Introduction of Several Groups to the D-ring of Grayanotoxin

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Summary

Grayanotoxin (GTX), one of the lipid-soluble Na^+ channel openers, contains four rings (A, B, C and D) and the chemical groups essential for the pharmacological action are located on the A- and B-rings. To study the biological significance of functional groups on the D-ring, 51 new derivatives were prepared from α-dihydro GTX-II. These new compounds and the previously prepared GTXs were directly applied to the intracellular phase of internally perfused squid giant axons.

Introduction

It has been found that GTX[11], the Ericaceae toxins, exerts a depolarizing action upon a variety of electrically excitable cells, through a specific increase in the membrane permeability to Na^+ ion.[18] A systematic study of the structure-activity relationship for GTX[16] has demonstrated that the essential groups for the pharmacological action included 3β-OH, 5-OH, 6β-OH and 10-CH_3. With regard to the D-ring of GTX, however, the efficacy of the functional groups synthetically induced has been unclear.

Quite recently, we reported biological activities of the newly synthesized GTX derivatives.[21] The purposes of this study were to search for substitution position(s) acceptable to suitable substituents for the synthesis of pharmacological probes and to clarify detailed parmacological effects of functional groups on the D-ring. In the experiments, the GTX derivatives were directly applied to the intracellular phase of internally perfused squid giant axons, and EC_{50} and the maximum value of depolarization for these new compounds as well as the previously synthesized GTXs were evaluated. α-Dihydro GTX-II (**1**)[11], obtained from hydrogenation of GTX-II, was found to have the highest

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activity (EC_{50} 2.19 $\times 10^{-6}$M) among all analogs tested, while the other 23 analogs showed very low activity ($EC_{50} < 10^{-4}$M). After surveying the chemical characteristics of these 23 analogs, we found two distinguished positions, C-15 and C-16, on the D-ring at which chemical modification brought about the significant decrease of the biological activity. The substituents introduced into those positions were classified as follows :

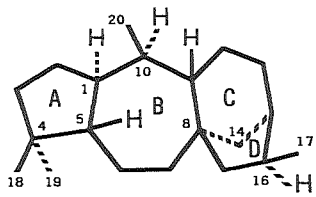

Fig. 1 Grayanotoxane.

C-16 A. dissociative groups, such as NH_2, CH_2NH_2, CH_2NHR, CO_2H.
B. electronegative groups, such as β-OH, β-OCH_3, >C=O, >C=NOH.
C. others, such as CO_2R, $CH_2NHCOCH_3$.

C-15 α- and β-OH, >C=O.

Based on the studies described above, we demonstrated that the positions on GTX suitable for synthesis of pharmacological probes should be C-17 in grayanotox-15-ene (GX-15-ene) derivatives and C-14*R* in α-dihydro GTX-II (**1**).

This paper describes the synthesis of GTX derivatives with various functional groups on the D-ring together with their biological activities.

The nomenclature for the GTX analogs follows the Chemical Abstracts System, in which α-dihydro GTX-II (**1**) is designated as grayanotoxane (GX)-3β, 5, 6β, 14*R*, 16-pentaol.

Results and Discussion

Syntheses of GX-15-ene-17-Substituted Analogs (Fig. 2 and 3)

α-Dihydro GTX-II (**1**) was converted to 3, 6, 14, 16-tetraacetyl α-dihydro GTX-II (**1a**).[11] Compound **1a** lost one mol. of acetic acid on heating at 230℃ to yield **2a**. The ^{1}H NMR spectrum of **2a** showed a one-proton broad singlet at δ 5.00 and a three-proton doublet at δ 1.70 (an allylic coupling ; J = 1.5 Hz) corresponding to a partial structure -CH=C-CH_3, indicating the presence of a double bond between C-15 and C-16. Alkaline hydrolysis of **2a** afforded the known GX-15-ene-3β, 5, 6β, 14*R*-tetraol (**2**).[15]

Briggs *et al*[3] reported that on treatment with *N*-bromosuccinimide (NBS), (-)-isokaurene was converted to 17-bromokaur-15-ene as a major product. Similarly, the allylic bromination of **2** and **2a** with NBS gave mainly 17-bromo-15-enes (**3** and **3a**), respectively. The bromine of **3a** was displaced with a hydroxy group on treatment with THF/H_2O (1 : 3) yielding **4a**, which was converted to **4** on alkaline hydrolysis. The ^{1}H NMR spectra of **4** and **4a** showed a two-proton singlet due to 17-H_2 at δ 4.15 and 4.20, respectively. Treatment of **3a** with sodium methoxide or ethoxide gave triacetyl 17-methoxy-15-ene (**5a**) or triacetyl 17-ethoxy-15-ene (**6a**). On alkaline hydrolysis, **5a** or **6a** afforded the corresponding methoxy (**5**) or ethoxy compound (**6**). Compound **3** was also converted to 15-ene-17-(4'-hydroxy)butanoate (**7**) or 15-ene-17-(6'-hydroxy)hexanoate (**8**), by treatment with 4-tetrahydropyranyloxybutanoic acid or 6-tetrahydropyranyloxyhexanoic acid in the presence of potassium carbonate and subsequent heating with 50%

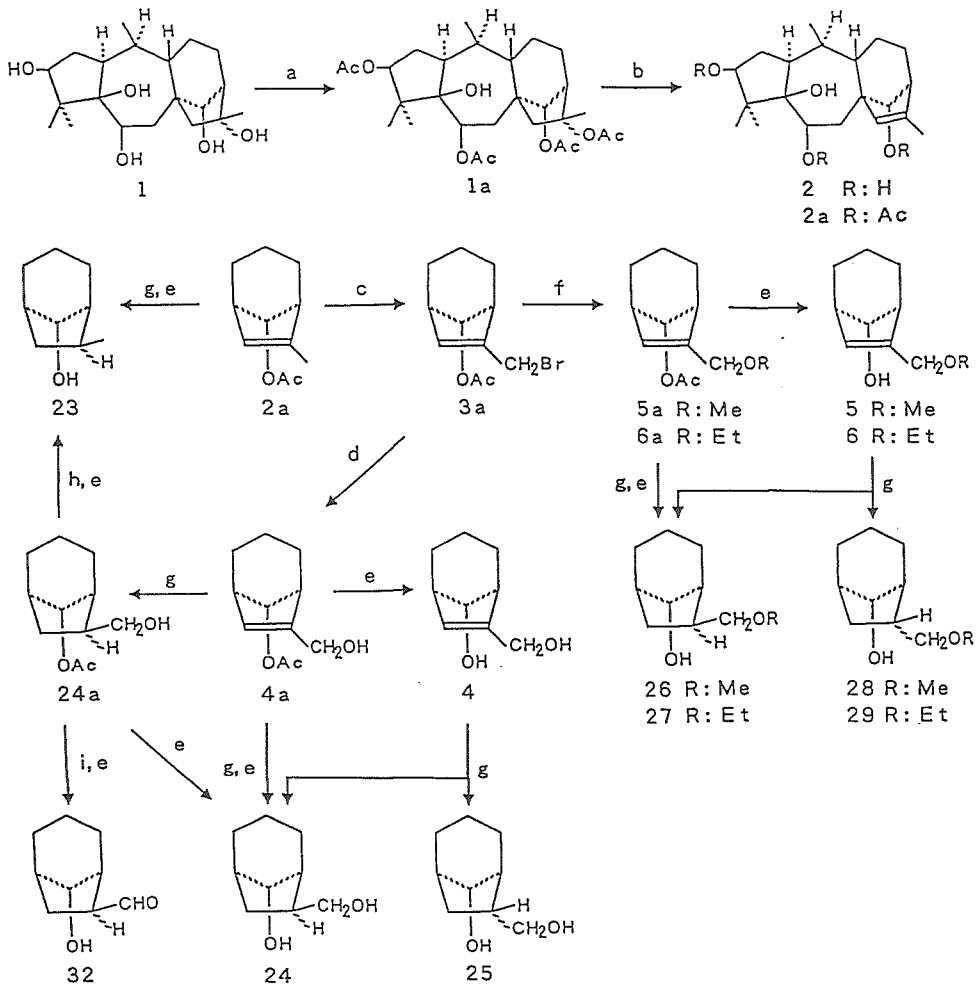

Fig. 2 a) Ac_2O-Py, 100℃, 20 hr ; b) 230℃ ; c) NBS-CCl_4 ; d) H_2O ; e) OH^- ; f) NaOR ; g) H_2, Pd-C ; h) 1. TsCl-Py, 2. $NaBH_4$-DMSO ; i) PCC.

acetic acid. Compound **3** and 4-acetoxybutanoic acid afforded 15-ene-17-(4'-acetoxy) butanoate (**9**) as well. Compound **3** was converted with sodium acetate to 15-ene-17-acetate (**10**). Amination of **3** was achieved by treatment with ammonia-MeOH to give 15-ene-17-amine (**11**). The *N*-methylimine (**12**), *N*-ethylimine (**13**), *N*-propylimine (**14**), *N*-isopropylimine (**15**) and *N*-benzylimine (**16**) were also obtained from compound **3** and the corresponding alkyl amine. Acetylation of **11** and subsequent alkaline hydrolysis gave *N-acetoxyimine (***17**). 17-Mercapto-GX-15-ene-3β, 5, 6β, 14*R*-tetraol (**18**) was obtained from **3** and 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione (HEDPPT).[17] The ^{1}H NMR signals due to the 17-methylene groups and the 15-methine groups in these 15-ene-17-substituted analogs (**5**-**18**) appeared at δ 3. 26-4. 74 (a two-proton singlet, a doublet or a doublet of doublets) and δ 5. 18-5. 35 (a one-proton singlet), respectively, indicating presence of a group -CH=C-CH_2-.

Oxidation with pyridinium chlorochromate (PCC) of **4a** and subsequent alkaline hydrolysis afforded an α, β-unsaturated aldehyde (**19**), whose IR spectrum and ^{1}H NMR

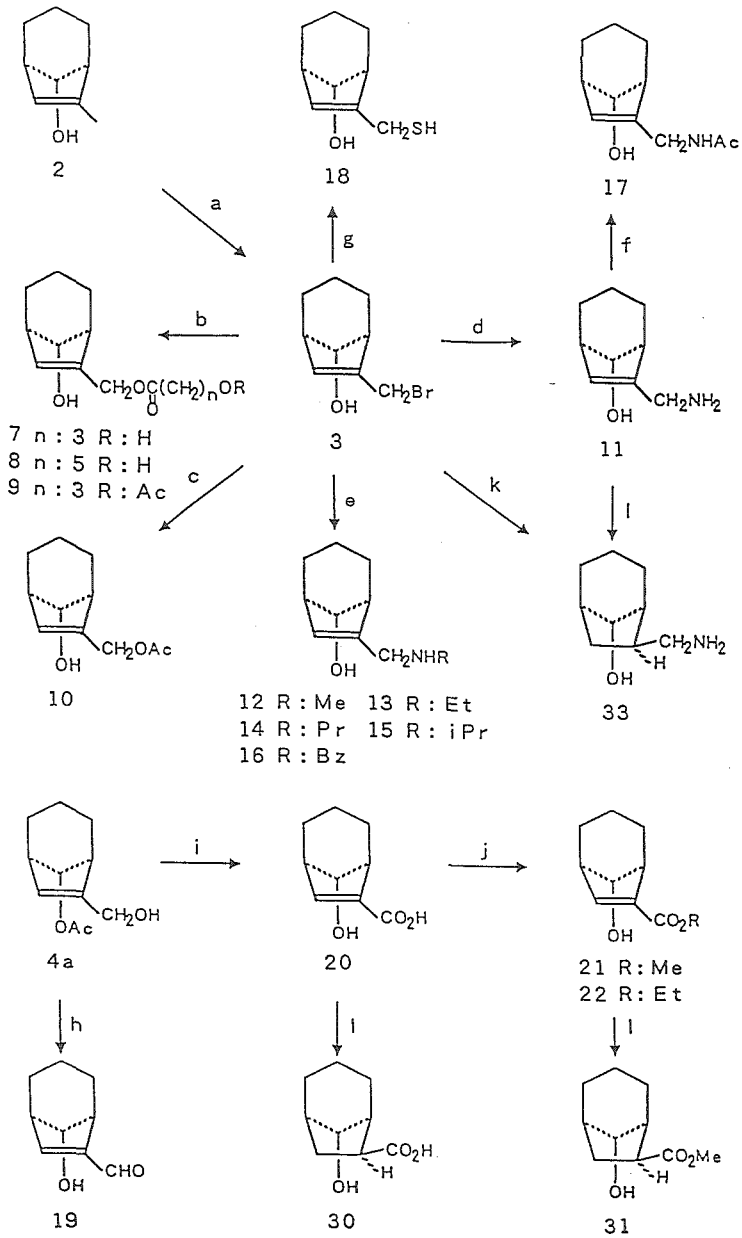

Fig. 3 a) NBS-C_6H_6 ; b) 1. $THPO(CH_2)_nCO_2H$ or $AcO(CH_2)_nCO_2H$, K_2CO_3, 2. 50% AcOH ; c) NaOAc ; d) NH_3 ; e) RNH_2 ; f) 1. Ac_2O-Py, 2. OH^- ; g) HEDPPT ; h) 1. PCC, 2. OH^- ; i) 1. Jones oxd., 2. OH^- ; j) CH_2N_2 or EtOH/HCl ; k) 1. Amberlite-N_3, 2. H_2, PtO_2 ; l) H_2, Pd-C.

showed the presence of the group. The Jones oxidation of **4a** and subsequent hydrolysis gave 15-ene-17-carboxylic acid (**20**). The carboxylic acid was converted to a methyl ester (**21**) and an ethyl ester (**22**).

Hydrogenation of GX-15-ene-17-Substituted Analogs (Fig. 2 and 3)

Hydrogenation of the 15-16 double bond in these unsaturated compounds described above took place at the α-face or the α- and β-face of the molecule owing to a class of

the 17-substituents. Compound **2a** was hydrogenated over palladium on charcoal (Pd-C) followed by alkaline hydrolysis to give GX-3β, 5, 6β, 14R-tetraol (**23**) as a sole product. Comparing of the ^{1}H NMR spectrum of **23** with that of the corresponding 16-epimer (**44**), which will be described afterward, a three-proton doublet signal at δ 1.04 due to 17-CH_3 in **23** was shifted to δ 1.15 in **44** and a one-proton multiplet at δ 2.43 due to 16-H in **23** to δ 1.66 in **44**. The downward shifts of 17-CH_3 signal in **44** and 16-H signal in **23** were caused by the 1, 3-diaxial effect[1] with 14R-OH. On hydrogenation of the double bond, **4a** yielded **24a** alone. The structure of **24a** was determined as follows : **24a** was derived to the corresponding 17-tosylate, which was converted to **23** on $NaBH_4$-DMSO reduction and subsequent saponification. Hydrogenation of **4** gave however an epimeric mixture of **24** and **25** in which the former predominated. The ^{1}H NMR signal (at δ 2.62) due to 16-H in **24** was shifted to δ 2.00 in **25**. In hydrogenation of **5a** or **6a** and subsequent saponification, **26** or **28** was a sole product. But **5** or **6** gave an epimeric mixture of **26** and **27**, or of **28** and **29**. In both cases **26** and **28** were the major products. In these cases, it would suggest that the presence of 14R-acetoxy or hydroxy group controls the face of the hydrogen attack. The presence of carboxyl or carboxymethyl group at C-16 (**20** or **21**) makes however the hydrogen attack occur solely at the α-face to give **30** or **31**. Compound **32** was obtained from **24a** through PCC oxidation and subsequent alkaline hydrolysis. Treatment of **3** with Amberlite IRA-400-azide[8] followed by hydrogenation gave 17β-amine (**33**), which was also obtained by hydrogenation of **11**.

