Tetrahedron. Vol 28, pp. 4905 to 4913. Pergamon Press 1972. Printed in Great Britain

CONVERSION OF GRAYANOTOXIN TO A 20-NOR-(−)-KAURANE DERIVATIVE

CONFORMATIONAL MOBILITY OF THE SEVEN-MEMBERED RING OF GRAYANOTOXINS

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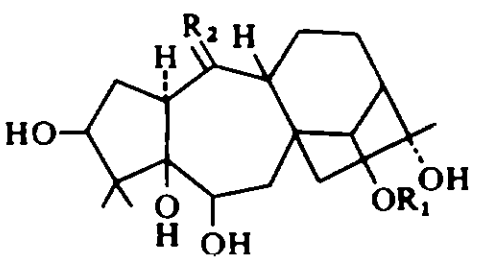
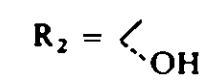
(*Received in Japan* 8 *December* 1971; *Received in the UK for publication* 14 *March* 1972)

Abstract—Grayanotoxin II has been converted to 20-nor-kaurane derivatives through a 20-nor-1β, 10β-dihydroxy grayanotoxin derivative. Evidence for the conformational change of the seven-membered ring of grayanotoxins upon ketalization of 5,6-glycol group has been presented.

GRAYANOTOXINS I–IV (**1–4**)[1–3] are A-nor-B-homo-(−)-kauranoids isolated from *Leucothoe grayana Max*. Structures of these diterpenoids suggest that the terpenes might be formed *in vivo* through a certain (−)-kaurane intermediate and such a route seems to be also of interest for the chemical synthesis of the A-nor-B-homo-kauranes.



1 R_1 = Ac R_2 = 
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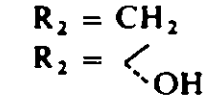
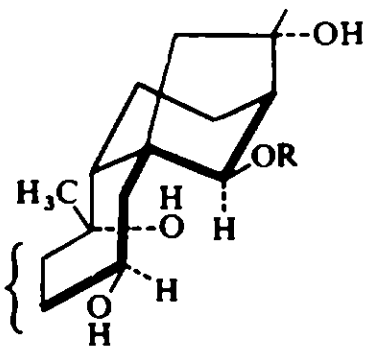
3 R_1 = H R_2 = 
4 R_1 = Ac R_2 = CH_2



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The present paper is mainly concerned with the reverse process of the suggested *in vivo* synthesis, conversion of grayanotoxin to a 20-nor-(−)-kaurane derivative which is hoped to be revertible to the toxins. Attempted direct conversion without loss of the 20-methyl group to the (−)-kaurane skeleton and evidence for the flexibility of the seven-membered ring of the toxins will also be described.

At the preliminary stage of the present study, although the stereochemistry at C-1 of grayanotoxins was still obscure, there was ample evidence[1,4,5] for the spacial proximity of the C-10 OH and the C-14 proton as well as for the equatorial nature of the C-6β OAc of grayanotoxin acetates. A partial conformation (**5**), which was later verified by X-ray analysis,[3] satisfied these requirements and this suggested to us the

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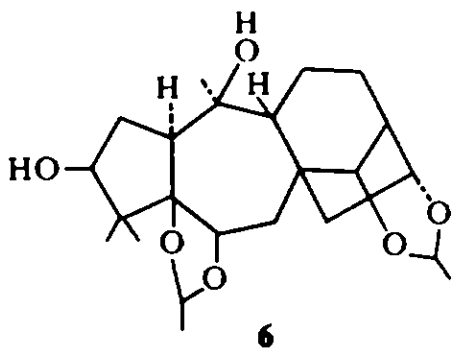

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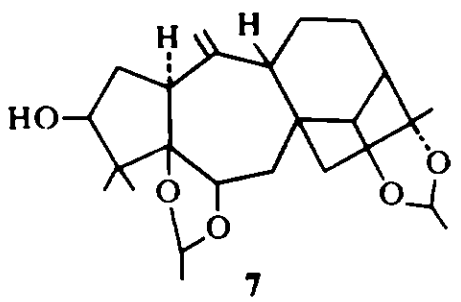

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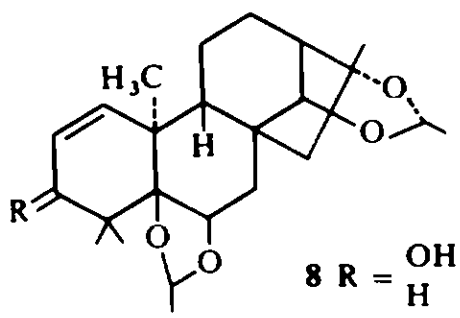
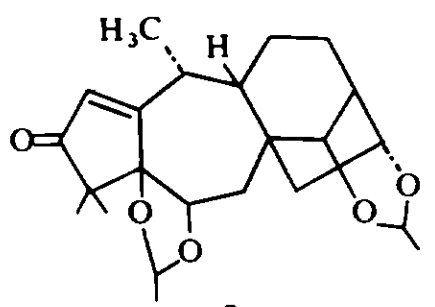


