Cardona, J. C. Orr, and A. Bowers, J. Org. Chem., $\underline{29}$, 3481 (1964).

9) D. Caine and J. F. DeBardeleben, Jr., Tetrahedron Letters, 4585 (1965).