Syntheses of 15-Substituted Analogs (Fig. 4)

On treatment with *m*-chloroperbenzoic acid (MCPBA), **2a** gave the 15α, 16α-epoxide (**34a**)[14], which was rearranged to 16-ene-15α-hydroxy compound (**35a**) according to the method reported by Briggs *et al*[2]. Alkaline hydrolysis of **35a** yielded **35**. The ^{1}H NMR signal of 15β-H appeared at δ 3.82 (**35a**) or 3.86 (**35**), and that of the exo methylene group at δ 5.23 and 5.44 (**35a**) or δ 5.21 and 5.43 (**35**). Compound **35** was hydrogenated over platinum oxide in acetic acid to give an epimeric mixture of 16-epi-GX-3β, 5, 6β, 14R, 15α-pentaol (**36**) and GX-3β, 5, 6β, 14R, 15α-pentaol (**37**), in which the former was predominated. The structure of **36** was determined by X-ray diffraction analysis (Table 1 and Fig. 5). Hydrogenation of **35a** under the same condition as described above gave also an epimeric mixture of **36**- and **37**-triacetate, but in which a ratio of the former became larger than the case of hydrogenation of **35**. Hydroboration of **2a** and subsequent H_2O_2-OH^- oxidation gave also **37**.

In deuteriomethanol the ^{1}H NMR signals (doublets) of 17-CH_3 in **36** and **37** appeared at the same field (δ 1.70), but in deuteriopyridine at δ 1.47 (**36**) and 1.29 (**37**) showing the 1, 3-diaxial effect caused by 14R-OH. Although the 16-H in **37** occupies a 1, 3-diaxial position with respect to 14R-OH, the proton resonates at the same field (δ 2.15) as that in **36** (δ 2.21) in deuteriomethanol. It is considered that this phenomenon is a consequence of the anisotropy of 15α C-O bond on the adjacent carbon atom. The similar stereostructural situation is observed on the 2β-H of α-dihydro GTX-II (**1**) and other GTXs ; the hydrogen occupies a 1, 3-diaxial position with respect to 5-OH and at the same face as 3β-OH. The 2β-H resonates however at higher field (δ 1.87 in α-dihydro GTX-II) than 2α-H (δ 2.21) in deuteriomethanol. The 2β-H resonance occurs as a doublet of

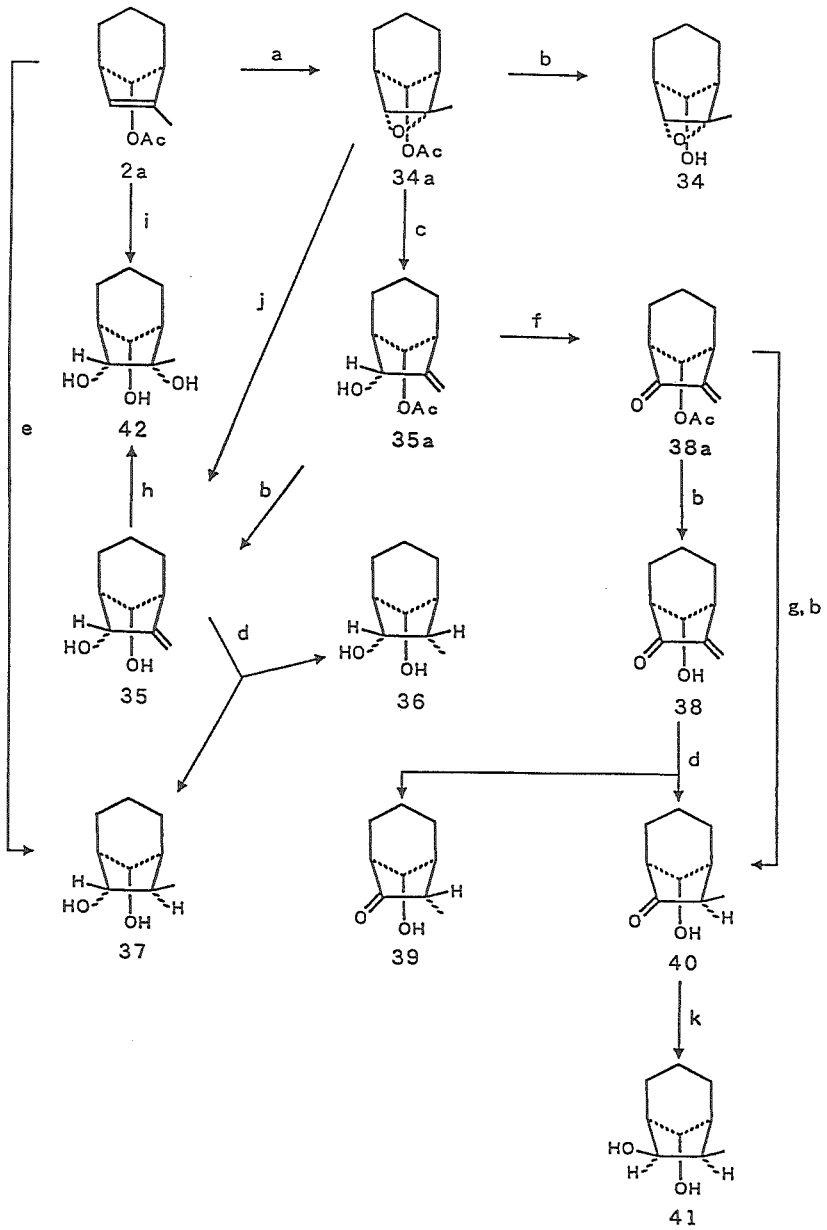

Fig. 4 a) MCPBA ; b) OH^- ; c) Mg-$BrCH_2CH_2Br$-Et_2O ; d) H_2, PtO_2, AcOH ; e) 1. BH_3-THF, 2. H_2O_2-OH^- ; f) PCC ; g) $NaBH_4$; h) 1. $Hg(OAc)_2$; 2. $NaBH_4$, OH^- ; i) 1. OsO_4, 2. Na_2SO_3 ; j) 10% NaOH ; k) $LiAlH_4$.

doublets (J = 5.0, 12.0 Hz), due to coupling with the 1α- and 2β-Hs, since vicinal coupling to the 3α-H is very small.

PCC oxidation of **35a** afforded a conjugated keto acetate (**38a**), which was converted to the corresponding unsaturated ketone (**38**). Hydrogenation of **38** in the presence of platinum oxide gave a mixture of 3β, 5, 6β, 14R-tetrahydroxy-16-epi-GX-15-one (**39**) and 3β, 5, 6β, 14R-tetrahydroxy-GX-15-one (**40**) in which the former predominated. In the ^{1}H NMR spectra of the two epimers, a three-proton doublet signal due to 17-CH_3

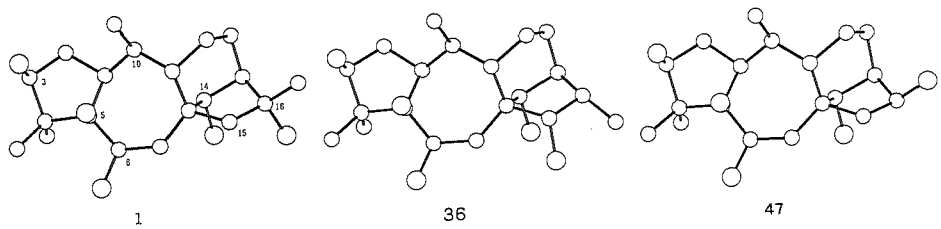

Fig. 5 Stereoscopic view. Hydrogen atoms were omitted.

Table 1 Crystal data

Compound No		36	47
Molecular formula		$C_{20}H_{34}O_5$	$C_{19}H_{32}O_5$
Molecular weight		354.5	340.5
Crystal system		orthorhombic	orthorhombic
Space group		$P2_12_12_1$	$P2_12_12_1$
Cell dimensions	a	13.600(2)Å	15.026(1)Å
	b	19.560(2)Å	18.069(1)Å
	c	7.009(1)Å	6.331(1)Å
V		1864.6(3)Å^3	1718.8(3)A^3
Z		4	4
D_c		1.263 g cm^{-3}	1.316 g cm^{-3}
μ (Cu Kα)		7.27cm^{-1}	7.67cm^{-1}
Crystal size :		0.25×0.25×0.25mm^3	0.3×0.3×0.2mm^3
Diffractometer : Rigaku AFC-5R		40kv, 150mA	40kv, 100mA
Radiation :		CuKα(λ=1.54178Å)	
Scan method :		ω-2θ	
$2\theta_{max}$		130°	
Number of unique reflections measured :		1840	1715
Number of observed reflections with $\mid F_o \mid < 3\sigma(F_o)$:		1767	1664
Structure determination :		direct method	
Refinement by block-diagonal least-squares method :		$\Sigma(w \mid \Delta F \mid^2)$ minimized	
Parameters refined :		positional ones for all the atoms anisotropic thermal ones for the non-H atoms (Temperature factor of each H atom set equal to B_{eq} of the bonded atom)	
Weighting scheme w :		$[\sigma^2(F_o)+0.00135 \mid F_o \mid^2]^{-1}$ for observed reflections	$[\sigma^2(F_o)+0.00125 \mid F_o \mid^2]^{-1}$
		0 for reflections with $w^{1/2} \mid \Delta F \mid > 4$ (13 reflections) and very intense ones (12 reflections)	0 for reflections with $w^{1/2} \mid \Delta F \mid > 4$ (27 reflections) and very intense ones (17 reflections)
Numer of reflections used for the final cycle :		1742	1620
R		0.035	0.034
Rw		0.050	0.048
S		1.251	1.266

Computer : FACOM M-340R at Shionogi Res. Lab. Program used for computation : MULTAN 84, PLUTO, XPACK 86 SHIONOGI

appeared at δ 1.33 (**39**) or 1.14 (**40**) and a one-proton doublet of double doublets signal due to 16-H at δ 2.18 (**39**) or 2.73 (**40**). The downward shifts of 17-CH_3 signal in **39** and 16-H signal in **40** were caused by 14*R*-OH. Reduction of **38a** with sodium borohydride followed by alkaline hydrolysis gave also the saturated ketone (**40**). Lithium aluminium hydride reduction of **40** afforded GX-3β, 5, 6β, 14*R*, 15β-pentaol (**41**). In comparison of the ^{1}H NMR spectrum of **41** with that of the corresponding 15-epimer (**37**), a one-proton doublet signal at δ 3.37 due to 15-H in **37** was shifted to δ 4.10 (J = 10.7 Hz) in **41**, which was caused by the 1, 3-diaxial effect with 14*R*-OH. Oxymercuration-demercuration of **35** gave GX-3β, 5, 6β, 14*R*, 15α, 16-hexaol (**42**), which was obtained previously[14] by osmium tetraoxide oxidation of **2a**. Alkaline epoxy-ring opening of **34a** was attempted, but the product was GX-16-ene-3β, 5, 6β, 14*R*, 15α-pentaol (**35**).

Modification of 16-ketone (Fig. 6)

α-Dihydro GTX-II (**1**) was converted with acetone-perchloric acid at 0-5℃[7] to a 5, 6-isopropylidene derivative, which was acetylated to a corresponding 3, 14-diacetate. On treatment of the isopropylidene-diacetate with phosphorus oxychloride-pyridine at room temperature, 16-OH was dehydrated to give a mixture of 15- and 16-ene (**43a**).[22] The ^{1}H NMR spectrum of **43a** exhibited two singlets due to 15-H of the 15-ene and 17-H_2 of the 16-ene at δ 5.28 and 4.82, respectively. Hydrogenation of **43a** followed by alkaline hydrolysis gave two dihydro compounds, which were treated separately with trifluoroacetic acid to give **23** and 16-epi-GX-3β, 5, 6β, 14*R*-tetraol (**44**), the former predominated. A comparison of ^{1}H NMR spectra of **44** and **23** was described before. Ozonolysis of **43a** afforded diacetyl-isopropylidene-16-ketone (**45a**), which was converted to triacetyl 16-ketone (**45b**). Alkaline hydrolysis of **44a** and subsequent treatment with trifluoroacetic acid gave **45**, whose IR spectrum exhibited a cyclopentanone band at 1730 cm^{-1}. On the Grignard reaction with methylmagnesium bromide in THF followed by trifluoroacetic acid treatment, **45a** gave 16-epi-α-dihydro GTX-II (**46**) as expected.[6,7,20] When the ^{1}H NMR spectrum of **46** was compared with that of α-dihydro GTX-II (**1**), the 17-methyl signal of the former appeared at δ 1.56 and that of the latter at δ 1.36. This downfield shift was caused by the 1, 3-diaxial effect with 14*R*-OH. Reduction of **45b** with sodium borohydride gave **47a**, which was hydrolyzed to 17-nor-GX-3β, 5, 6β, 14*R*, 16β-pentaol (**47**). The structure of **47** was determined by X-ray analysis (Table 1 and Fig. 5). Treatment of **47a** with boron trifluoride-etherate in the presence of diazomethane-methylene chloride[5,19] followed by alkaline hydrolysis yielded the corresponding 16β-methoxy compound (**48**). The ^{1}H NMR spectra of **47** and **48** showed a doublet of double doublets signal due to 16α-H at δ 4.59 and 4.14, respectively. The Wolff-Kishner reduction of **45** gave 17-nor-GX-3β, 5, 6β, 14*R*-tetraol (**49**). On treatment with hydroxylamine-hydrochloride, **45** gave the corresponding oxime (**50**). The oxime was reduced with platinum oxide-acetic acid to a mixture of the epimeric 16-amines. The mixture was treated with benzylchloroformate to give an epimeric mixture of the *N*-benzyloxycarbonyl (Z) amines, which was separated with silica gel column chromatography to each other followed by hydrogenolysis to give 16α-amine (**51**) and 16β-amine (**52**). In the ^{1}H NMR spectra of the two epimers, a one-proton signal due to 16-H appeared at δ 3.13 (**51**) or 3.70 (**52**). The downward shift of the signal in **52** was caused by 14*R*-OH.