8 R = OH, H

8′ R = O



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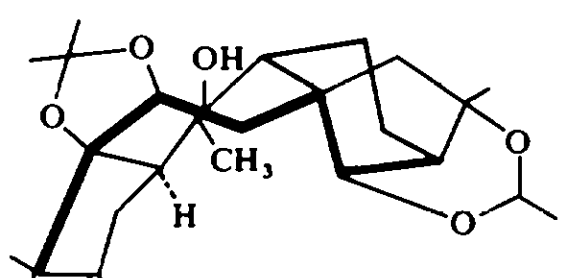

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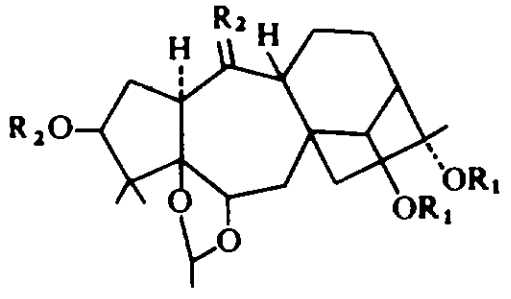
possibility of conversion of suitably protected 10-epi-grayanotoxins to (−)-kaurane derivatives through antiparallel bond migration. Based on this expectation, grayanotoxin II was first converted to 10β,20-epoxide, m.p. 199·5–201° (H_2O_2, PhCN, $KHCO_3$, in MeOH, r.t., 60%), which was reduced (LAH in THF) to afford 10-epi-grayanotoxin III, m.p. 246–250° (dec.). Treatment of the epimer with CH_3CHO–$ZnCl_2$ gave diethylidene-10-epi-grayanotoxin III (**6**), amorph, and diethylidene grayanotoxin II (**7**).[4] Anticipated concurrent formation of the kauranoid **8** or allied compounds was not observed in this reaction. Attempted rearrangement of 3-dehydrodiethylidene epi-grayanotoxin III with MsCl-pyridine[6] to a six-membered α,β-enone **8′** was also unsusuccessful, giving rise to a five-membered α,β-enone with probable structure **9**, λ_{max}^{EtOH}β 229 nm ε = 9,800, δ ($CDCl_3$) 1·28 (d, J = 6 Hz, C-10 Me), 7·45 (s, 1H, olefinic protons).

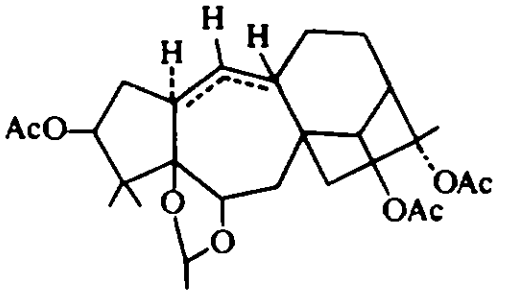
In the course of studies of the above transformations, we became interested in the coupling constants of the C-6 protons of diethylidene compounds. In contrast to the C-6 protons of 6-O-acetyl grayanotoxins,[1,4,5] which exhibit $J_{AX} + J_{BX}$ = *ca.* 15 Hz, the corresponding values of the above diethylidene compounds were about 7 Hz.* These values mean axial → equatorial change of the C-6 proton upon dioxolane

* The interproton coupling constants of dioxolanes are normal; W. E. Willy, G. Binsch and E. L. Eliel, *J. Am. Chem. Soc.* **92**, 5394 (1970)

ring formation and are best explained by assuming a twist boat[7] like seven-membered ring for the diethylidene compounds, as depicted in **10**.* In this conformation the 10β substituent takes a quasi-axial orientation and formation of an intramolecular hydrogen bond between the 10β OH and the 5β ethereal oxygen atom is expected. In agreement with this anticipation, in the high dilution IR spectrum (CCl_4) of compound **10**, an absorption band due to bonded OH was observed at 3,505 cm^{-1}. The failure of the above attempted rearrangements may then be ascribed, at least in part, to the unfavourable non-antiparallel orientation of the 10β OH group relative to the migrating bond. Attempted transposition of 10-epi-grayanotoxin III tetra-acetate, in which the 10β OH group is equatorial and suitably orientated, in Ac_2O-*p*-TsOH however also resulted in the formation of the 10 exo-methylene compound as main product.

Since direct conversion to the kaurane skeleton thus seemed difficult, we next turned our attention to the transformation to a 20-nor-kauranoid. Hereafter the isopropylidene group was used as the masking group, because the diethylidene compounds were not readily crystallizable. Grayanotoxin II was at the outset acetonized to monoacetonide **11**[1] which was treated with Ac_2O and pyridine at 100° to afford amorphous triacetate **12**. Oxidation of **12** with ozone furnished the 20-nor-ketone **13**, m.p. 117–119°, a = −123 (MeOH). That the ketone was not epimerized either at C-1 or C-9 was demonstrated by reverting the ketone to grayanotoxin III acetonide by means of MeMgI.





