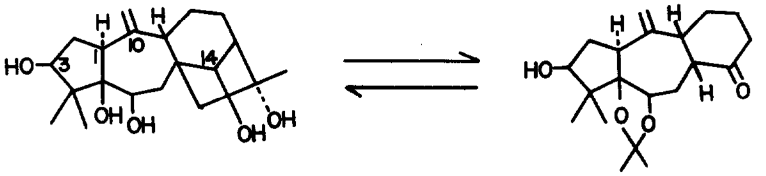
Tetrahedron Letters No. 30, pp 3087 - 3090, 1972. Pergamon Press. Printed in Great Britain.

Partial Synthesis of Grayanotoxin

Nobuyuki Hamanaka and Takeshi Matsumoto
Department of Chemistry, Faculty of Science,
Hokkaido University, Sapporo, Japan

(Received in Japan 14 June 1972; received in UK for publication 20 June 1972)

Grayanotoxin (G) II (1)[1a], a toxic diterpenoid isolated together with other related grayanoids[1] from Leucothoe grayana Max., is characterized by the A-nor-B-homo-kaurane skeleton and by the dense arrangement of functionality. We report herein a partial synthesis of G II from a tricyclic degradation product 2, which is in principle synthetically accessible by a number of routes. The following processes therefore open a way to a relay total synthesis of G II.



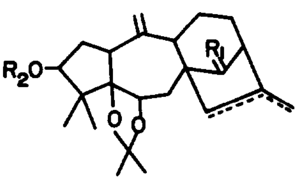
1 2

Towards the objective of obtaining compound 2, bis-anhydro G I acetonide 3[1a] was at first converted to 3-O-THP ether 4[2]. Subsequent hydrolysis (1N-NaOH-EtOH) of acetate group followed by oxidation (pyridine-CrO_3) gave a 1:1[3] mixture 5[2,4] of Δ^{15} and Δ^{16} ketones, mp 183.5-184.5° (70% yield from 3). Further oxidation of 5 with OsO_4 (0.05 mol)-$NaIO_4$ (4 mol) in dioxane-water (3:1) (7 day, rt) afforded an enolic compound 6[2,4], mp 156-157° (δ 16.15 (1H, s), 9.72 (1H, s)), a nor-ketone 7[2,4], mp 193-194.5° (ν (nujol) 1775 and 1740 cm^{-1}) and a bisnor-ketone 8[2] (mp of deTHP compound[4] 188-189°), in 27, 24, 4% yields respectively. Treatment of the enol 6 with 0.2N-KOH-dioxane (1:10) (reflux, 5 hr) afforded the desired tricyclic intermediate 2[2,4], mp 150-151°, (ν(nujol)

1700 cm^{-1}) in 60% yield together with an amorphous seco-keto acid **9**2) (30% yield). The assigned B/C cis structure of **2** is based on the following observations. The compound exhibits λ_{max} 287 nm (ε 166) due to an "antiparallel" γ,δ-unsaturated carbonyl system6), $J_{6,7ax} + J_{6,7ex}$ of 7 Hz showing equatrial nature7) of the C-6 proton and a weak negative Cotton effect. These data are compatible only with cis structure **10**.

The tricyclic ketone **2** was reconverted to G II by the pathway described below. Treatment of the methylene thioether **11**2,4), mp 68-70°, derived from **2** in the usual manner8), with a large excess of allyl bromide in the presence of tert. AmONa (10 mol) in benzene (1hr, rt then 3 hr,reflux) followed by removal of the butyl mercaptomethylene group (1N-KOH-EtOH, overnight at reflux) yielded the 8β-allylated compound **12**2) in 60% yield from **11** as single isolable product. The success of this selective alkylation from β-face depends on the steric screening of C-10 atom, as shown in formula **13**8). The compound **12** was next oxidized with OsO$_4$ (0.02 mol)-NaIO$_4$ (4 mol) in tert. BuOH-H$_2$O (3:1) (5 hr, rt) to give an oily hemiacetal **14**2), which on treatment with 1N-EtONa-EtOH (12 hr reflux) furnished the five-membered ketone **15**2). The product was an epimeric mixture at C-16 and oxidation (CrO$_3$-pyridine) of the mixture afforded a single 16-dehydro compound **16**2,4,10), in 40% overall yield from **12**. Removal of the THP group and subsequent acetylation of **16** yielded 3-O-acetate **17**2,4), mp 171-172°, identical in all respects with the OsO$_4$-NaIO$_4$ oxidation product of **18**2,4), mp 170-171°, derived from **4**.

methylation of **17** with MeMgI (1.5 eq., ether, rt) gave two products **19**2,4), mp 142-146° and **20**2,4), mp 181-181.5°, ORD a=139.1°, in 43 and 34% yields respectively. Dehydration of **19** (POCl$_3$-pyridine, 3 hr, 0°) furnished a mixture of Δ^{15} and Δ^{16} compound **18** (60% yield) which on reduction with Na-iso-PrOH11) afforded the known 3,14-dihydroxy compound **21** in 60% yield. Conversion of **21** to G II acetonide was achieved by oxymercuration12) (24%) and removal of the isopropylidene group was effected through G II acetonide triacetate12), which on being treated with HClO$_4$ in ethylene glycol (4 day, 0°) gave G II triacetate. Finally hydrolysis of the product with alcoholic NaOH furnished grayanotoxin II, identical in all respects with the natural product.