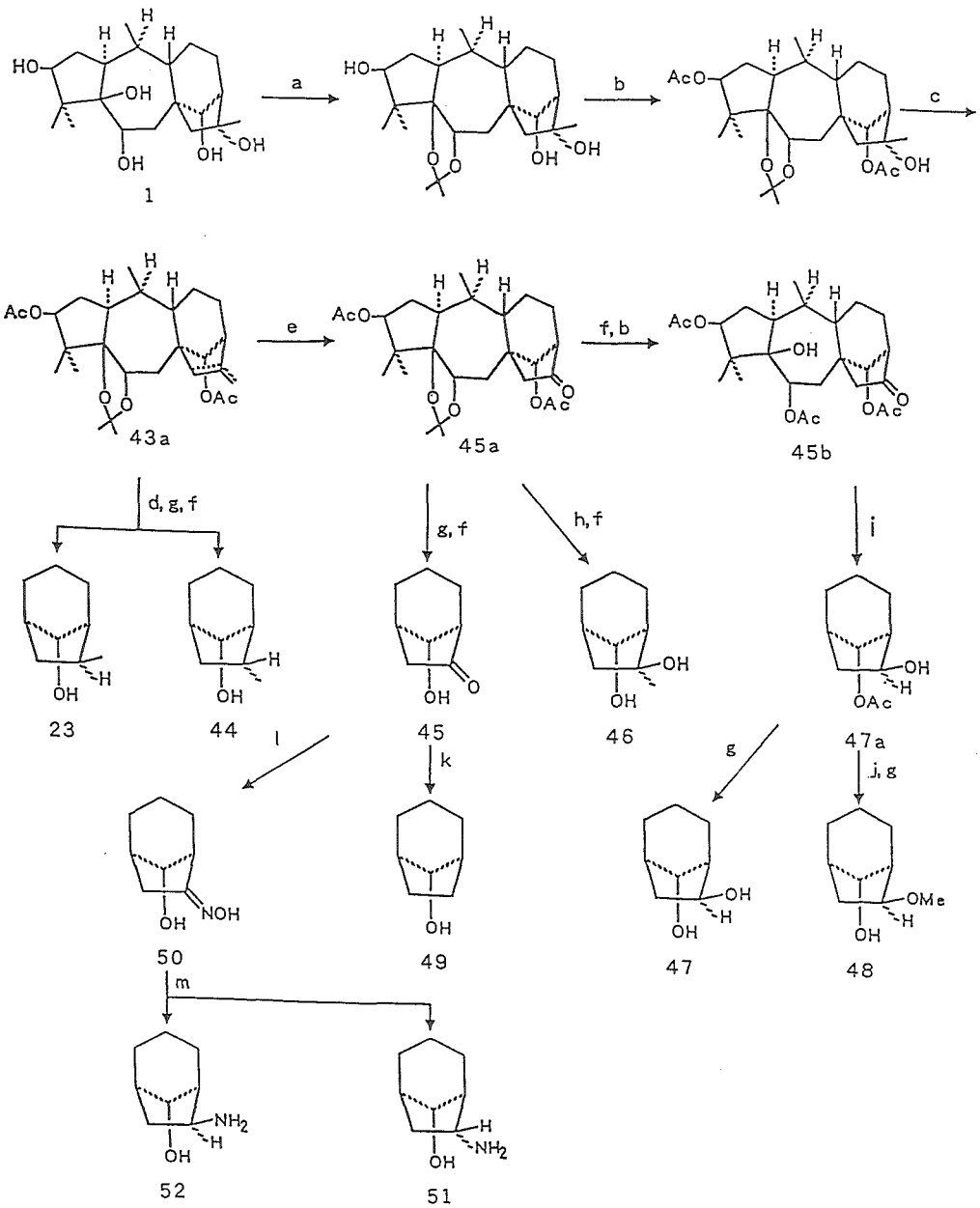

Fig. 6 a) Me_2CO, $HClO_4$, 0-5℃ ; b) Ac_2O-Py ; c) $POCl_3$-Py ; d) H_2, Pd-C ; e) 1. O_3, 2. Zn-AcOH ; f) CF_3CO_2H - CH_2Cl_2 ; g) OH^- ; h) MeMgBr ; i) $NaBH_4$; j) CH_2N_2- BF_3 ; k) NH_2NH_2, KOH, 200℃ ; l) NH_2OH ; m) H_2, PtO_2, AcOH.

Syntheses of 14-Substituted Analogs (Fig. 7)

α-Dihydro GTX-II 3, 6, 14, 16-tetraacetate (**1a**) was hydrolyzed partialy with potassium carbonate-methanol to give 14, 16-diacetate (**53**).[14] The diacetate was converted to 3, 6-dibenzyl-14, 16-diacetate, which was hydrolyzed with lithium aluminium hydride to 3, 6-dibenzyl-α-dihydro GTX-II. The dibenzyl compound was treated with acetic

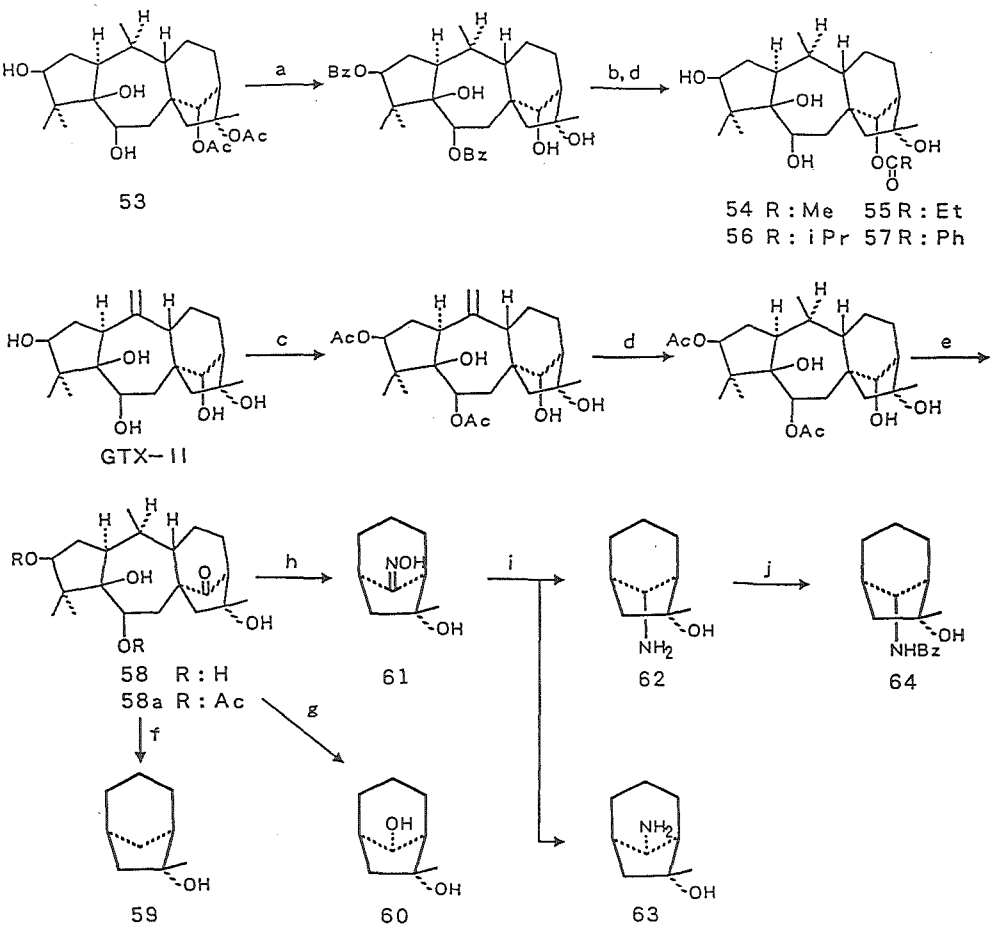

Fig. 7 a) 1. NaH, BzBr, 2. $LiAlH_4$; b) $(RCO)_2O$-Py ; c) Ac_2O-Py ; d) H_2, Pd-C ; e) Jones oxd. ; f) NH_2NH_2, KOH, 200℃ ; g) $NaBH_4$; h) NH_2OH ; i) H_2, PtO_2, AcOH ; j) BzBr, K_2CO_3.

anhydride-pyridine followed by hydrogenolysis to give α-dihydro GTX-II 14-acetate (**54**). Along with the similar way, α-dihydro GTX-II 14-propionate (**55**), 14-isobutyrate (**56**) and 14-benzoate (**57**) were also obtained.

Acetylation of GTX-II with acetic anhydride-pyridine at 0-5℃ yielded 3, 6-diacetate[9], which was hydrogenated over Pd-C to 3, 6-diacetyl-α-dihydro GTX-II. The Jones oxidation of the diacetate afforded 3,6-diacetyl-14-ketone (**58a**), which was hydrolyzed with potassium carbonate to the corresponding ketone (**58**) as reported previously[14]. The Wolff-Kishner reduction of **58** gave GX-3β, 5, 6β, 16-tetraol (**59**). Sodium borohydride reduction of **58** yielded a mixture of the 14-hydroxy epimers, which was separated each other with silica gel column chromatography to afford α-dihydro GTX-II (**1**) and GX-3β, 5, 6β, 14*S*, 16-pentaol (**60**), the latter predominated. Comparing the ^{1}H NMR signal due to 14-H of **1** with that of **60**, a one-proton singlet at δ 3.98 in **1** was shifted to δ 4.34 (a doublet, J = 4.4 Hz) in **60**. The splitting[12] and the downward shift of the signal support the structure of **60**. On treatment with hydroxylamine hydrochloride

in pyridine at 100 ℃, **58** gave 14-oxime (**61**). The oxime (**61**) was hydrogenated over platinum oxide to give a mixture of the epimeric 14-amines. The mixture was separated each other with preparative silica gel TLC to give 14*R*-amine (**62**) and 14*S*-amine (**63**) as previously reported.[10] The ^{1}H NMR spectrum of **62** showed a one-proton singlet due to 14-H at δ 3.30 and that of **63** a one-proton doublet (J = 3.5 Hz) due to 14-H at δ 3.47 ; this finding supports the configuration of the epimers. Compound **62** was converted to 14*R*-*N*-benzylimino-GX-3β, 5, 6β, 16-tetraol (**64**) on treatment with benzyl bromide in the presence of potassium carbonate. Introduction of the benzyl group to 14*R*-NH_2 caused a diamagnetic shift of ^{1}H NMR signals due to 1-H, 2α-H, 14-H and 19-H_3 in **61** (1-H : δ 2.51→1.64~1.68 ; 2α-H : 2.20→1.82 ; 14-H : 3.30→2.83 ; 19-H_3 : 1.05→0.77). It would suggest that these protons may lie in the shielded field by the benzene ring, and therefore suffer the diamagnetic shift.

Experimental

Melting points (mp) were determined with a Yanagimoto micromelting point apparatus and uncorrected. Evaporation was conducted under reduced pressure. TLC spots were visualized with spraying of anisaldehyde-H_2SO_4 and then heating. IR spectra were recorded on a Hitachi EPI-G3 spectophotometer and ^{1}H NMR spectra on a Varian VXR-500 Instrument. The coupled NMR signals were assigned with ^{1}H-^{1}H COSY spectra. Letters (br.) s, d, t, q, and m represent (broad) singlet, doublet, triplet, quartet and multiplet, respectively. Mass spectra on a JEOL JMS-D 300. Biological activities (EC_{50} and Max. mV of depolarization) were determined using squid giant axons by means of the method described in the previous paper[21]. All stock solutions of GTX analogs were dissolved in DMSO at a final concentration of 10^{-1}M. Tested solutions were diluted with the standard internal solution.

*GX-10(20)-ene-3β, 5, 6β, 14R, 16-pentaol (GTX-*II*).*[11] Dried leaves (1 kg) of *Leucothoe grayana* Max. were extracted twice with 15 l of boiling water and the aqueous solution was concentrated to 1.2 l under atmospheric pressure. The concentrate was extracted continuously with ether for 4 days to yield a mixture of resine and crystals, to which EtOAc was added for dissolving the resine. Filtration and recrystallization of the crystals from EtOAc gave 6.2 g of GTX-II, mp 206-207℃.

*GX-3β, 5, 6β, 14R, 16-pentaol (α-dihydro GTX-*II*)* (**1**).[11,13] ^{1}H-NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.22 (3H, d, J = 6.5 Hz, 20-H), 1.24 (3H, s, 18-H_3), 1.36 (3H, s, 17-H_3), 1.84 (1H, d, J = 14.9 Hz, 15β-H), 1.87 (1H, dd, J = 5.0, 14.5 Hz, 2β-H), 1.88 (1H, dd, J = 11.3, 13.3 Hz, 7b-H[a]), 1.94 (1H, d, J = 14.9 Hz, 15α-H), 2.01 (1H, br. s, 13-H), 2.11 (1H, dd, J = 4.5, 13.3 Hz, 7a-H[a]), 2.21 (1H, ddd, J = 4.8, 12.2, 14.5 Hz, 2α-H), 2.59 (1H, ddd, J = 4.9, 5.3, 12.2 Hz, 1-H), 3.62 (1H, d, J = 4.8 Hz, 3-H), 3.92 (1H, dd, J = 4.5, 11.3 Hz, 6-H), 3.98 (1H, s, 14-H). Activity : EC_{50} 2.19×10^{-6} M ; Max. 64.0 mV.

*GX-3β, 5, 6β, 14R, 16-pentaol 3, 6, 14, 16-tetraacetate (3,6,14,16-tetraacetyl α-dihydro GTX-*II*)* (**1a**)[11]. α-Dihydro GTX-II (1) in acetic anhydride-pyridine was heated at 100℃ for 20 hr to give the tetraacetate (**1a**). ^{1}H-NMR δ ($CDCl_3$-D_2O) : 0.85 (3H, s, 19-H_3), 1.05 (3H, s, 18-H_3),

a) Since the B ring of GTX is flexible, the configuration of two hydrogens on C_7 couldn't be assigned as 7α or 7β in each GTX. Therefore, they were designated as 7a-H or 7b-H according to their coupling pattern.

1.10 (3H, d, J = 6.5 Hz, 20-H_3), 1.60 (3H, s, 17-H_3), 1.80 (1H, dd, J = 5.0, 15.5 Hz, 2β-H), 1.88 (1H, dd, J = 11.5, 13.5 Hz, 7b-H), 1.90 (1H, dd, J = 5.0, 13.5 Hz, 7a-H), 1.95 (1H, d, J = 15.5 Hz, 15β-H), 2.15 (1H, d, J = 15.5 Hz, 15α-H), 2.30 (1H, ddd, J = 5.5, 12.5, 16.0 Hz, 2α-H), 2.76 (1H, ddd, J = 5.0, 5.5, 12.5 Hz, 1-H), 2.77 (1H, dr. s, 13-H), 4.70 (1H, dd, J = 5.0, 13.5 Hz, 6-H), 4.80 (1H, d, J = 5.5 Hz, 3-H), 5.10 (1H, s, 14-H).

GX-15-ene-3β, 5, 6β, 14R-tetraol 3, 6, 14-triacetate (**2a**). 3, 6, 14, 16-Tetraacetyl α-dihydro GTX-II (**1a**, 1.8 g) was heated at 230℃ for 7 min. An EtOAc solution of the product was washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl followed by dehydration with anhydrous Na_2SO_4. Evaporation of the solvent gave a viscous oil, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (80 : 20) gave **2a** (1.1 g), mp 117-118℃. IR ν_{max} (KBr) cm^{-1} : 3560 (OH), 3040 (-CH=C-), 1735 (AcO). ^1H NMR δ ($CDCl_3$-D_2O) : 0.85 (3H, s, 19-H_3), 1.05 (3H, s, 18-H_3), 1.10 (3H, d, J = 5.5 Hz, 20-H_3), 1.68 (1H, dd, J = 5.5, 6.5 Hz, 10-H), 1.70 (3H, d, J = 1.5 Hz, 17-H_3), 1.80 (1H, dd, J = 5.0, 16.0 Hz, 2β-H), 1.85 (1H, dd, J = 5.0, 13.5 Hz, 7a-H), 1.90 (1H, dd, J = 10.5, 13.5 Hz, 7b-H), 2.02 (3H, s, AcO), 2.05 (3H, s, AcO), 2.15 (3H, s, AcO), 2.30 (1H, ddd, J = 5.5, 12.5, 16.0 Hz, 2α-H), 2.45 (1H, d, J = 4.0 Hz, 13-H), 2.75 (1H, ddd, J = 5.0, 5.5, 11.5 Hz, 1-H), 4.70 (1H, dd, J = 5.0, 10.5 Hz, 6-H), 4.80 (1H, d, J = 5.0 Hz, 3-H), 5.00 (1H, br. s, 15-H), 5.10 (1H, s, 14-H).

GX-15-ene-3β, 5, 6β, 14R-tetraol (**2**). To a solution of **2a** (1.5 g) in EtOH (10 ml) was added 2N KOH (5 ml) and the mixture was then kept for 12 hr at room temperature. After evaporation of the solvent, the residue was worked up as usual[b] to give a solid, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (20 : 80) gave **2** (920 mg), which was crystallized from EtOAc, mp 120-122℃. The IR spectrum was identical with that of the 15-ene in the previous paper.[15] ^1H NMR δ (CD_3OD) : 1.05 (3H, 19-H_3), 1.23 (3H, d, J = 7.3 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.76 (3H, s, 17-H_3), 1.87 (1H, dd, J = 5.0, 14.3 Hz, 2β-H), 1.88 (1H, dd, J = 11.4, 13.6 Hz, 7b-H), 1.98 (1H, dd, J = 4.5, 13.6 Hz, 7a-H), 2.21 (1H, ddd, J = 4.8, 12.3, 14.3 Hz, 2α-H), 2.41 (1H, J = 3.4 Hz, 13-H), 2.57 (1H, ddd, J = 5.0, 6.0, 12.3 Hz, 1-H), 3.62 (1H, d, J = 4.8 Hz, 3-H), 3.86 (1H, s, 14-H), 3.88 (1H, dd, J = 4.5, 11.4 Hz, 6-H), 5.00 (1H, s, 15-H). Activity : EC_{50} 6.78×10^{-6} M ; Max. 65.7 mV.