11 $R_1 = H$ $R_2 = CH_2$
12 $R_1 = Ac$ $R_1 = Ac$ $R_2 = CH_2$
13 $R_1 = Ac$ $R_2 = O$
14a $R_1 = Ac$ $R_2 =$ 
14b $R_1 = Ac$ $R_2 =$ 

15a Δ^9 1α—H
15b $\Delta^{1,(10)}$ 9β—H

The nor-ketone **13** was next reduced with $NaBH_4$ to give a mixture of epimeric alcohols (**14a** m.p. 241–243° and **14b** m.p. 133·5–134·5°) separated by column chromatography. Configuration of the C-10 OH group of these alcohols was determined by spectroscopic methods. In the NMR spectrum of **14a**, as a result of the closeness of the C-10α OH and C-14 proton the singlet peak due to the C-14 proton appears at characteristically low field (δ 5·39), like other 10α-OH derivatives (Table 1), while the corresponding peak of **14b** appears at a normal position (δ 4·67). Moreover, the IR spectrum in highly dilute solution (CCl_4) of **14b** exhibited a single absorption band at 3,504 cm^{-1} due to a bonded OH group, indicating clearly the β-orientation of C-10 OH.

* It may be noted that such a twist boat conformation is possible in 1-α (A/B *trans*) structure but not in the 1-β one and thus provides spectroscopic evidence for A/B *trans* fusion of grayanotoxins.

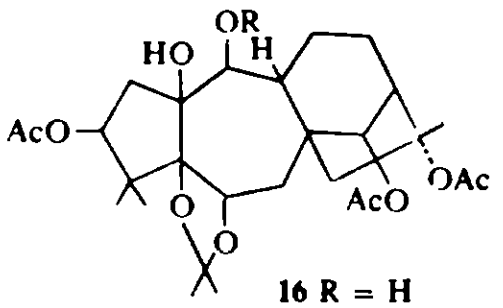
Treatment of **14b** with MsCl-pyridine gave the corresponding mesylates, which on being passed through alumina afforded stereospecifically Δ^9 compound **15a**, m.p. 199·5–201° and $\Delta^{1(10)}$ compound **15b**, m.p. 134–136°, respectively. Although at this stage the position of the double bond in each product was assigned tentatively by assuming the *trans* elimination mechanism, subsequent reactions verified this hypothesis as described later. On treatment with OsO_4 in pyridine, the $\Delta^{1(10)}$ compound

TABLE 1. THE CHEMICAL SHIFTS OF C-14 PROTONS

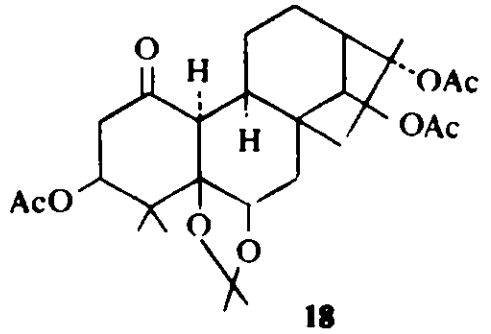
Compounds G–I an*	Configurations 10β Me, 10α OH	Chemical Shifts 5·86
4	10 = CH_2	4·96
12	10 = CH_2	4·96
13	10 = O	4·83
14a	10α OH	5·39
14b	10β OH	4·67
15a	1α H, Δ^9	4·73
15b	9β H, $\Delta^{1(10)}$	4·58
16	1β, 10β-diol	4·90
18	10α H	4·98
20	9α, 10α-diol	5·52
21a	1α H, 10β H	4·72

* Grayanotoxin I acetonide[1]

underwent oxidation from the less hindered β-face and afforded 1β,10β-diol **16**, m.p. 114–115·5°. In agreement with this formula in which the C-14 proton and C-10 OH are far apart, the NMR signal due to the C-14 proton appears at a normal position (δ 4·58, Table 1). The diol was next converted to 10-O-mesylate **17**, which on treatment with NaOAc in acetone did give rise to the desired nor-ketone compound **18** (ν 1729 and 1713 cm^{-1}), m.p. 181·5–183°. The C-3 acetoxyl group of **18** was readily



16 R = H
17 R = Ms



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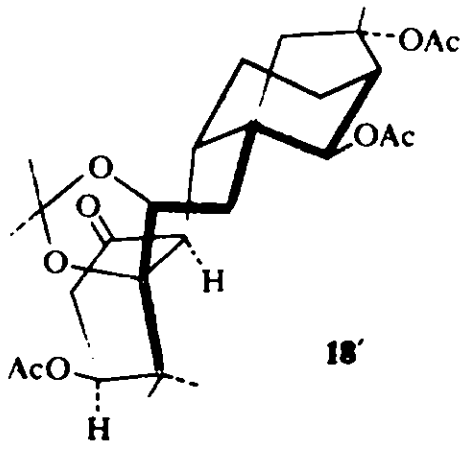

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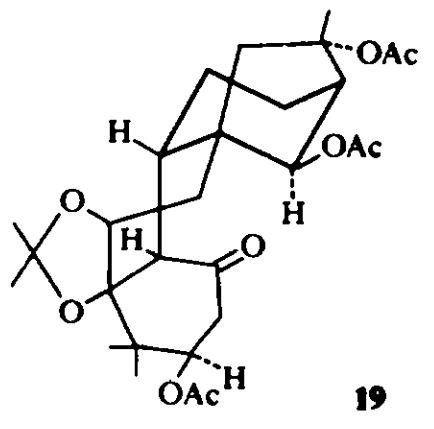