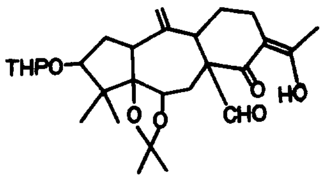
3 $R_1=<^{OAc}_{H}$ R_2=H

4 $R_1=<^{OAc}_{H}$ R_2=THP

5 R_1= O R_2=THP

18 R_1= O R_2=Ac

21 $R_1=<^{OH}_{H}$ R_2=H



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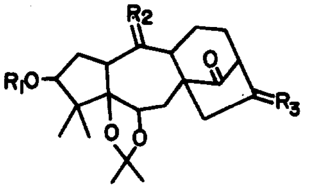


7 R_1=THP $R_2=CH_2$ R_3= O

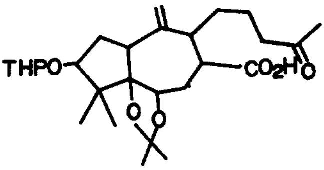
8 R_1=H R_2=O R_3= O

15 R_1=THP $R_2=CH_2$ $R_3=<^{OH}_{H}$

16 R_1=THP $R_2=CH_2$ R_3= O

17 R_1=Ac $R_2=CH_2$ R_3= O

19 R_1=Ac $R_2=CH_2$ $R_3=<^{OH}_{CH_3}$



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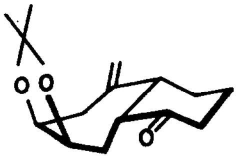

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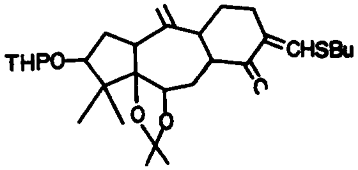

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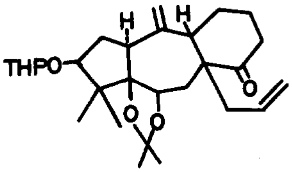

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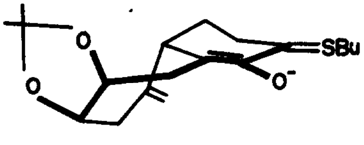

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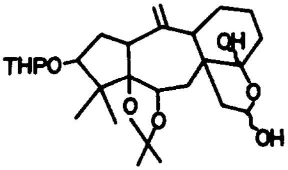

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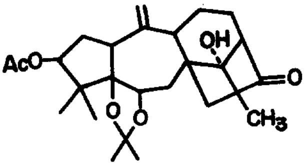

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REFERENCE AND NOTES

1) a) H. Kakisawa, T. Kozima, M. Yanai and K. Nakanishi, *Tetrahedron*, **21**, 3091 (1965).

b) J. Iwasa and Y. Nakamura, *Tetrahedron Letters*, **1969**, 3973; P. Narayanan, M. Rohrl, K. Zechmeister and W. Hoppe, *Tetrahedron Letters*, **1970**, 3943.

c) T. Okuno, N. Hamanaka, H. Miyakoshi and T. Matsumoto, *Tetrahedron*, **26**, 4765 (1970).

d) For isolation and structure of G XV see; A. Furusaki, N. Hamanaka, H. Miyakoshi and T. Matsumoto, *Chemistry Letters*, in press.

2) Satisfactory IR and NMR spectra were obtained for this intermediate.

3) Determined by comparing the peak intensity at δ 5.61 and 4.95 in the NMR spectrum.

4) Elemental composition of this compound was confirmed by analysis.

5) All NMR spectra were taken in chloroform solution.

6) M. D. Brown, J. Hudec and J. M. Mellor, *Chem. Commun.*, **1971**, 1640.

7) Conformational mobility of the seven-membered ring of Gs; Ref. 13.

8) R. F. Church, R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966).

9) Inspection of the molecular models indicated that in the enolate anion of **11** the conformer **13** is the stable form, in contrast to the case of the parent ketone **2**.

10) The IR spectrum of **16** is slightly different from that of **7** in the finger print region, probably because of the difference of the configuration at the THP ring.

11) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, **1956**, 3289.

12) H. C. Brown and P. Geoghegen, *J. Am. Chem. Soc.*, **89**, 1522 (1966).

13) S. Gasa, N. Hamanaka, T. Okuno, J. Omi, M. Watanabe and T. Matsumoto, Tetrahedron, in press.