GX-16-ene-3β, 5, 6β, 14R-tetraol[15]. ^1H NMR δ ($CDCl_3$-D_2O) : 1.00 (3H, s, 19-H_3), 1.18 (3H, d, J = 6.8 Hz, 20-H_3), 1.20 (3H, s, 18-H_3), 1.83 (1H, dd, J = 11.3, 13.3 Hz, 7b-H), 1.84 (1H, dd, J = 4.9, 15.0 Hz, 2β-H), 1.93 (1H, dd, J = 4.6, 13.0 Hz, 7a-H), 2.18 (1H, ddd, J = 5.1, 12.3, 15.0 Hz, 2α-H), 2.52 (1H, ddd, J = 5.3, 6.4, 12.7 Hz, 1-H), 2.58 (1H, d, J = 4.8 Hz, 13-H), 3.63 (1H, d, J = 4.9 Hz, 3-H), 3.82 (1H, dd, J = 4.5, 11.3 Hz, 6-H), 3.88 (1H, s, 14-H), 4.90 (2H, d, J = 13.3 Hz, 17-H_2). Activity : EC_{50} 6.90×10^{-6} M ; Max. 71.2 mV.

17-Bromo-GX-15-ene-3β, 5, 6β, 14R-tetraol 3, 6, 14-triacetate (**3a**). To a stirred solution of **2a** (1.0 g) in CCl_4 (15 ml) was added NBS (300 mg) and the mixture was refluxed for 1.5 hr. The mixture was filtered and the filtrate was evaporated to dryness. The residue was worked up as usual to give an oil, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (80 : 20) yielded 720 mg of **3a** as a viscous oil. IR ν_{max} (KBr) cm^{-1} : 3650 (OH), 3030 (-CH=C-), 1740 (AcO), 630 (Br). ^1H NMR δ ($CDCl_3$-D_2O) : 0.87 (3H, s, 19-H_3), 1.05 (3H, s, 18-H_3),

b) "Worked up as usual" means extraction with EtOAc and the extract was washed with sat. aq. NaCl, dried over Na_2SO_4, followed by evaporation of the solvent under reduced pressure. In case of using solvent other than EtOAc for the extraction, the solvent was described.

1.11 (3H, d, J = 6.5 Hz, 20-H_3), 1.80 (1H, dd, J = 5.0, 15.5 Hz, 2β-H), 1.88 (1H, dd, J = 5.0, 13.5 Hz, 7a-H), 1.93 (1H, dd, J = 11.5, 13.5 Hz, 7b-H), 2.02 (3H, s, AcO), 2.05 (3H, s, AcO), 2.15 (3H, s, AcO), 2.30 (1H, ddd, J = 5.5, 12.5, 16.0 Hz, 2α-H), 2.71 (1H, ddd, J = 5.0, 5.5, 12.5 Hz, 1-H), 2.72 (1H, br. s, 13-H), 4.04 (2H, s, 17-H_2), 4.68 (1H, dd, J = 5.0, 11.5 Hz, 6-H), 4.80 (1H, d, J = 5.0 Hz, 3-H), 5.12 (1H, s, 14-H), 5.47 (1H, s, 15-H).

17-Bromo-GX-15-ene-3β, 5, 6β, 14R-tetraol (**3**). To a solution of **2** (800 mg) in benzene (50 ml) was added NBS (400 mg) and the mixture was then refluxed for 1.5 hr. The mixture was diluted with water and worked up as usual to give an oil, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (20 : 80) afforded 625 mg of **3**, which was crystallized from EtOAc, mp 115-120℃. IR υ_{max} (KBr) cm^{-1} : 3440 (OH), 3030 (-CH=C-), 630 (Br). ^1H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.20 (3H, d, J = 6.7 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 2.20 (1H, ddd, J = 4.9, 12.8, 15.2 Hz, 2α-H), 2.42 (1H, br. d, J = 4.2 Hz, 13-H), 2.50 (1H, ddd, J = 5.0, 6.2, 11.2 Hz, 1-H), 3.68 (1H, br. s, 3-H), 3.86 (1H, d, J = 8.3 Hz, 6-H), 3.88 (1H, s, 14-H), 4.04 (1H, d, J = 10.5 Hz, 17-H), 4.11 (1H, d, J = 10.5 Hz, 17-H), 5.47 (1H, s, 15-H). EI-MS m/z : 416 [$M^+(^{81}Br)$] , 414 [$M^+(^{79}Br)$] , 380 [$M^+(^{81}Br)$-$2H_2O$] , 378 [$M^+(^{79}Br)$-$2H_2O$] . Activity : EC_{50} 5.47×10^{-5} M ; Max. 34.1 mV.

GX-15-ene-3β, 5, 6β, 14R, 17-pentaol 3, 6, 14-triacetate (**4a**). A stirring solution of **3a** (2.0 g) in THF (10 ml) was added slowly to THF/H_2O (1 : 3, 200 ml) at room temperature and the stirring was continued for 3 days. The mixture was evaporated and the aqueous solution was worked up as usual to give an oily product, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (50 : 50) gave **4a** (1.35 g), which was recrystallized from n-hexane/EtOAc, mp 182-183℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 3030 (-CH=C-), 1740 (AcO). ^1H NMR δ ($CDCl_3$-D_2O) : 0.89 (3H, s, 19-H_3), 1.07 (3H, s, 18-H_3), 1.17 (3H, d, J = 6.5 Hz, 20-H_3), 1.83 (1H, dd, J = 4.6, 15.7 Hz, 2β-H), 1.91 (1H, dd, J = 5.0, 13.3 Hz, 7a-H), 1.97 (1H, dd, J = 11.5, 13.3 Hz, 7b-H), 2.04 (3H, s, AcO), 2.07 (3H, s, AcO), 2.17 (3H, s, AcO), 2.32 (1H, ddd, J = 5.1, 12.3, 15.7 Hz, 2α-H), 2.68 (1H, d, J = 3.5Hz, 13-H), 2.79 (1H, ddd, J = 5.0, 5.5, 12.3 Hz, 1-H), 4.20 (2H, s, 17-H_2), 4.70 (1H, dd, J = 5.0, 11.5 Hz, 6-H), 4.81 (1H, d, J = 5.1 Hz, 3-H), 5.17 (1H, s, 14-H), 5.31 (1H, s, 15-H). Found : C, 65.32 ; H, 7.87. Calcd. for $C_{26}H_{38}O_8$: C, 65.25 ; H, 8.00 %.

GX-15-ene-3β, 5, 6β, 14R, 17-pentaol (**4**). A solution of **4a** (200 mg) in EtOH (5 ml) was refluxed with 2N KOH (2 ml) for 2 hr. The mixture was evaporated and the residue was worked up as usual to give **4** (146 mg), which was recrystallized from EtOAc, mp 260-262℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 3030 (-CH=C-). ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.22 (3H, d, J = 5.0 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.71 (1H, m, 10-H), 1.87 (1H, dd, J = 4.7, 14.6 Hz, 2β-H), 1.92 (1H, dd, J = 11.3, 13.0 Hz, 7b-H), 1.99 (1H, dd, J = 4.7, 13.0 Hz, 7a-H), 2.22 (1H, ddd, J = 4.7, 12.3, 14.6 Hz, 2α-H), 2.57 (1H, ddd, J = 4.7, 5.8, 12.3 Hz, 1-H), 2.61 (1H, d, J = 3.4 Hz, 13-H), 3.62 (1H, d, J = 4.7 Hz, 3-H), 3.88 (1H, dd, J = 4.7, 11.3 Hz, 6-H), 3.90 (1H, s, 14-H), 4.15 (2H, s, 17-H_2), 5.26 (1H, s, 15-H). Found : C, 68.33 ; H, 9.07. Calcd. for $C_{20}H_{32}O_5$: C, 68.15 ; H, 9.15 %. Activity : EC_{50} 7.01×10^{-6} M ; Max. 65.7 mV.

17-Methoxy-GX-15-ene-3β, 5, 6β,14R-tetraol (**5**). To a solution of **3a** (200 mg) in MeOH (10 ml) was added a sodium methoxide-methanol solution (100 mg of Na in 10 ml of MeOH) and the mixture was stirred for 1.5 hr at room temperature and then refluxed for 30 min. The mixture was neutralized with 5 % HCl and worked up as usual to give a viscous oil, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (60 : 40) gave 190 mg of

5-triacetate (**5a**) as a viscous oil, which was dissolved in MeOH (5 ml) and refluxed with 2*N* KOH (2 ml) for 2 hr. The product was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (30 : 70) gave a solid (**5**, 120 mg), which was recrystallized from EtOAc, mp 160-162℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 3020 (-CH=C-). ^1H NMR δ ($CDCl_3$-D_2O) : 1.00 (3H, s, 19-H_3), 1.19 (3H, d, J = 6.7 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.83 (1H, dd, J = 4.7, 15.0 Hz,2β-H),1.88 (2H, m, 7-H_2), 2.18 (1H, ddd, J = 5.0, 12.2, 14.8 Hz, 2α-H), 2.51 (1H, ddd, J = 5.0, 5.5, 12.2 Hz, 1-H), 2.66 (1H, d, J = 3.3 Hz, 13-H), 3.37 (3H, s, OCH_3), 3.63 (1H, d, J = 5.0 Hz, 3-H), 3.84 (1H, s, 14-H), 3.87 (1H, dd, J = 6.1, 9.3 Hz, 6-H), 3.94 (1H, dd, J = 1.3, 13.6 Hz, 17-H), 3.98 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 5.31 (1H, s, 15-H). Found : C, 68.50 ; H, 9.46. Calcd. for $C_{21}H_{34}O_5$: C, 68.82 ; H, 9.35 %. Activity : EC_{50} 3.98×10^{-5} M ; Max. 32.3 mV.

17-Ethoxy-GX-15-ene-3β, 5, 6β, 14R-tetraol (**6**). On treatment with NaOEt followed by the similar way to the above, **3a** (200 mg) gave **6** (110 mg, mp 157-160℃) *via* 6-triacetate (**6a**).IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 3020 (-CH=C-). ^1H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.19 (3H, d, J = 6.6 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.22 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.83 (1H, dd, J = 4.7, 14.8 Hz, 2β-H), 1.89 (2H, m, 7-H_2), 2.18 (1H, ddd, J = 5.0, 13.2, 15.0 Hz, 2α-H), 2.51 (1H, ddd, J = 5.0, 6.0, 13.2 Hz, 1-H), 2.67 (1H, d, J = 3.4 Hz, 13-H), 3.53 (2H, q, J = 7.0 Hz, OCH_2CH_3), 3.64 (1H, dd, J = 4.8 Hz, 3-H), 3.83 (1H, s, 14-H), 3.87 (1H, dd, J = 5.8, 10.0 Hz, 6-H), 4.00 (2H, d, J = 1.4 Hz, 17-H_2), 5.30 (1H, s, 15-H). Found : C, 69.06 ; H, 9.65. Calcd. for $C_{22}H_{36}O_5$: C, 69.44 ; H, 9.54 %. Activity : EC_{50} 7.00×10^{-5} M ; Max. 22.6 mV.

GX-15-ene-3β, 5, 6β, 14R, 17-tetraol 17-(4'-hydroxy)butanoate (**7**). 1, 4-Butanediol or 1, 6-hexanediol was converted to 4-tetrahydropyranyl (THP) oxybutanol or 6-THPoxyhexanol with dihydropyrane (1 eq.) in the presence of pyridinium *p*-toluene sulfonate, which was oxidized with Jones reagent at -10℃ to give 4-THPoxybutanoic acid or 6-THPoxyhexanoic acid, respectively. The product in each step was purified by silica gel column chromatography eluted with *n*-hexane/EtOAc (60 : 40).

To a solution of **3** (400 mg) in acetone (30 ml), 4-THP oxybutanoic acid (95 mg) and potassium carbonate (140 mg) were added and the mixture was then stirred at room temperature for 1 hr. The mixture was diluted with water and worked up as usual to give an oil, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (40 : 60) gave a solid (340 mg, mp 78℃), which was refluxed with 50 % AcOH for 1 hr. The reaction mixture was worked up as usual to give an oil, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (20 : 80) afforded **7** (220 mg), which was recrystallized from EtOAc, mp 72℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 3020 (-CH=C-), 1740 (-COO-). ^1H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.19 (3H, d, J = 6.8 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.84 (1H, dd, 5.0, 14.5 Hz, 2β-H), 1.89 (3H, m, 7-H and $OCOCH_2CH_2CH_2OH$), 2.19 (1H, ddd, J = 5.0, 12.5, 15.0 Hz, 2α-H), 2.48 (2H, t, J = 7.0 Hz, $OCOCH_2CH_2OH$), 2.51 (1H, ddd, J = 6.0, 6.5, 12.5 Hz, 1-H), 2.67 (1H, br. s, 13-H), 3.66 (1H, d, J = 5.0 Hz, 3-H), 3.69 (2H, t, J = 6.5 Hz, $OCOCH_2CH_2CH_2OH$), 3.84 (1H, s, 14-H), 3.87 (1H, dd, J = 6.0, 10.0 Hz, 6-H), 4.65 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 4.68 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 5.35 (1H, s, 15-H). Found : C, 67.53 ; H, 9.75. Calcd. for $C_{24}H_{40}O_6$: C, 67.90 ; H, 9.50 %. Activity : EC_{50} 2.06×10^{-5} M ; Max. 46.8 mV.

GX-15-ene-3β, 5, 6β, 14R, 17-pentaol 17-(6'-hydroxy)hexanoate (**8**). Compound **8** (300 mg, mp 76 ℃) was obtained from **3** (400 mg), 6-THPoxyhexanoic acid (115 mg) and potassium carbonate (140 mg) by the similar method to the above. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 3020

(-CH=C-), 1740 (-COO-). ^{1}H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.20 (3H, d, J = 6.8 Hz, 20-H_3), 1.22 (3H, s, 18-H_3), 1.84 (1H, dd, J = 4.8, 15.0 Hz, 2β-H), 1.89 (2H, d, J = 7.6 Hz, 7-H_2), 2.20 (1H, ddd, J = 4.9, 12.4 , 14.9 Hz, 2α-H), 2.37 (2H, t, J = 7.4 Hz, $OCOCH_2(CH_2)_3CH_2OH$), 2.50 (1H, ddd, J = 5.2, 6.0, 12.7 Hz, 1-H), 2.66 (1H, s, 13-H), 3.65 (2H, t, J = 6.0 Hz, $OCOCH_2(CH_2)_3CH_2OH$), 3.67 (1H, d, J = 5.0 Hz, 3-H), 3.84-3.90 (2H, m, 6-H and 14-H), 4.61 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 4.68 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 5.35 (1H, s, 15-H). Found : C, 70.02 ; H, 10.35. Calcd. for $C_{26}H_{44}O_6$: C, 70.55 ; H, 10.02 %. Activity : EC_{50} 1.88×10^{-4} M ; Max. 26.6 mV.

GX-15-ene-3β, 5, 6β, 14R, 17-pentaol 17-(4'-acetoxy) butanoate (**9**). 4-Acetoxybutanoic acid was obtained from 1, 4-butanediol with acetic anhydride (1 eq.)-pyridine at room temperature for 5 hr followed by Jones oxidation.