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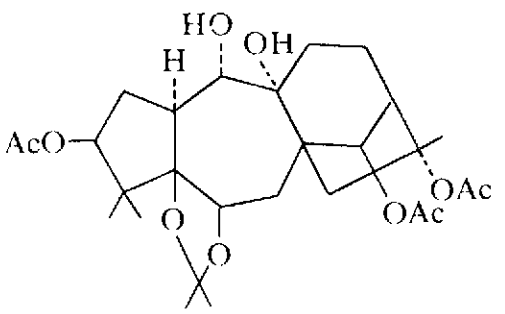
eliminated by passing through alumina to give an α,β-unsaturated ketone (λ_{max}^{EtOH} 224 nm, ε = 7,200), m.p. 196·5–198°, providing compelling evidence for the 1,10 diol and therefore $\Delta^{1(10)}$ structures of the intermediates **16** and **15b** respectively. It should be noted that the $J_{AX} + J_{BX}$ value of C-6 proton of **18** is 6Hz, indicating a non chair, probably twist boat conformation of B ring. The configuration of C-1 H in **18** is anticipated to be α (A/B *trans*), since this is both thermodynamically and kinetically the more favourable one. Evidence for the A/B *trans* strcture was provided by the chemical shift of the C-14 proton of **18**. If an A/B *cis* structure were to be assumed, since the C-14 proton should lie just over the C-1 carbonyl oxygen atom (formula **19**), it should resonate at an unusually high field.[8] However, the observed chemical shift (δ 4·98, s) was quite normal.* Further, the *J* value of the 3α proton (6 + 8 Hz) indicates that the A ring also adopts a boat like conformation and accordingly the stereochemistry of **18** is best expressed by **18′**. Probably the five-membered dioxolane ring causes ring B to adopt a twist boat form (dihedral angle around C-1—C-5 bond 30°) and this in turn brings about deformation of ring A.

Oxidation of the Δ^9 compound (**15a**) with OsO_4 gave diol **20**. Since in **15a** the α side is less crowded, formation of 9α,10α-diol is expected and this configuration was demonstrated by the chemical shift (δ 5·56) of the C-14 proton, which in this case lies very



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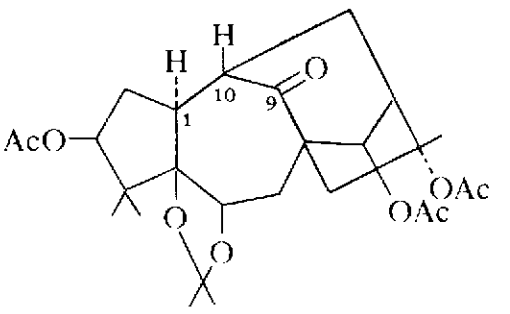

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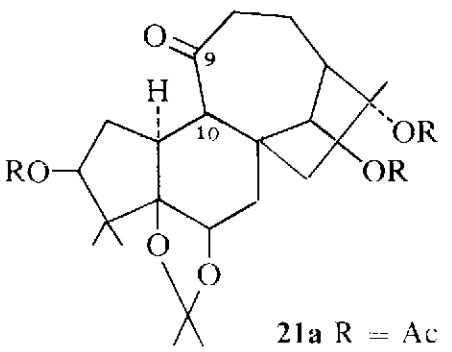
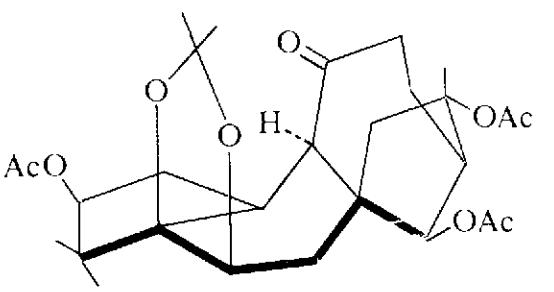


21a R = Ac
22b R = H



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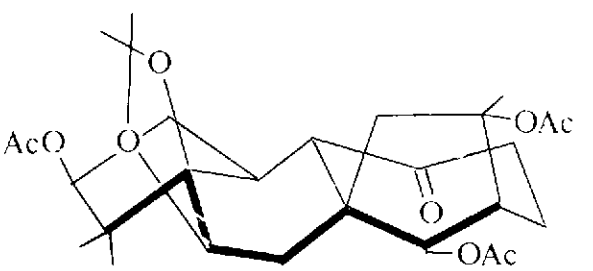

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* The $NaBH_4$ reduction product of **18**, although crude, exhibits the signal due to the C-14 proton at 4·95. In the A/B *cis* structure a much higher value (lower field signal) is expected and observation supports this.

close to the C-9 OH group. Conversion of **20** to 10-O-mesylate followed by treatment with alumina gave rise to B-nor-C-homo ketone **21a** (1703 cm^{-1}), amorph, which on hydrolysis with NaOH gave crystalline triol **21b**, m.p. 187·5–189·5°. An alternative, kinetically less probable formula (**22**) can be excluded, since on treatment with NaOD-D_2O in MeOD, triol **21b** yielded a D_2 compound. Inspection of molecular models indicates that the $\Delta^{9(10)}$ enolic form of **21b** is energetically unstable and incorporation of two D atoms is consistent with **21b**, but obviously not with desacetyl **22**. The models also show 10α epimer **23** of **21a** is energetically unstable and this is in accord with the stability of the B-nor-C-homo ketone **21b** to base. The gross stereochemical formula of **21a** may be expressed by **24**.

EXPERIMENTAL

All m.ps are uncorrected. The NMR spectra were obtained on Hitachi H-60 spectrometer in $CDCl_3$ containing TMS, unless otherwise stated. Chemical shifts are reported as p.p.m on δ scale. The IR spectra were measured on a Jasco model IR-S spectrophotometer. The ORD curves were obtained on a Jasco ORD/UV-5 spectrophotometer.

Epoxidation of grayanotoxin II **2**. A soln of **2** (2 g), $KHCO_3$ (450 mg), benzonitrile (0·95 ml) in MeOH (15 ml) was stirred for 15 hr. A ppt formed was collected and recrystallized from EtOAc to give needles, m.p. 199·5–201°; ν_{max}^{nujol} 3390 cm^{-1}; NMR δ (pyridine) 1·14, 1·20 and 1·55 (each 3H, s). (Found: C, 65·30; H, 8·84. $C_{20}H_{32}O_6$: C, 65·19; H, 8·75%).

Reduction of grayanotoxin II *epoxide*. The epoxide (2 g) and LAH (2 g) in dry THF (80 ml) was refluxed for 40 hr. The reagent was decomposed with aq THF and resultant ppt filtered off. The filtrate was concentrated under reduced press. The residue was crystallized from AcOEt to give 10-epi-grayanotoxin III as needles, m.p. 246–250° (dec.); ν_{max}^{nujol} 3500–3200 cm^{-1}; NMR δ (pyridine) 0·76, 1·23, 1·36 and 1·59 (each 3H, s). (Found: C, 64·63; H, 9·10. $C_{20}H_{44}O_6$: C, 64·84; H, 9·25%).

Diethylidene 10-*epi-grayanotoxin* III **6**. Anhydrous $ZnCl_2$ (2 g) was added to the soln of 10-epi-grayanotoxin III (800 mg) in acetaldehyde (40 ml) and the soln allowed to stand overnight at room temp. Acetaldehyde was removed *in vacuo*, and the residue dissolved in AcOEt. The solution was washed with water and evaporation of solvent gave oily material. The product was chromatographed on silica gel. Benzene–EtOAc (9:1) eluted the diethylidene grayanotoxin II[4] (210 mg). Further elution with benzene–EtOAc (3:2) gave **6** (449 mg), amorph; ν_{max}^{neat} 3540 cm^{-1}; NMR δ 0·82, 1·32 (each 3H, s), 1·08 (6H, s), 1·29, 1·44 (ethylidene Me, J = 5 Hz), 3·92 (1H, s), 4·28 (1H, q, $J_{AX} + J_{BX}$ = 7 Hz), 4·90 and 5·30 (2H, m); Mass M^+ 422.

Diethylidene-3-*keto*-10-*epi-grayanotoxin* III. A pyridine soln (10 ml) of diethylidene 10-epi-grayanotoxin III **6** (900 mg) was added to CrO_3 (2 g)–pyridine (20 ml) complex and the mixture left overnight at room temp. The resultant ppt was filtered off and the filtrate diluted with ether. The ether soln was washed with dil HCl and water, dried (Na_2SO_4) and evaporated. The residue would crystallize and was obtained as an amorphous solid; ν_{max}^{neat} 1745 cm^{-1}; 3505 cm^{-1} (in CCl_4, 9·8 × 10^{-4} mol/l); NMR δ 1·00, 1·12, 1·20, 1·40 (each 3H, s), 1·35 and 1·40 (ethylidene Me, J = 5Hz); Mass M^+ 420.

Reaction of diethylidene 3-*keto*-10-*epi-grayanotoxin* III *with* MsCl. To a pyridine soln (5 ml) of diethylidene 3-keto-10-epi-grayanotoxin III (180 ml) MsCl (2 ml) was added. The soln was heated (70°, 5 days) under N_2. After usual work-up, the production was purified by prep TLC (Wako gel B-5, benzene–EtOAc (3:7)). A mobile fraction gave **9** (27 mg), m.p. 217–219°; ν_{max}^{nujol} 1713 and 1558 cm^{-1}; NMR δ 1·14, 1·30, 1·37 (each 3H, s), 1·23, 1·40 (each 3H, d, J = 5 Hz, ethylidene Me), 1·28 (3H, d, J = 6 Hz), 3·43 (1H, s), 4·50 (1H, q, $J_{AX} + J_{BX}$ = 2 + 5 Hz), 7·45 (1H, s); λ_{max}^{EtOH} 229·5 nm (ε = 9800).

Acethylation of 10-*epi-grayanotoxin* III. A mixture of 10-epi-grayanotoxin III (45 mg), pyridine (2 ml) and Ac_2O (0·5 ml) was kept at 100° overnight. Usual work-up gave a tetracetate (40 mg) as oil, which was used without further purification; NMR δ 0·97, 1·01, 1·25, 1·40 (each 3H, s), 1·95, 2·01 (× 2) and 2·03 (OAc).

Reaction of 3,6,14,16-O-*tetraacetyl* 10-*epi-grayanotoxin* III *with* p-TsOH *and* Ac_2O. A mixture of the substance (40 mg), *p*-TsOH and Ac_2O was heated at 100° for 2 hr. The mixture was poured into ice–water and the product ether extracted. Evaporation of solvent gave amorphous solid which was purified by column chromatography on silica gel. Elution with EtOAc–benzene (15:85) gave tetraacetyl grayanotoxin II[5] (10 mg). NMR spectrum of the crude product indicated absence of the C-10 Me group of the kaurane skeleton.