To a solution of **3** (400 mg) in acetone (30 ml), 6-acetoxybutanoic acid (115 mg) and potassium carbonate (140 mg) was added and the mixture was then stirred at room temperature for 1 hr. The product was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (40 : 60) gave **9** (330 mg), which was recrystallized from EtOAc, mp 71℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 3020 (-CH=C-), 1740 (-COO-). ^{1}H NMR δ ($CDCl_3$-D_2O) : 1.02 (3H, s, 19-H_3), 1.20 (3H, d, J = 6.8 Hz, 20-H_3), 1.22 (3H, s, 18-H_3), 1.84 (1H, dd, J = 4.8, 14.9 Hz, 2β-H), 1.88 (1H, d, J = 2.6 Hz, 7-H), 1.90 (1H, s, 7-H), 1.98 (2H, m, $-OCOCH_2CH_2CH_2OCOCH_3$), 2.05 (3H, s, $-OCOCH_2CH_2CH_2OCOCH_3$), 2.20 (1H, ddd, J = 4.8, 11.3, 14.9 Hz, 2α-H), 2.44 (2H, t, J = 7.4 Hz, $-OCOCH_2CH_2CH_2OCOCH_3$), 2.50 (1H, ddd, J = 4.8, 6.2, 11.3 Hz, 1-H), 2.66 (1H, br. s, 13-H), 3.67 (1H, d, J = 4.8 Hz, 3-H), 3.86 (1H, s, 14-H), 3.87 (1H, dd, J = 6.7, 9.1 Hz, 6-H), 4.11 (2H, t, J = 6.4 Hz, $-OCOCH_2CH_2CH_2OCOCH_3$), 4.64 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 4.69 (1H, dd, J = 1.5, 13.6 Hz, 17-H), 5.35 (1H, s, 15-H). Found : C, 66.54 ; H, 9.43. Calcd. for $C_{26}H_{42}O_7$: C, 66.93 ; H, 9.08 %. Activity : EC_{50} 1.00×10^{-4} M ; Max. 22.1 mV.

GX-15-ene-3β, 5, 6β, 14R, 17-pentaol 17-acetate (**10**). To a solution of **3** (180 mg) in MeOH (5 ml) was added sodium acetate (100 mg) and the mixture was refluxed for 1.5 hr. The reaction mixture was diluted with water and worked up as usual to give a solid, which was recrystallized from EtOAc to yield 110 mg of **10**, mp 163-165℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 3030 (-CH=C-), 1730 (AcO). ^{1}H NMR δ ($CDCl_3$-D_2O) : 1.05 (3H, s, 19-H_3), 1.23 (3H, d, J = 6.6 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.87 (1H, dd, J = 4.8, 14.6 Hz, 2β-H), 1.92 (1H, dd, J = 11.1, 13.3 Hz, 7b-H), 1.98 (1H, dd, J = 4.8, 13.3 Hz, 7a-H), 2.10 (3H, s, AcO), 2.22 (1H, ddd, J = 4.7, 12.2, 14.6 Hz, 2α-H), 2.56 (1H, ddd, J = 4.7, 6.5, 12.2 Hz, 1-H), 2.60 (1H, d, J = 3.9 Hz, 13H), 3.62 (1H, d, J = 4.7 Hz, 3-H), 3.88 (1H, dd, J = 4.8, 11.1 Hz, 6-H), 3.90 (1H, s, 14-H), 4.67 (1H, d, J = 13.6 Hz, 17-H), 4.74 (1H, d, J = 13.6 Hz, 17-H), 5.33 (1H, s, 15-H). Found : C, 67.01 ; H, 8.65. Calcd. for $C_{22}H_{34}O_6$: C, 66.98 ; H, 8.69 %. Activity : EC_{50} 5.10×10^{-4}M ; Max. 42.2 mV.

17-Amino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**11**). To a cooled solution of **3** (300 mg) in MeOH (5 ml) surrounded by a Dry Ice-MeOH bath (-78℃), dried NH_3 gas was passed for 30 min and the mixture was then kept for 1 hr. The reaction mixture was evaporated to dryness. The residue was dissolved in 1*N* HCl and extracted continuously with ether. The aqueous layer was made alkaline with 1*N* KOH and then extracted continuously with ether. The extract was purified by silica gel column chromatography. Elution with EtOAc/MeOH/isopropylamine (425 : 25 : 30) gave **11** (110 mg), which was crystallized from EtOAc, mp 220-230℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH, NH), 3030 (-CH=C-), 1665 (NH_2). ^{1}H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.23 (3H, d, J = 5.5 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.71 (1H, m, 10-H), 1.88 (1H, dd, J = 4.6, 14.6 Hz,

2β-H), 1.93 (1H, dd, J = 11.3, 13.3 Hz, 7b-H), 2.00 (1H, dd, J = 4.7, 13.3 Hz, 7a-H), 2.22 (1H, ddd, J = 4.6, 12.2, 14.6 Hz, 2α-H), 2.57 (2H, m, 1-H and 13-H), 3.33 (2H, s, 17-H_2),3.63 (1H, d, J = 4.6 Hz, 3-H), 3.89 (1H, dd, J = 4.7, 11.3 Hz, 6-H), 3.91 (1H, s, 14-H), 5.22 (1H, s, 15-H). Found : C, 66.50 ; H, 9.18 ; N, 3.88. Calcd. for $C_{20}H_{33}NO_4 \cdot 1/2H_2O$: C, 66.67 ; H, 9.44 ; N, 3.89 %. Activity : 5.8 and 6.0 mV at 0.9×10^{-3} M.

17-N-Methylimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**12**). To a cooled (-78℃) solution of **3** (700 mg) in MeOH (15 ml), dried methylamine gas was passed for 30 min and the mixture was then kept for 2 hr. The mixture was worked up as described above. The basic product was purified by silica gel column chromatography. Elution with EtOAc/MeOH/isopropylamine (425 : 25 : 30) gave **12** (580 mg), which was crystallized from EtOAc, mp 123-125℃. IR ν_{max} (KBr) cm^{-1} : 3420 (OH, NH), 3020 (-CH=C-). ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H), 1.23 (3H, d, J = 6.3 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.71 (1H, m, 10-H), 1.88 (1H, dd, J = 4.8, 14.6 Hz, 2β-H), 1.92 (1H, dd, J = 11.3, 13.6 Hz, 7b-H), 1.99 (1H, dd, J = 4.8, 13.6 Hz, 7a-H), 2.05 (1H, s, -N*H*CH_3), 2.22 (1H, ddd, J = 4.8, 12.2, 14.6 Hz, 2α-H), 2.49 (3H, s, -NHC*H*$_3$), 2.57 (1H, ddd, J = 4.8 , 6.2 , 12.2 Hz, 1-H), 2.58 (1H, d, J = 3.3 Hz, 13-H), 3.26 (1H, dd, J = 1.6, 14.8 Hz, 17-H), 3.28 (1H, dd, J = 1.6, 14.8 Hz, 17-H), 3.63 (1H, d, J = 4.8 Hz, 3-H), 3.89 (1H, dd, J = 4.8, 11.3 Hz, 6 -H), 3.90 (1H, s, 14-H), 5.25 (1H, s, 15-H). Found : C, 67.13 ; H, 9.49 ; N, 3.78. Calcd. for $C_{21}H_{35}NO_4 \cdot 1/2H_2O$: C, 67.38 ; H, 9.63 ; N, 3.74 %. Activity : negative at 1×10^{-3} M.

17-N-Ethylimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**13**). Compound **13** (680 mg, mp 165-167℃) was obtained from **3** (750 mg) and dried ethylamine gas by the similar method to the above. IR ν_{max} (KBr) cm^{-1} : 3420 (OH, NH), 3030 (-CH=C-). ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.19 (3H, t, J = 7.2 Hz, -$NHCH_2CH_3$), 1.23 (3H, d, J = 6.7 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.71 (1H, m, 10-H), 1.87 (1H, dd, J = 4.6, 14.6 Hz, 2β-H), 1.93 (1H, dd, J = 11.2, 12.9 Hz, 7b-H), 1.98 (1H, dd, J = 4.8, 12.9 Hz, 7a-H), 2.22 (1H, ddd, J = 4.9, 12.2, 14.6 Hz, 2α-H), 2.58 (1H, ddd, J = 4.8, 6.0, 12.2 Hz, 1-H), 2.59 (1H, d, J = 3.5 Hz, 13-H), 2.75 (2H, q, J = 7.2 Hz, -NHC*H*$_2$$CH_3$), 3.28 (2H, d, J = 6.4 Hz, 17-H_2), 3.62 (1H, d, J = 4.9 Hz, 3-H), 3.88 (1H, m, 6-H), 3.89 (1H, s, 14-H), 5.22 (1H, s, 15-H). Found : C, 68.29 ; H, 9.80 ; N, 3.59. Calcd. for $C_{22}H_{37}NO_4 \cdot 1/2H_2O$: C, 68.04 ; H, 9.79 ; N, 3.61 %. Activity : EC_{50} 1.05×10^{-3} M ; Max. 47.9 mV.

17-N-Propylimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**14**). To a solution of **3** (60 mg) in THF (2 ml), propylamine (300 μg) was added at room temperature and left for 1 hr. Evaporation of the solvent gave **14** (48 mg), which was recrystallized from EtOAc, mp 183℃. IR ν_{max} (KBr) cm^{-1} : 3420 (OH, NH), 3020 (-CH=C-). ^1H NMR[c] δ (CD_3OD) : 0.88 (3H, s, 19-H_3), 1.04 (3H, s, 18-H_3), 1.18 (3H, d, J = 6.5 Hz, 20-H_3), 1.08 (3H, t, -$NHCH_2CH_2CH_3$), 1.70 (2H, m, -$NHCH_2CH_2CH_3$), 2.80 (2H, t, -$NHCH_2CH_2CH_3$), 3.76 (2H, m, 17-H_2), 5.21 (1H, m, 15-H). Found : C, 69.53 ; H, 10.07 ; N, 3.32. Calcd. for $C_{23}H_{39}NO_4$: C, 70.19 ; H, 9.99 ; N, 3.56 %. Activity : EC_{50} 3.55×10^{-4} M ; Max. 19.0 mV.

17-N-Isopropylimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**15**). Compound **15** (54 mg, mp 180-182℃) was obtained from **3** (120 mg) and isopropylamine (2 ml) by the similar method to the above. IR ν_{max} (KBr) cm^{-1} : 3400 (OH, NH), 3030 (-CH=C-). ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.13 (3H, d, J = 6.3 Hz, -NHCHC*H*$_3$), 1.15 (3H, d, J = 6.3 Hz, -NHCHC*H*$_3$), 1.23 (3H, d, J = 6.6 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.71 (1H, m, 10-H), 1.87 (1H, dd, J = 4.6, 14.6 Hz, 2β-H), 1.92 (1H,

c) The spectrum was taken on a Hitachi R-24 spectrometer.

dd, J = 11.4, 13.4 Hz, 7b-H), 1.99 (1H, dd, J = 4.8, 13.4 Hz, 7a-H), 2.22 (1H, ddd, J = 4.6, 12.2, 14.6 Hz, 2α-H), 2.57 (1H, ddd, J = 4.6, 6.5, 12.2 Hz, 1-H), 2.59 (1H, d, J = 3.4 Hz, 13-H), 2.91 (1H, m, J = 6.3 Hz, -NHCH(CH_3)$_2$), 3.26 (2H, s, 17-H_2), 3.63 (1H, d, J = 4.6 Hz, 3-H), 3.88 (1H, dd, J = 4.8, 11.4 Hz, 6-H), 3.89 (1H, s, 14-H), 5.22 (1H, s, 15-H). Found : C, 70.17 ; H, 10.03 ; N, 3.30. Calcd. for $C_{23}H_{39}NO_4$: C, 70.19 ; H, 9.99 ; N, 3.56 %. Activity : EC_{50} 3.10×10^{-4} M ; Max. 45.9 mV.

17-N-Benzylimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**16**). To a solution of **11** (160 mg) in MeOH (2 ml) was added benzyl bromide (46 mg) and K_2CO_3 (30 mg). The mixture was kept for 1 day at room temperature with stirring. The reaction mixture was neutralized with 2N HCl and then evaporated. The residue was worked up as usual to give an oily product, which was purified by silica gel column chromatography. Elution with EtOAc/MeOH (90 : 10) gave a solid, which was recrystallized from EtOAc to afford 55 mg of **16**, mp 123-126℃. ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.24 (3H, d, J = 6.0 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.88 (1H, dd, J = 4.5, 14.7 Hz, 2β-H), 1.93 (1H, dd, J = 11.5, 13.5 Hz, 7b-H), 2.00 (1H, dd, J = 4.4, 13.5 Hz, 7a-H), 2.22 (1H,ddd, J = 4.4, 12.5, 14.6 Hz, 2α-H), 2.56 (1H, ddd, J = 4.7, 6.3, 12.5 Hz, 1-H), 2.62 (1H, s, 13-H), 3.39 (2H, s, 17-H_2), 3.62 (1H, d, J = 4.4 Hz, 3-H), 3.84 (1H, dd, J = 4.3, 11.1 Hz, 6-H), 3.92 (2H, s, -NHCH_2-Ph), 3.96 (1H, s, 14-H), 5.30 (1H, s, 15-H), 7.42 (5H, m, aromatic H). Found : C, 72.98 ; H, 9.06 ; N, 3.53. Calcd. for $C_{27}H_{39}NO_4$: C, 73.43 ; H, 8.90 ; N, 3.17 %. Activity : 3.0 and 5.9 mV at 1.4×10^{-3} M. The tested solution was cloudy because of its low solubility.

17-N-Acetoimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (**17**). To a solution of **11** (160 mg) in pyridine (3 ml) was added acetic anhydride (3 ml) and the mixture was heated for 4 hr at 100℃. MeOH was added and the mixture was then evaporated to dryness. A solution of the residue in MeOH was refluxed with 2N KOH for 3 hr. After neutralization with 2N HCl, the mixture was worked up as usual to give a solid, which was purified by silica gel column chromatography. Elution with EtOAc/MeOH/isopropylamine (425 : 25 : 30) gave **17** (110 mg), which was recrystallized from EtOAc, mp 244-246℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 3280, 3080 (NH), 3020 (-CH=C-), 1650, 1580 (NHCO). ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.22 (3H, d, J = 6.6 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.70 (1H, m, 10-H), 1.87 (1H, dd, J = 4.4, 14.6 Hz, 2β-H), 1.91 (1H, dd, J = 11.2, 13.5 Hz, 7b-H), 1.98 (1H, dd, J = 4.8, 13.5 Hz, 7a-H), 2.01 (3H, s, -NHCOCH_3), 2.22 (1H, ddd, J = 4.5, 12.2, 14.6 Hz, 2α-H), 2.52 (1H, d, J = 3.5 Hz, 13-H), 2.56 (1H, ddd, J = 4.4, 4.6, 12.2 Hz, 1-H), 3.63 (1H, d, J = 4.5 Hz, 3-H), 3.77 (1H, d, J = 16.5 Hz, 17-H), 3.88 (1H, dd, J = 4.8, 11.2 Hz, 6-H), 3.89 (1H, s, 14-H), 3.95 (1H, d, J = 16.5 Hz, 17-H), 5.18 (1H, s, 15-H). Found : C, 65.98 ; H, 9.02 ; N, 3.48. Calcd. for $C_{22}H_{35}NO_5 \cdot 1/2H_2O$: C, 65.67 ; H, 8.96 ; N, 3.48 %. Activity : 3-5 mV at 1×10^{-3} M.