Triacetyl grayanotoxin II *acetonide* **12**. Grayanotoxin II acetonide **11** (100 mg) was dissolved in a mixture of pyridine (5 ml) and Ac_2O (1 ml) and the soln heated at 100° for 24 hr. After cooling, the mixture was poured into saturated $NaHCO_3$ and the product EtOAc extracted. The extract was washed with dil HCl, saturated $NaHCO_3$ and brine. Solvent evaporation gave an oil which was chromatographed on silica gel. Elution with EtOAc–benzene (1:9) gave 100 mg of **12** as amorphous solid; $\nu_{max}^{CCl_4}$ 1733 and 1235 cm^{-1}; NMR δ 0·96, 0·93, 1·30, 1·36, 1·62 (each 3H, s), 1·95, 2·02, 2·05 (OAc), 4·12 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), and 4·96–5·09 (3H, m). (Found: C, 67·14; H, 8·05. $C_{29}H_{42}O_8$ required: C, 67·16; H, 8·16%).

20-*Nor*-10-*keto-triacetyl grayanotoxin acetonide* **13**. A mixture of ozone and oxygen was passed through 70 ml of AcOEt soln containing 750 mg of **12** at dry ice–acetone bath temp. After the soln became blue excess ozone was removed by passing oxygen through the soln. The ozonide was decomposed with KI and $Na_2S_2O_3$. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of solvent *in vacuo* gave crystals (636 mg) which recrystallized from EtOAc as needles of **13**, m.p. 117–119°; $\nu_{max}^{CHCl_3}$ 1733 and 1702 cm^{-1}; NMR δ 0·96 (6H, s), 1·30, 1·62 1·95 (each 3H, s), 2·03 (6H, s), 4·29 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), and 4·83 (1H, s); ORD (MeOH, $c = 1$) $[\phi]_{309\,nm}^{min} = -6580$, $[\phi]_{271\,nm}^{max} = +5753$, a $= -123$. (Found: C, 64·73; H, 7·74. $C_{28}H_{40}O_9$ requires: C, 64·59, H, 7·74%).

Triacetyl grayanotoxin III *acetonide*. To the Grignard reagent prepared from Mg (60 mg), MeI (0·5 ml) and ether soln (5 ml) of **13** (100 mg) was added and the mixture refluxed for 1 hr. After cooling, ice was added to the soln to decompose excess Grignard. The product was ether extracted and the organic layer washed with water and dried (Na_2SO_4). Solvent was removed *in vacuo*, and the residue acetylated with Ac_2O (1 ml) and pyridine (3 ml) at 100° for 15 hr. After work-up in usual manner, the product was purified by column chromatography to give triacetyl grayanotoxin III acetonide (34 mg), m.p. 217–218·5°; ν_{max}^{nujol} 3340 and 1740 cm^{-1}; NMR δ 0·94, 0·98 (3H, s), 1·34 (6H, s), 1·39, 1·50, 2·07 (each 3H, s), 2·09 (6H, s), 4·20 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), 4·82 (1H, t, $J = 7$ *Hz*) and 5·88 (1H, s). (Found: C, 65·03; H, 8·51. $C_{29}H_{44}O_9$ requires: C, 64·90; H, 8·26%). The identical compound was obtained by acetylating grayanotoxin III acetonide.

Reduction of the ketone **13**. 20-*Nor*-10β-*hydroxy triacetyl grayanotoxin acetonide* **14b** *and the* 10α-*epimer* **14a**. To an ethanolic soln (40 ml) of **13** (200 mg), $NaBH_4$ (60 mg) was added and the mix was left at room temp for 24 hr poured into water and EtOH evaporated *in vacuo* at room temp. Residual aq soln was extracted with EtOAc and the extracts dried (Na_2SO_4). Evaporation of solvent left amorphous products which showed 2 spots on TLC and were separated by prep TKC (Wako gel B-5, 20% AcOEt–benzene). A more mobile fraction gave **14b** (112 mg), m.p. 133·5–134·5° (from isopropyl ether); $\nu_{max}^{CHCl_3}$ 3560 and 1727 cm^{-1}; 3504 cm^{-1} (in CCl_4, $4·67 \times 10^{-3}$ mole/l); NMR δ 0·84 (6H, s), 1·24 (6H, s), 1·54 (3H, s), 1·95, 1·93, 1·85 (OAc), 4·12 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), 4·67 (1H, s) and 4·82 (1H, t, $J = 7$ Hz). (Found: C, 64·28; H, 8·08. $C_{28}H_{42}O_9$ requires: C, 64·35; H, 8·10%). A less mobile fraction afforded amorphous material which was crystallized and recrystallized from isopropyl ether to yield **14a** (82 mg), m.p. 241–243°; $\nu_{max}^{CHCl_3}$ 3500 and 1726 (m^{-1}; NMR δ 0·87 (6H, s) 1·25, 1·36, 1·53 (each 3H, s) 1·89, 1·94, 1·97 (each) OAc, 4.12 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), 4·79 (1H, t, $J = 7$ *Hz*) and 5·39 (1H, s). (Found: C, 64·32; H, 8·19. $C_{28}H_{42}O_9$ requires: C, 64·35; H, 8·10%).

Mesylation of 10β-*alcohol* **14b**. To a soln of **14b** (20 mg) in pyridine (10 ml) MsCl (0·5 ml) was added and the whole left at room temp for 18 hr. The mixture was poured into ice–water and the product extracted with AcOEt. The extract was washed with water and brine. Evaporation of solvent gave an oily material (21 mg) which was employed for the next step without purification; NMR δ 0·90 (6H, s), 1·28, 1·53, 1·60 (each 3H, s), 1·93 (OAc), 2·03 (2 × OAc), 3·02 (3H, s).

Elimination reaction of the 10β-*mesylate*. The above 10β-mesylate (77 mg) was dissolved in $CHCl_3$ and adsorbed on aluminia column (2 g, Wako basic alumina). After standing at room temp for 24 hr, the column was eluted with EtOAc and the eluate concentrated to give oil which was purified by column chromatography on silica gel. Elution with EtOAc–benzene (1:9) gave $\Delta^{1(10)}$ olefin **15b** (51 mg), m.p. 134–135°; $\nu_{max}^{CHCl_3}$ 1727 and 1252 cm^{-1}; NMR δ 0·83, 1·03, 1·33, 1·48, 1·62 (each 3H, s), 1·92, 1·98, 2·03 (OAc), 4·22 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), 4·58 (1H, s), 4·85 (1H, q, $J_{AX} + J_{BX} = 2 + 7$ Hz) and 5·62 (1H, d, $J = 6$ Hz). (Found: C, 66·72; H, 7·97. $C_{28}H_{40}O_8$ requires: C, 66·64; H, 7·99%). Further elution with same solvent gave Δ^9 olefin **15a** (4 mg), 199·5–201° (from MeOH); $\nu_{max}^{CHCl_3}$ 1726 cm^{-1}; NMR δ 0·91, 0·95, 1·28, 1·33, 1·59 (each 3H, s), 1·93 (OAc), 2·02 (2 × OAc), 4·16 (1H, q, $J_{AX} + J_{BX} = 2 + 5$ Hz), 4·71 ($J_{AX} + J_{BX} = 2 + 7$ Hz) and 5·03 (1H, d, $J = 6$ Hz). (Found: C, 66·61; H, 8·04. $C_{28}H_{40}O_8$ requires: C, 66·64; H, 7·99%).

Oxidation of $\Delta^{1(10)}$-*olefin* **15b** with OsO_4. The olefin **15b** (200 mg) in distilled pyridine (5 ml) was treated with OsO_4 (201 mg). After standing for 20 days at room temp, the mixture was diluted with benzene and H_2S was passed through the soln. The resultant ppt was filtered, washed with benzene and the combined

filtrate washed with water and dried (Na_2SO_4). Solvent was removed to give amorphous product which was chromatographed on silica gel (3 g). Elution with EtOAc–benzene (1:9) gave 21 mg of starting material and EtOAc–benzene (1:1) gave 105 mg of 1β, 10β-glycol **16**, which crystallized from isopropyl ether, m.p. 114–115°; ν_{max}^{nujol} 3480 and 1726 cm^{-1}; NMR δ 0·98 (6H, s), 1·31, 1·51, 1·65 (each 3H, s), 1·93 (OAc), 2·01 (2 × OAc), 3·68 (1H, d, J = 7 Hz), 4·16 (1H, q, $J_{AX} + J_{BX}$ = 2 + 5 Hz), 4·75 (1H, t, $J_{AX} + J_{BX}$ = 2 + 7 Hz) and 4·90 (1H, s). (Found: C, 62·53; H, 7·98. $C_{28}H_{42}O_{10}$ requires: C, 62·43; H, 7·86%).

Mesylation of 1β,10β-*glycol* **16**. The glycol **16** (54 mg) was treated under similar conditions as for **14** giving in mesylate **17** (55 mg); NMR δ 1·00 (6H, s), 1·33, 1·55, 1·62 (each 3H, s), 1·93 (OAc), 2·00 (× OAc) and and 3·09.

Rearrangement of mesylate **17**. To an acetone soln (10 ml) of mesylate **17** (12 mg) NaOAc (3·2 mg) was added and the mixture refluxed with stirring for 7 hr. Solvent was removed and the residue diluted with EtOAc. The soln was washed with water, dried (Na_2SO_4) and concentrated to give a semisolid. The rearranged product was recrystallized from ether to give **18** (9 mg), m.p. 181·5–183°; $\nu_{max}^{CHCl_3}$ 1729 and 1713 (shoulder) cm^{-1}; NMR δ 1·03, 1·13, 1·28, 1·37, 1·57 (each 3H, s), 1·92, 2·00, 2·05 (OAc), 4·20 (1H, q, $J_{AX} + J_{BX}$ = 1 + 5 Hz), 4·98 (1H, s) and 5·08 (1H, q, $J_{AX} + J_{BX}$ = 6 + 7 Hz); ORD (MeOH, c = 1), $[\phi]_{303\,nm}^{max}$ +4379, $[\phi]_{262\,min}^{min}$ −9086, a = +135. (Found: C, 64·90; 7·66. $C_{28}H_{40}O_9$ requires: C, 64·59; H, 7·74%).