17-Mercapto-GX-15-ene-3β, 5, 6β, 14R-tetraol (**18**). HEDPPT (30 mg) was added to a solution of **3** (290 mg) in benzene (30 ml) at room temperature and the mixture was stirred for 1 day in an atmosphere of nitrogen. After filtration, the filtrate was evaporated to give an oily product, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (30 : 70) gave 180 mg of crude **18**, which was crystallized from EtOAc, mp 204-209℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 3030 (-CH=C-). ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.24 (3H, d, J = 6.7 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.87 (1H, dd, J = 4.6, 14.6 Hz, 2β-H), 1.90 (1H, dd, J = 11.2, 13.6 Hz, 7b-H), 1.97 (1H, dd, J = 4.8, 13.6 Hz, 7a-H), 2.22 (1H, ddd, J = 4.6, 12.1, 14.6 Hz, 2α-H), 2.56 (1H, ddd, J = 4.6, 6.1, 12.1 Hz, 1-H), 2.65 (1H, s, 13-H), 3.33 (2H, s, 17-H_2), 3.62 (1H,

d, J = 4.6 Hz, 3-H), 3.88 (1H, dd, J = 4.8, 11.2 Hz, 6-H), 3.90 (1H, s, 14-H), 5.24 (1H, s, 15-H). Found : C, 64.77 ; H, 9.01. Calcd. for $C_{20}H_{32}O_4S$: C, 65.18 ; H, 8.75 %. Activity : EC_{50} 3.75×10^{-6} M ; Max. 59.1 mV.

3β, 5, 6β, 14R-Tetrahydroxy-GX-15-ene-17-al (**19**). To a stirring solution of **4a** (200 mg) in $CHCl_3$ (20 ml), PCC (120 mg) was added at room temperature and the mixture was then kept for 1 day with stirring. The mixture was diluted with ether and filtered through Florisil column. The filtrate was evaporated to give an oil, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (50 : 50) yielded a viscous oil, which was hydrolyzed with 2*N* K_2CO_3 (10 ml)-MeOH (20 ml) for 1 day at room temperature. After neutralization with 2*N* HCl, the solvent was evaporated and the residue was worked up as usual. The product was purified by silica gel column chromatography. Elution with EtOAc gave **19** (80 mg) as a viscous oil. IR ν_{max} (KBr) cm^{-1} : 3380 (OH), 2870 (CHO), 1680 (CHO), 1610 (-C=C-CO). ^1H NMR δ ($CDCl_3$) : 1.00 (3H, s, 19-H_3), 1.20 (3H, s, 18-H_3), 1.20 (3H, d, J = 6.5 Hz, 20-H_3), 1.80 (1H, dd, J = 5.0, 15.0 Hz, 2β-H), 1.88 (1H, dd, J = 5.0, 13.5 Hz, 7a-H), 1.90 (1H, dd, J = 13.5, 14.0 Hz, 7b-H), 2.20 (1H, ddd, J = 5.0, 12.5, 15.0 Hz, 2α-H), 2.25 (1H, d, J = 4.7 Hz, 13-H), 2.48 (1H, ddd, J = 5.0, 5.5, 12.5 Hz, 1-H), 3.68 (1H, dd, J = 5.0, 5.5 Hz, 3-H), 3.85 (1H, dd, J = 5.2, 14.2 Hz, 6-H), 4.00 (1H, d, J = 7.3 Hz, 14-H), 6.47 (1H, s, 15-H), 9.70 (1H, s, CHO). Found : C, 68.39 ; H, 8.78. Calcd. for $C_{20}H_{30}O_5$: C, 68.64 ; H, 8.63 %. Activity : EC_{50} 7.31×10^{-5} M ; Max. 57.1 mV.

3β, 5, 6β, 14R-Tetrahydroxy-GX-15-ene-17-oic acid (**20**). To a cooled (0℃) solution of **4a** (400 mg) in acetone (10 ml), Jones reagent was added slowly with stirring. After decomposition of excess oxidant with addition of isopropyl alcohol, the mixture was evaporated and extracted with ether. The ether solution was worked up as usual to give a solid, which was recrystallized from *n*-hexane/EtOAc, mp 220-223℃ (240 mg). To a solution of the product (110 mg) in MeOH (2 ml), 2*N* KOH (2 ml) was added and the mixture was refluxed for 3 hr. After acidification with 2*N* HCl, the reaction mixture was evaporated and worked up as usual to give a solid, which was recrystallized from CH_3CN to yield 57 mg of **20**, mp 269-271℃. IR ν_{max} (KBr) cm^{-1} : 3500-3020 (COOH), 3380 (OH), 3030 (-CH=C-), 1680 (COOH), 1610 (-C=C-CO-). ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.24 (3H, s, 18-H_3), 1.26 (3H, d, J = 6.8 Hz, 20-H_3), 1.75 (1H, m, 10-H), 1.88 (1H, dd, J = 4.6, 14.6 Hz, 2β-H), 1.98 (1H, dd, J = 11.1, 13.3 Hz, 7b-H), 2.04 (1H, dd, J = 4.8, 13.3 Hz, 7a-H), 2.23 (1H, ddd, J = 4.6, 12.2, 14.6 Hz, 2α-H), 2.56 (1H, ddd, J = 4.6, 6.3, 12.2 Hz, 1-H), 2.96 (1H, br. s, 13-H), 3.64 (1H, d, J = 4.6 Hz, 3-H), 3.88 (1H, dd, J = 4.8, 11.1 Hz, 6-H), 4.00 (1H, s, 14-H), 6.39 (1H, s, 15-H). Found : C, 64.31 ; H, 8.26. Calcd. for $C_{20}H_{30}O_6 \cdot 1/2H_2O$: C, 64.00 ; H, 8.27 %. Activity : 0 and 2.7 mV at 2.5×10^{-3} M.

Methyl 3β, 5, 6β, 14R-tetrahydroxy-GX-15-ene-17-oate (**21**). To a solution of **20** (60 mg) in MeOH (3 ml), a diazomethane-ether solution was added. The mixture was evaporated to give a solid, which was recrystallized from EtOAc to yield 60 mg of **21**, mp 197-199℃. IR ν_{max} (KBr) cm^{-1} : 3500, 3400 (OH), 1700 (C=O), 1620 (-C=C-CO). ^1H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.25 (3H, s, 18-H_3), 1.26 (3H, d, J = 6.3 Hz, 20-H_3), 1.75 (1H, m, 10-H), 1.88 (1H, dd, J = 4.4, 14.6 Hz, 2β-H), 1.99 (1H, dd, J = 10.7, 13.2 Hz, 7b-H), 2.03 (1H, dd, J = 5.1, 13.2 Hz, 7a-H), 2.23 (1H, ddd, J = 4.6, 12.1, 14.6 Hz, 2α-H), 2.56 (1H, ddd, J = 4.4, 6.0, 12.1 Hz, 1-H), 2.98 (1H, s, 13-H), 3.64 (1H, d, J = 4.6 Hz, 3-H), 3.78 (3H, s, $COOCH_3$), 3.88 (1H, dd, J = 5.1, 10.7 Hz, 6-H), 4.00(1H, s, 14-H), 6.42 (1H, s, 15-H). Found : C, 65.12 ; H, 8.54. Calcd. for $C_{21}H_{32}O_6 \cdot 1/2H_2O$: C, 64.78 ; H, 8.48 %. Activity : 1.1 and 3.0 mV at 2.6×10^{-3} M.

Ethyl 3β, 5, 6β, 14R-GX-15-ene-17-oate (**22**). A solution of **20** (200 mg) in EtOH (50 ml) was heated with conc. hydrochloric acid (1 ml) for 4 hr under reflux. After neutralization with 2*N* KOH, the solution was evaporated and worked up as usual to give a solid, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (20 : 80) gave a solid, which was recrystallized from EtOAc to give 150 mg of **22**, mp 193-194℃. IR ν_{max} (KBr) cm^{-1} : 3500, 3400 (OH), 1700 (C=O), 1620 (-C=C-CO). ^1H NMR δ ($CDCl_3$) : 1.00 (3H, s, 19-H_3), 1.19 (3H, d, J = 6.5 Hz, 20-H_3), 1.20 (3H, s, 18-H_3), 1.28 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 1.83 (1H, dd, J = 5.0, 15.0 Hz, 2β-H), 2.19 (1H, ddd, J = 5.5, 12.5, 15.0 Hz, 2α-H), 2.33 (1H, d, J = 5.3 Hz, 13-H), 2.48 (1H, ddd, J = 5.0, 5.5, 12.5 Hz, 1-H), 3.66 (1H, dd, J = 5.0, 5.0 Hz, 3-H), 3.85 (1H, dd, J = 7.0, 17.0 Hz, 6-H), 3.94 (1H, d, J = 8.8 Hz, 14-H), 4.19 (2H, dq, J = 2.0, 7.2 Hz, $COOCH_2CH_3$), 6.40 (1H, s, 15-H). Found : C, 65.28 ; H, 8.65. Calcd. for $C_{22}H_{34}O_6 \cdot 1/2H_2O$: C, 65.51 ; H, 8.68 %. Activity : negative at 3×10^{-4} M.

GX-3β, 5, 6β, 14R-tetraol (**23**). A solution of **2a** (130 mg) in EtOH (5 ml) was hydrogenated over Pd-C (10 %) for 5 hr. The reaction mixture was worked up as usual to give an oily product, which was dissolved in MeOH (5 ml) and refluxed with 5 % NaOH (2 ml) for 1 hr. After removal of MeOH, the residue was worked up as usual to give a solid (**23**, 80 mg), which was recrystallized from EtOAc, mp 222-223℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH). ^1H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.04 (3H, d, J = 7.1 Hz, 17-H_3), 1.18(3H, d, J = 6.2 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.28 (1H, dd, J = 7.3, 13.5 Hz, 15α-H), 1.73 (1H, m, 15β-H), 1.75 (1H, dd, J = 11.4, 13.7 Hz, 7b-H), 1.83 (1H, dd, J = 4.8, 15.0 Hz, 2β-H), 1.88 (1H, br. s, 13-H), 1.93 (1H, dd, J = 4.7, 13.7 Hz, 7a-H), 2.18 (1H, ddd, J = 5.1, 12.3, 15.0 Hz, 2α-H), 2.43 (1H, m, 16-H), 2.54 (1H, ddd, J = 4.8, 5.1, 12.3 Hz, 1-H), 3.63 (1H, d, J = 5.0 Hz, 3-H), 3.82 (1H, dd, J = 4.7, 11.4 Hz, 6-H), 3.92 (1H, s, 14-H). Found : C, 70.30 ; H, 10.22. Calcd. for $C_{20}H_{34}O_4$: C, 70.97 ; H, 10.12 %. Activity : EC_{50} 9.01×10^{-6} M ; Max. 64.6 mV.

GX-3β, 5, 6β, 14R, 17-pentaol (**24**) and *16-epi-GX-3β, 5, 6β, 14R, 17-pentaol* (**25**). A solution of **4** (180 mg) in EtOH (5 ml) was hydrogenated over Pd-C (10 %). The product was separated by silica gel colum chromatography yielding **24** (140 mg) and its 16-epimer (**25**, 30 mg) eluted with EtOAc. Each was recrystallized from EtOAc, mp 188-190℃ (**24**) and mp 232-234℃ (**25**), respectively. **24** : IR ν_{max} (KBr) cm^{-1} : 3580, 3400 (OH). ^1H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.22 (3H, d, J = 6.3 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.40 (1H, dd, J = 7.3, 12.0 Hz, 15β-H), 1.75 (1H, d, J = 12.0 Hz, 15α-H), 1.84 (1H, dd, J = 11.6, 13.3 Hz, 7b-H), 1.87 (1H, dd, J = 4.5, 14.4 Hz, 2β-H), 2.00 (1H, dd, J = 4.5, 13.3 Hz, 7a-H), 2.13 (1H, br. s, 13-H), 2.21 (1H, ddd, J = 4.8, 12.0, 14.5 Hz, 2α-H), 2.62 (2H, m, 1-H and 16-H), 3.62 (1H, d, J = 4.8 Hz, 3-H), 3.73 (2H, dd, J = 4.0, 8.2 Hz, 17-H_2), 3.90 (1H, dd, J = 4.5, 11.6 Hz, 6-H), 3.94 (1H, s, 14-H). Found : C, 66.36 ; H, 9.42. Calcd. for $C_{20}H_{34}O_5 \cdot 1/2H_2O$: C, 66.12 ; H, 9.64 %. Activity : EC_{50} 6.72×10^{-4} M ; Max. 43.2 mV.

25 : ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.24 (3H, d, J = 6.5 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.86 (1H, dd, J = 4.6, 15.3 Hz, 2β-H), 1.98 (1H, dd, J = 4.5, 14.4 Hz, 7a-H), 2.00 (1H, dd, J = 6.1, 14.6 Hz, 16-H), 2.12 (1H, d, J = 3.9 Hz, 13-H), 2.20 (1H, ddd, J = 4.9, 12.2, 14.6 Hz, 2α-H), 2.61 (1H, ddd, J = 5.0, 5.7, 12.5 Hz, 1-H), 3.62 (3H, m, 3-H and 17-H_2), 3.79 (1H, s, 14-H), 3.90 (1H, dd, J = 4.5, 11.5 Hz, 6-H). Found : C, 67.48 ; H, 9.73. Calcd. for $C_{20}H_{34}O_5$: C, 67.76 ; H, 9.67 %. Activity : EC_{50} 5.70×10^{-5} M ; Max. 48.3 mV.

GX-3β, 5, 6β, 14R, 17-pentaol 3, 6, 14-triacetate (**24a**). A solution of **4a** (1.60 g) in EtOH (20

ml) was hydrogenated over Pd-C (10 %) to give a solid (1.49 g), which was recrystallized from *n*-hexane/EtOAc to yield **24a**, mp 148-149℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 1740 (AcO). ^1H NMR δ ($CDCl_3$-D_2O) : 0.87 (3H, s, 19-H_3), 1.05 (3H, s, 18-H_3), 1.11 (3H, d, J = 6.5 Hz, 20-H_3), 1.73 (2H, dd, J = 11.8, 14.0 Hz, 15-H_2), 1.80 (1H, dd, J = 5.0, 15.7 Hz, 2β-H), 1.87-1.90 (2H, m, 7-H_2), 2.02 (3H, s, AcO), 2.05 (3H, s, AcO), 2.15 (3H, s, AcO), 2.20 (1H, d, J = 4.4 Hz, 13-H), 2.29 (1H, ddd, J = 5.5, 12.0, 15.7 Hz, 2α-H), 2.54 (1H, ddd, J = 5.5, 8.0, 12.5 Hz, 16-H), 2.78 (1H, ddd, J = 5.0, 5.5, 12.0 Hz, 1-H), 3.78 (2H, d, J = 8.0 Hz, 17-H_2), 4.70 (1H, dd, J = 6.0, 10.0 Hz, 6-H), 4.80 (1H, d, J = 5.0 Hz, 3-H), 5.17 (1H, s, 14-H). The triacetate (**24a**, 200 mg) was hydrolyzed with 2*N* KOH in EtOH to give a solid, which was recrystallized from EtOAc, mp 188-190℃. The IR spectrum and ^1H NMR were identical with those of **24**.