Elimination of acetic acid from **18**. Ketone **18** (30 mg) was dissolved in $CHCl_3$ and adsorbed on alumina (1 g) and left for 1·5 hr. Elution with EtOAc and evaporation of solvent gave 30 mg oil. This was purified by column chromatography on silica gel. Benzene–EtOAc (1:4) eluted α,β-unsaturated ketone as needles, m.p. 196·5–198°; λ_{max}^{EtOH} 224 nm (ε = 7200); ν_{max}^{nujol} 1725, 1690 and 1622 cm^{-1}; NMR δ 1·20 (6H, s), 1·29, 1·43, 1·62 (each 3H, s), 1·90, 2·00 (OAc), 4·20 (1H, q, $J_{AX} + J_{BX}$ = 2 + 5 Hz), 4·99 (1H, s), 5·73 and 6·15 (each 1H, ABq, J = 10 Hz). (Found: C, 65·68; H, 8·19. $C_{26}H_{36}O_7$ requires: C, 65·83; H, 8·19%).

Mesylation of 10α-*alcohol* **14a**. Treatment of **14a** (48 mg) under the conditions described above for 10β-alcohol **14b** gave the 10α-mesylate which used for the next step without purification; NMR δ 0·92 (6H, s), 1·31, 1·43, 1·59 (each 3H, s), 1·95, (OAc), 2·03 (2 × OAc), 3·07 (3H, s).

Elimination reaction of 10α-*mesylate*. For the 10α-mesylate (50 mg) the same procedure was used as for the 10β-mesylate. The yields of Δ^9-olefin and $\Delta^{1(10)}$-olefin were 43 mg and 5 mg, respectively.

Oxidation of Δ^9-*olefin with* OsO_4. A soln of the Δ^9-olefin **15a** (40 mg) in pyridine (1 ml) was treated with OsO_4 (40 mg) under similar conditions as for **15b**. After 3 days working-up afforded 9α,10α-glycol **20** (42 mg) amorph; $\nu_{max}^{CHCl_3}$ 3580, 3520 and 1729 cm^{-1}; NMR δ 0·94, 1·00, 1·31, 1·52 1·58 (each 3H, s), 1·93, 2·01, 2·04 (OAc), 3·26 (1H, m),4·14 (1H, q, $J_{AX} + J_{BX}$ = 2 + 5 Hz), 4·77 (1H, q, $J_{AX} + J_{BX}$ = 4 + 5 Hz) and 5·56 (1H, s). (Found: C, 62·50; H, 8·39. $C_{28}H_{42}O_{10}$ requires: C, 62·43; H, 8·30%).

Mesylation of **20**. Glycol **20** (54 mg) was treated under similar conditions for **16**. The monomesylate (55 mg) was obtained; NMR δ 0·93, 1·01, 1·30, 1·58, 1·60 (each 3H, s), 1·91, 2·00, 2·03 (OAc) and 3·00 (3H, s).

Rearrangement of the monomesylate of **20**. The mesylate of **20** (12 mg) was dissolved in $CHCl_3$, adsorbed on an alumina column (1 g) and left for 12 hr. The product was eluted and purified by column chromatography on silica gel with benzene–EtOAc (9:1) to give rearranged ketone **21a** (7 mg) and starting material (4 mg). **21a** was obtained in amorphous form; $\nu_{max}^{CHCl_3}$ 1723 and 1703 cm^{-1}; NMR δ 0·96, 0·99, 1·34, 1·51, 1·61 (each 3H, s), 1·95, 1·98, 2·02 (OAc), 4·20 (1H, q, $J_{AX} + J_{BX}$ = 1 + 5 Hz), 4·62 (1H, s) and 4·91 (1H, t, $J_{AX} + J_{BX}$ = 7 + 7 Hz); ORD (MeOH, c = 1), $[\phi]_{324\,nm}^{max}$ +953, $[\phi]_{278\,nm}^{min}$ −2427, a = +34; Mass M^+ 520.

Hydrolysis of the rearranged ketone **21a**. The keto acetate **21a** (80 mg) was added to a methanolic soln (10 ml) of NaOMe (from 15 mg of Na) and the soln allowed to stand for 15 hr at room temp. A small amount of water was then added, the solvent evaporated *in vacuo* and residue extracted with EtOAc. Evaporation of solvent gave crystalline hydroxyl compound **21b**, m.p. 187·5–189·5°; ν_{max}^{nujol} 3560 and 1706 cm^{-1}; NMR δ 0·91, 1·09 (each 3H, s), 1·35 (6H, s), 1·49 (3H, s), 3·49 (1H, s), 3·70 (2H, m), 4·32 (1H, q, $J_{AX} + J_{BX}$ = 6 Hz); ORD (MeOH, c = 1), $[\phi]_{320\,nm}^{max}$ +1015, $[\phi]_{274\,nm}^{min}$ −2328, a = +33; Mass M^+ 394. (Found: C, 66·95; H, 8·70. $C_{22}H_{34}O_6$ requires: C, 66·98; H, 8·69%).

Deuteration of hydroxy ketone **21b**. Ketone **21b** (12 mg) was refluxed in a soln prepared from MeOD (1 ml), D_2O (0·5 ml) and sodium (40 mg) for 3 days. After cooling, the product was extracted with ether, the organic layer washed with brine and dried (Na_2SO_4). Evaporation of solvent gave the d_2 compound in amorphous form: ν_{max}^{nujol} 2200 and 2120 cm^{-1}; Mass M^+ 396.

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