To a solution of **24a** (426 mg) in pyridine (5 ml) was added tosyl chloride (1.54 g) and the mixture was kept at 5℃ over night. The reaction mixture was poured onto ice and the resulting precipitate (480 mg) was collected, which was recrystallized from EtOAc, mp 208℃. ^1H NMR δ ($CDCl_3$-D_2O) : 0.88 (3H, s, 19-H_3), 1.05 (3H, s, 18-H_3), 1.08 (3H, d, J = 6.6 Hz, 20-H_3), 1.69 (2H, dd, J = 11.7, 13.8 Hz, 15-H_2), 1.80 (1H, dd, J = 5.0, 16.1 Hz, 2β-H), 1.80 (1H, dd, J = 5.0, 13.3 Hz, 7a-H), 1.85 (1H, dd, J = 11.0, 13.5 Hz, 7b-H), 2.04 (3H, s, AcO), 2.06 (3H, s, AcO), 2.14 (1H, s, 13-H), 2.15 (3H, s, AcO), 2.30 (1H, ddd, J = 5.3, 12.2, 15.8 Hz, 2α-H), 2.45 (3H, s, Ph-CH_3), 2.65 (1H, m, 16-H), 2.75 (1H, ddd, J = 5.0, 5.3, 12.2 Hz, 1-H), 4.15 (2H, m, 17-H_2), 4.67 (1H, dd, J = 5.2, 10.7 Hz, 6-H), 4.79 (1H, d, J = 5.2 Hz, 3-H), 5.14 (1H, s, 14-H), 7.36 (2H, d, J = 8.4 Hz, aromatic H), 7.79 (2H, d, J = 8.4 Hz, aromatic H). Found : C, 62.44 ; H, 7.30. Calcd. for $C_{33}H_{46}O_{10}S$: C, 62.33 ; H, 7.28 %. To a solution of the tosylate (50 mg) in DMSO (1.5 ml) was added $NaBH_4$ (15 mg) and the mixture was heated at 90℃ for 9 hr. Working up as usual afforded crude product (40 mg), which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (80 : 20) yielded the main product. The product (13 mg) in EtOH was hydrolyzed with 2 % KOH at room temperature over night. Working up as usual gave 9 mg of the pure prduct, whose ^1H NMR spectrum was identical with that of **23**.

17-Methoxy-GX-3β, 5, 6β, 14R-tetraol (**26**) and *17-methoxy-16-epi-GX-3β, 5, 6β, 14R-tetraol* (**28**). A solution of **5** (150 mg) in EtOH (15 ml) was hydrogenated over Pd-C (10 %). The product was separated each other to give **26** (mp 185-190℃, 130 mg) and **28** (mp 197-198℃, 40 mg) by silica gel column chromatography eluted with *n*-hexane/EtOAc (70 : 30). **26** : IR ν_{max} (KBr) cm^{-1} : 3400 (OH). ^1H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.17 (3H, d, J = 6.7 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.38 (1H, dd, J = 7.4, 13.6 Hz, 15β-H), 1.72 (1H, dd, J = 11.8, 13.5 Hz, 15α-H), 1.81 (1H, dd, J = 11.1, 13.5 Hz, 7b-H), 1.83 (1H, dd, J = 5.1, 14.1 Hz, 2β-H), 1.94 (1H, dd, J = 4.7, 13.7 Hz, 7a-H), 2.10 (1H, br. s, 13-H), 2.17 (1H, ddd, J = 5.1, 12.4, 15.4 Hz, 2α-H), 2.53 (1H, ddd, J = 5.2, 5.8, 11.2 Hz, 1-H), 2.65 (1H, m, 16-H), 3.36 (3H, s, OCH_3), 3.49 (1H, t, J = 9.2 Hz, 17-H), 3.53 (1H, t, J = 9.2 Hz, 17-H), 3.62 (1H, d, J = 5.1 Hz, 3-H), 3.84 (1H, dd, J = 4.7, 11.3 Hz, 6-H), 3.93 (1H, s, 14-H). Found : C, 68.00 ; H, 9.75. Calcd. for $C_{21}H_{36}O_5$: C, 68.44 ; H, 9.85 %. Activity : EC_{50} 7.81×10^{-5} M ; Max. 43.7 mV.

28 : ^1H NMR δ ($CDCl_3$-D_2O) : 1.00 (3H, s, 19-H_3), 1.19 (3H, d, J = 6.8 Hz, 20-H_3), 1.20 (3H, s, 18-H_3), 1.73 (1H, dd, J = 10.7, 13.6 Hz, 7b-H), 1.82 (1H, dd, J = 4.9, 15.0 Hz, 2β-H), 1.93 (1H, dd, J = 4.5, 13.3 Hz, 7a-H), 1.98 (1H, m, 16-H), 2.10 (1H, d, J = 4.4 Hz, 13-H), 2.17 (1H, ddd, J = 5.1, 12.4, 14.9 Hz, 2α-H), 2.57 (1H, ddd, J = 5.4, 6.3, 11.7 Hz, 1-H), 3.37 (1H, dd, J = 3.2, 9.0 Hz, 17-H), 3.40 (3H, s, OCH_3), 3.42 (1H, dd, J = 2.9, 9.0 Hz, 17-H), 3.60 (1H, d, J = 5.1 Hz, 3-H), 3.63 (1H,

s, 14-H), 3.91 (1H, dd, J = 4.5, 11.1 Hz, 6-H). Found : C, 68.06 ; H, 9.77. Calcd. for $C_{21}H_{36}O_5$: C, 68.44 ; H, 9.85 %. Activity : EC_{50} 3.80×10^{-4} M ; Max. 39.4 mV.

A solution of **5a** (100 mg) in EtOH (10 ml) was hydrogenated over Pd-C (10 %) to give 90 mg of **26a** as a viscous oil, which was hydrolyzed with 2N NaOH to **26**.

17-Ethoxy-GX-3β, 5, 6β, 14R-tetraol (**27**) and *17-ethoxy-16-epi-GX-3β, 5, 6β, 14R-tetraol* (**29**). Compound **27** (100 mg, mp 115-119℃) and **29** (40 mg, mp 130-132℃) were obtained from **6** (150 mg) by the similar way to the above. **27** : IR υ_{max} (KBr) cm^{-1} : 3400 (OH). ^1H NMR δ ($CDCl_3$-D_2O) : 0.99 (3H, s, 19-H_3), 1.16 (3H, d, J = 6.5 Hz, 20-H_3), 1.17 (3H, t, J = 6.3 Hz, OCH_2CH_3), 1.19 (3H, s, 18-H_3), 1.71 (1H, dd, J = 12.0, 13.5 Hz, 7b-H), 1.82 (1H, dd, J = 5.5, 11.0 Hz, 7a-H), 1.93 (1H, dd, J = 5.1, 14.9 Hz, 2β-H), 2.09 (1H, br. s, 13-H), 2.16 (1H, ddd, J = 5.5, 11.0, 14.9 Hz, 2α-H), 2.53 (1H, ddd, J = 5.3, 6.0, 11.3 Hz, 1-H), 2.63 (1H, ddd, J = 6.0, 7.4, 12.3 Hz, 16-H), 3.47 (2H, dq, J = 2.5, 7.0 Hz, OCH_2CH_3), 3.53 (2H, dd, J = 2.7, 8.2 Hz, 17-H_2), 3.62 (1H, d, J = 5.5 Hz, 3-H), 3.83 (1H, dd, J = 6.0, 12.0 Hz, 6-H), 3.93 (1H, s, 14-H). Found : C, 68.67 ; H, 10.12. Calcd. for $C_{22}H_{38}O_5$: C, 69.07 ; H, 10.01 %. Activity : EC_{50} 4.92×10^{-5} M ; Max. 51.7 mV.

29 : ^1H NMR δ ($CDCl_3$) : 0.99 (3H, s, 19-H_3), 1.22 (3H, t, J = 6.3 Hz, OCH_2CH_3), 1.17 (3H, d, J = 6.5 Hz, 20-H_3), 1.19 (3H, s, 18-H_3), 1.80 (1H, dd, J = 4.8, 14.5 Hz, 7a-H), 1.93 (1H, dd, J = 5.0, 14.8 Hz, 2β-H), 1.97 (1H, ddd, J = 3.0, 6.5, 13.0 Hz, 16-H), 2.10 (1H, d, J = 4.5 Hz, 13-H), 2.17 (1H, ddd, J = 4.0, 12.6, 15.0 Hz, 2α-H), 2.57 (1H, m, 1-H), 3.38 (1H, dd, J = 3.0, 9.0 Hz, 17-H), 3.43 (1H, dd, J = 3.0, 9.0 Hz, 17-H), 3.52 (2H, dq, J = 2.0, 7.0 Hz, OCH_2CH_3), 3.60 (1H, dd, J = 5.5, 6.0 Hz, 3-H), 3.60 (1H, d, J = 9.5 Hz, 14-H), 3.92 (1H, ddd, J = 4.8, 6.0, 11.0 Hz, 6-H). Found : C, 68.72 ; H, 10.20. Calcd. for $C_{22}H_{38}O_5$: C, 69.07 ; H, 10.01 %.

A solution of **6a** (100 mg) in EtOH (10 ml) was hydrogenated over Pd-C (10 %) to afford 90 mg of **27a** as a viscous oil, which was saponified to **27**.

3β, 5, 6β, 14R-Tetrahydroxy-GX-17-oic acid (**30**). A solution of **20** (110 mg) in EtOH (5 ml) was hydrogenated over Pd-C (10 %). After filtration of the catalyst, the filtrate was evaporated to give a solid, which was crystallized from EtOAc to give 100 mg of **30**, mp 163-168℃. IR υ_{max} (KBr) cm^{-1} : 3600-2500 (COOH, OH), 1680 (COOH). ^1H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.21 (3H, d, J = 6.7 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.74 (1H, dd, J = 12.0, 13.6 Hz, 15β-H), 1.86 (1H, dd, J = 11.5, 13.2 Hz, 7b-H), 1.86 (1H, dd, J = 5.0, 14.7 Hz, 2β-H), 1.98 (1H, dd, J = 4.6, 13.3 Hz, 7a-H), 2.11 (1H, dd, J = 6.4, 13.7 Hz, 15α-H), 2.21 (1H, ddd, J = 4.9, 12.2, 14.6 Hz, 2α-H), 2.43 (1H, br. s, 13-H), 2.59 (1H, ddd, J = 4.6, 6.0, 12.2 Hz, 1-H), 3.26 (1H, dd, J = 6.4 , 11.9 Hz, 16-H), 3.61 (1H, d, J = 4.7 Hz, 3-H), 3.88 (1H, dd, J = 4.6, 11.4 Hz, 6-H), 4.00 (1H, s, 14-H). Found : C, 64.75 ; H, 8.86. Calcd. for $C_{20}H_{32}O_6$: C, 65.19 ; H, 8.75 %. Activity : 0.8, 1.4 and 2.1 mV at 2.0×10^{-3} M.

Methyl 3β, 5, 6β, 14R-tetrahydroxy-GX-17-oate (**31**). A solution of **21** (200 mg) in EtOH (5 ml) was hydrogenated over Pd-C (10 %). The product (200 mg) was recrystallized from EtOAc to yield **31**, mp 228-233℃. IR υ_{max} (KBr) cm^{-1} : 3520, 3400 (OH), 1740 (COO). ^1H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.21 (3H, d, J = 6.7 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.55 (1H, m, 10-H), 1.76 (1H, dd, J = 11.9, 13.6 Hz, 15β-H), 1.86 (2H, m, 2β-H and 7b-H), 1.98 (1H,dd, J = 4.4, 13.3 Hz, 7a-H), 2.13 (1H, dd, J = 6.4, 13.6 Hz , 15α-H), 2.21 (1H, ddd, J = 5.0, 12.5, 15.0 Hz, 2α-H), 2.44 (1H, br. s, 13-H), 2.58 (1H, ddd, J = 5.0, 6.0, 12.1 Hz, 1-H), 3.30 (1H, dd, J = 6.4, 11.9 Hz, 16-H), 3.62 (1H, d, J = 4.6 Hz, 3-H), 3.72 (3H, s, $COOCH_3$), 3.88 (1H, dd, J = 4.4, 11.3 Hz, 6-H), 3.99 (1H, s, 14-H). Found : C, 65.54 ; H, 9.05. Calcd. for $C_{21}H_{34}O_6$: C, 65.94 ; H, 8.96 %. Activity : EC_{50}

1.15×10^{-3} M ; Max. 13.5 mV.

3β, 5, 6β, 14R-Tetrahydroxy-GX-17-al (**32**). To a stirring solution of **24a** (200 mg) in CH_2Cl_2 (20 ml), PCC (120 mg) was added at room temperature and the mixture was then kept for 1 hr with stirring. The mixture was treated in the same manner as that for **18** to give **32**-triacetate (200 mg), which was crystallized from *n*-hexane/EtOAc, mp 151-152℃. ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.89 (3H, s, 19-H_3), 1.06 (3H, s, 18-H_3), 1.09 (3H, d, J = 6.8 Hz, 20-H_3), 1.81 (1H, dd, J = 4.9, 15.1 Hz, 2β-H), 1.84 (1H, dd, J = 4.6, 13.2 Hz, 7a-H), 1.95 (1H, dd, J = 11.5, 13.4 Hz, 7b-H), 2.05 (3H, s, AcO), 2.07 (3H, s, AcO), 2.19 (3H, s, AcO), 2.31 (1H, ddd, J = 5.3, 12.1, 17.4 Hz, 2α-H), 2.64 (1H, br. s, 13-H), 2.74 (1H, ddd, J = 5.0, 6.8, 11.5 Hz, 16-H), 3.10 (1H, ddd, J = 5.8, 6.4, 11.9 Hz, 1-H), 4.70 (1H, dd, J = 4.7, 11.4 Hz, 6-H), 4.80 (1H, d, J = 5.1 Hz, 3-H), 5.21 (1H, s, 14-H), 9.88 (1H, s, CHO). The triacetate (130 mg) was hydrolyzed with 5 % KOH (1 ml) in MeOH (1 ml) at room temperature for 1 day. Addition of water gave 90 mg of **32**, which was crystallized from MeOH, mp 248-252℃. IR υ_{max} (KBr) cm^{-1} : 3380 (OH), 2870 (CHO), 1730 (C=O). ^{1}H NMR δ ($CDCl_3$) : 1.00 (3H, s, 19-H_3), 1.20 (3H, s, 18-H_3), 1.20 (3H, d, J = 6.5 Hz, 20-H_3), 1.80 (1H, dd, J = 5.0, 15.5 Hz, 7b-H), 1.88 (1H, dd, J = 5.0, 13.5 Hz, 7a-H), 2.19 (1H, ddd, J = 5.0, 12.5, 16.0 Hz, 2α-H), 2.25 (1H, br. s, 13-H), 2.48 (1H, ddd, J = 5.0, 5.5, 12.5 Hz, 1-H), 4.68 (1H, dd, J = 5.0, 5.0 Hz, 3-H), 4.80 (1H, dd, J = 5.0, 14.0 Hz, 6-H), 4.00 (1H, d, J = 7.0 Hz, 14-H), 9.70 (1H, s, CHO). Found : C, 68.12 ; H, 9.10. Calcd. for $C_{20}H_{32}O_5$; C, 68.15 ; H, 9.15 %.

17-Amino-GX-3β, 5, 6β, 14R-tetraol (**33**). To a solution of **3** (150 mg) in DMF (5 ml), Amberlite IRA-400 azide (1.0 g) was added and the mixture was then stirred for 2 hr at room temperature. The reaction mixture was filtrated and the filtrate was evaporated to dryness. The residue was dissolved in EtOH (5 ml) and the solution was hydrogenated over PtO_2. The product was dissolved in 5 % HCl and extracted continuously with ether. The aqueous layer was made alkaline with 5 % KOH and was then extracted continuously with ether to give a solid, which was purified by silica gel column chromatography. Elution with $CHCl_3$/MeOH/propylamine (80 : 5 : 15) gave pure **33** (60 mg), mp 181-185℃. Compound **33** was also obtained by hydrogenation of **11** over Pd-C (10 %). IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 1630 (NH_2). ^{1}H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.23 (3H, d, J = 6.8 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.86 (1H, dd, J = 9.8, 13.7 Hz, 7b-H), 1.87 (1H, dd, J = 4.8, 14.7 Hz, 2β-H), 2.01 (1H, dd, J = 4.4, 13.6 Hz, 7a-H), 2.10 (1H, d, J = 2.5 Hz, 13-H), 2.21 (1H, m, 2α-H), 2.48 (1H, m, 16-H), 2.63 (1H, m, 1-H), 3.35 (2H, s, 17-H_2), 3.62 (1H, d, J = 4.7 Hz, 3-H), 3.91 (1H, dd, J = 4.4, 11.3 Hz, 6-H), 3.95 (1H, s, 14-H). EI-MS m/z : 317 (M^+-2H_2O). Activity : negative at 3×10^{-3} M.

15α, 16α-Epoxy-GX-3β, 5, 6β, 14R-tetraol 3, 6, 14-triacetate (**34a**). To a solution of **2a** (1.2 g) in CH_2Cl_2 (20 ml) was added MCPBA (1.0 g) and left for 4 hr at room temperature. Excess peracid was decomposed by addition of 10 % Na_2SO_3 and the mixture was worked up as usual to give a solid, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (65 : 35) yielded a solid (1.2 g), which was recrystallized from *n*-hexane/EtOAc to yield **34a**, mp 173-175℃. IR υ_{max} (KBr) cm^{-1} : 3500 (OH), 1740 (AcO). On alkaline hydrolysis, **34a** was converted to **34**, mp 234℃, which was identical with the compound described previously.[14] Activity : EC_{50} 9.30×10^{-5} M ; Max. 60.5 mV.

GX-16-ene-3β, 5, 6β, 14R, 15α-pentaol 3, 6, 14-triacetate (**35a**). A solution of **34a** (500 mg) in dry ether (5 ml) was added slowly to a solution prepared from Mg (50 mg) and ethylenedibromide (0.3 ml) in dry ether (10 ml) under argon atomosphere with stirring and the mixture was

then refluxed for 3 hr. The reaction mixture was poured onto ice and acidified with 2*N* HCl. Extraction with ether followed by working up as usual yielded an oil, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (70 : 30) gave 340 mg of **35a**, which was crystallized from *n*-hexane/EtOAc, mp 90-93℃. IR ν_{max} (KBr) cm^{-1} : 3550 (OH), 3070 (CH_2=C-), 1740 (AcO). ^1H NMR δ ($CDCl_3$-D_2O) : 0.92 (3H,s, 19-H_3), 1.07 (3H, s, 18-H_3), 1.13 (3H, d, J = 6.8 Hz, 20-H_3), 1.76 (1H, dd, J = 11.7, 13.8 Hz, 7b-H), 1.80 (1H, dd, J = 5.5, 15.8 Hz, 2β-H), 2.06 (3H, s, AcO), 2.08 (3H, s, AcO), 2.15 (3H, s, AcO), 2.25 (1H, dd, J = 4.0, 13.8 Hz, 7a-H), 2.30 (1H, ddd, J = 5.1, 11.9, 15.8 Hz, 2α-H), 2.70 (1H, ddd, J = 5.5, 6.0, 11.9 Hz, 1-H), 2.72 (1H, d, J = 4.4 Hz, 13-H), 3.82 (1H, s, 15-H), 4.72 (1H, dd, J = 4.0, 11.7 Hz, 6-H), 4.80 (1H, d, J = 5.5 Hz, 3-H), 5.17 (1H, s, 14-H), 5.23 (1H, s, 17-H), 5.44 (1H, s, 17-H).

GX-16-ene-3β, 5, 6β, 14R, 15α-pentaol (**35**). A solution of **35a** (120 mg) in EtOH (5 ml) was refluxed with 2*N* KOH (2 ml) for 4 hr. Working up as usual afforded a solid, which was recrystallized from EtOAc to give 80 mg of **35**, mp 186-187℃. IR ν_{max} (KBr) cm^{-1} : 3370 (OH), 3050 (CH_2=C), 1665 (C=C). ^1H NMR δ ($CDCl_3$-D_2O) : 1.03 (3H, s, 19-H_3), 1.21 (3H, d, J = 6.8 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.72 (1H, dd, J = 11.2, 14.0 Hz, 7b-H), 1.83 (1H, dd, J = 5.5, 15.0 Hz, 2β-H), 2.20 (1H, ddd, J = 5.5, 12.0, 15.0 Hz, 2α-H), 2.40 (1H, dd, J = 4.0, 14.0 Hz, 7a-H), 2.52 (1H, ddd, J = 5.0, 5.5, 12.0 Hz, 1-H), 2.75 (1H, d, J = 4.4 Hz, 13-H), 3.66 (1H, d, J = 5.5 Hz, 3-H), 3.86 (1H, s, 15β-H), 3.90 (1H, dd, J = 4.0, 11.2 Hz, 6-H), 4.00 (1H, s, 14-H), 5.21 (1H, s, 17-H), 5.43 (1H, s, 17-H). EI-MS m/z : 334 (M^+-H_2O), 316 (M^+-2H_2O), 298 (M^+-3H_2O). Activity : EC_{50} 4.02×10^{-5} M ; Max. 52.1 mV.

16-Epi-GX-3β, 5, 6β, 14R, 15α-pentaol (**36**) and *GX-3β, 5, 6β, 14R, 15α-pentaol* (**37**). A solution of **35** (100 mg) in AcOH (5 ml) was hydrogenated over PtO_2 (30 mg) for 3 hr. The product was separated by silica gel column chromatography. Elution with EtOAc gave 60 mg of **36** and 20 mg of **37**. Each was recrystallized from EtOAc, mp 245℃ (**36**) and mp 221-222℃ (**37**), respectively. **36** : IR ν_{max} (KBr) cm^{-1} : 3560, 3380 (OH). ^1H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.17 (3H, d, J = 7.7 Hz, 17-H_3), 1.24 (3H, s, 18-H_3), 1.25 (3H, d, J = 4.6 Hz, 20-H_3), 1.68 (1H, dd, J = 11.5, 13.8 Hz, 7b-H), 1.83 (1H, dd, J = 5.5, 14.5 Hz, 2β-H), 1.97 (1H, d, J = 3.9 Hz, 13-H), 2.21 (2H, m, 2α-H and 16β-H), 2.36 (1H, dd, J = 3.7, 13.8 Hz, 7a-H), 2.56 (1H, ddd, J = 5.5, 5.8, 11.5 Hz, 1-H), 3.62 (1H, d, J = 5.0 Hz, 3-H), 3.65 (1H, d, J = 8.3 Hz, 15β-H), 3.92 (1H, dd, J = 3.7, 11.5 Hz, 6-H), 3.93 (1H, s, 14-H), δ (pyridine-d_5) : 1.14 (3H, s, 19-H_3), 1.47 (6H, d, J = 6.9 Hz, 17-H_3 and 20-H_3), 1.68 (3H, s, 18-H_3). EI-MS m/z : 336 (M^+-H_2O), 318 (M^+-2H_2O), 300 (M^+-3H_2O). X-ray analysis : The crystal data was shown in Table 1 and the stereoscopic view in Fig. 5 in comparison to that of α-dihydro GTX-II (**1**).[4] Activity : EC_{50} 2.01×10^{-4} M ; Max. 49.7 mV.

37 : ^1H NMR δ (CD_3OD) : 1.07 (3H, s, 19-H_3), 1.20 (3H, d, J = 7.2 Hz, 17-H_3), 1.23 (3H, d, J = 6.7 Hz, 20-H_3), 1.25 (3H, s, 18-H_3), 1.54 (1H, dd, J = 11.2, 13.7 Hz, 7b-H), 1.86 (1H, dd, J = 4.9, 14.6 Hz, 2β-H), 1.93 (1H, br. s, 13-H), 2.18-2.28 (2H, m, 2α-H and 16-H), 2.30 (1H, dd, J = 4.1, 14.1 Hz, 7a-H), 2.63 (1H, ddd, J = 5.6, 5.9, 12.2 Hz, 1-H), 3.37 (1H, d, 15β-H), 3.63 (1H, d, J = 4.5 Hz, 3-H), 3.93 (1H, dd, J = 4.1, 11.4 Hz, 6-H), 3.97 (1H, s, 14-H), δ (pyridine-d_5) : 1.17 (3H, s, 19-H_3), 1.29 (3H, d, J = 7.3 Hz, 17-H_3), 1.47 (3H, d, J = 6.8 Hz, 20-H_3), 1.70 (3H, s, 18-H_3). Found : C, 67.48 ; H, 9.75. Calcd. for $C_{20}H_{34}O_5$: C, 67.76 ; H, 9.67 %. Activity : EC_{50} 4.60×10^{-4} M ; Max. 33.2 mV.

A solution of **35a** (150 mg) in AcOH (5 ml) was hydrogenated over PtO_2 (30 mg) for 3 hr to give an epimeric mixture of **36**-triacetate (130 mg) and **37**-triacetate (10 mg).

To a cooled (0 ℃) solution of **2a** (50 mg) in dry THF (10 ml) was added slowly BH_3-THF (1 ml) with stirring in an atomosphere of argon. After the mixture had been stirred for 1 hr, 2*N* NaOH (2 ml) and 30 % H_2O_2 (1 ml) was added to the mixture cooled with ice-water . The mixture was heated under reflux. Extraction with THF followed by working up as usual gave an oily product, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (20 : 80) yielded a solid (15 mg), which was recrystallized from EtOAc, mp 224℃. The ^{1}H NMR spectrum of the product was identical with that of **37**.

3β, 5, 6β, 14R-Tetrahydroxy-GX-16-ene-15-one 3, 6, 14-triacetate (**38a**). To a solution of **35a** (400 mg) in CH_2Cl_2 (5 ml) was added a solution of PCC (250 mg) in CH_2Cl_2 (5 ml) and kept for 3 hr with stirring at room temperature. Working up in the same manner as that for **18** gave a viscous oil, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (60 : 40) yielded **38a** (mp 97-100℃). IR ν_{max} (KBr) cm^{-1} : 3580, 3500 (OH), 3080 (-CH=C-), 1740 (C=O), 1650 (-C=C-CO-). ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.95 (3H, s, 19-H_3), 1.07 (3H, s, 18-H_3), 1.12 (3H, d, J = 6.8 Hz, 20-H_3), 1.66 (1H, dd, J = 4.6, 13.8 Hz, 7a-H), 1.85 (1H, dd, J = 4.9, 15.6 Hz, 2β-H), 2.03 (3H, s, AcO), 2.07 (3H, s, AcO), 2.12 (3H, s, AcO), 2.23 (1H, dd, J = 11.9, 13.8 Hz, 7b-H), 2.34 (1H, ddd, J = 5.2, 12.1, 15.6 Hz, 2α-H), 2.72 (1H, ddd, J = 4.9, 6.5, 12.1 Hz, 1-H), 3.05 (1H, d, J = 3.4 Hz, 13-H), 4.67 (1H, dd, J = 4.6, 11.9 Hz, 6-H), 4.80 (1H, d, J = 5.2 Hz, 3-H), 5.32 (1H, s, 14-H), 5.49 (1H, s, 17-H), 6.07 (1H, s, 17-H).

3β, 5, 6β, 14R-Tetrahydroxy-GX-16-ene-15-one (**38**). A solution of **38a** (300 mg) in EtOH (5 ml) was refluxed with 2*N* KOH (2 ml) for 4 hr. Working up as usual gave a solid, which was recrystallized from EtOAc to yield 200 mg of **38**, mp 285-288℃. IR ν_{max} (KBr) cm^{-1} : 3550, 3400 (OH), 3070 (CH=C), 1730 (C=O), 1650 (-C=C-CO-). ^{1}H NMR δ (CD_3OD) : 1.07 (3H, s, 19-H_3), 1.24 (3H, d, J = 6.5 Hz, 20-H_3), 1.25 (3H, s, 18-H_3), 1.75 (1H, dd, J = 4.6, 13.6 Hz, 7a-H), 1.88 (1H, dd, J = 4.8, 14.6 Hz, 2β-H), 2.11 (1H, dd, J = 11.6, 13.6 Hz, 7b-H), 2.25 (1H, ddd, J = 4.8, 12.4, 14.6 Hz, 2α-H), 2.60 (1H, ddd, J = 4.8, 5.7, 12.4 Hz, 1-H), 3.03 (1H, br. s, 13-H), 3.63 (1H, d, J = 4.8 Hz, 3-H), 3.86 (1H, dd, J = 4.6, 11.6 Hz, 6-H), 4.34 (1H, s, 14-H), 5.37 (1H, s, 17-H), 6.02 (1H, s, 17-H), Found : C, 68.22 ; H, 8.66. Calcd. for $C_{20}H_{30}O_5$: C, 68.54 ; H, 8.63 %. Activity : EC_{50} 4.85×10^{-4} M ; Max. 46.1 mV.

3β, 5, 6β, 14R-Tetrahydroxy-16-epi-GX-15-one (**39**) and *3β, 5, 6β, 14R-tetrahydroxy-GX-15-one* (**40**). A solution of **38** (280 mg) in AcOH (5 ml) was hydrogenated over PtO_2 (30 mg) for 4 hr. The product was separated by silica gel column chromatography eluted with *n*-hexane/EtOAc (20 : 80) yielding **39** (190 mg) and **40** (30 mg). Each was recrystallized from EtOAc, mp 283-285℃ (**39**) and mp 240-242℃ (**40**), respectively. **39** : IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 1730 (C=O). ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.23 (3H, d, J = 6.8 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.33 (3H, d, J = 7.7 Hz, 17-H_3), 1.74 (1H, dd, J = 4.4, 13.2 Hz, 7a-H), 1.86 (1H, dd, J = 4.4, 14.6 Hz, 2β-H), 2.02 (1H, dd, J = 11.7, 13.2 Hz, 7b-H), 2.18 (1H, q, J = 7.7 Hz, 16-H), 2.23 (1H, ddd, J = 4.4, 12.0, 14.6 Hz, 2α-H), 2.27 (1H, br. s, 13-H), 2.58 (1H, ddd, J = 4.4, 6.0, 12.0 Hz, 1-H), 3.62 (1H, d, J = 4.4 Hz, 3-H), 3.87 (1H, dd, J = 4.4, 11.7 Hz, 6-H), 4.34 (1H, s, 14-H). Found : C, 68.07 ; H, 8.70. Calcd. for $C_{20}H_{32}O_5$: C, 68.54 ; H, 8.63 %. Activity : EC_{50} 5.55×10^{-4} M ; Max. 33.8 mV.

40 : IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 1720 (C=O). ^{1}H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.14 (3H, d, J = 7.0 Hz, 17-H_3), 1.21 (3H, d, J = 6.6 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.71 (1H, dd, J = 4.6, 13.7 Hz, 7a-H), 1.88 (1H, dd, J = 4.6, 14.6 Hz, 2β-H), 2.05 (1H, dd, J = 11.0, 13.7 Hz, 7b-H), 2.23 (1H, ddd, J = 4.7, 12.2, 14.6 Hz, 2α-H), 2.38 (1H, br. s, 13-H), 2.59 (1H, ddd, J = 4.6, 6.0, 12.2

Hz, 1-H), 2.73 (1H, ddd, J = 7.0, 7.2, 14.0 Hz, 16-H), 3.62 (1H, d, J = 4.7 Hz, 3-H), 3.85 (1H, dd, J = 4.6, 11.0 Hz, 6H), 4.35 (1H, s, 14-H). Found : C, 67.81 ; H, 8.85. Calcd. for $C_{20}H_{32}O_5$: C, 68.54 ; H, 8.63 %. Activity : EC_{50} 8.17×10^{-4} M ; Max. 52.9 mV.

To a solution of **38a** (130 mg) in EtOH (5 ml) was added $NaBH_4$ (50 mg) and the mixture was kept at room temperature for 3 hr. Acidification with 5 % HCl followed by working up as usual afforded an oily product, which was dissolved in MeOH (5 ml) and refluxed with 2N NaOH (2 ml) for 2 hr. Working up as usual gave a solid, which was purified with silica gel column chromatography. Elution with n-hexane/EtOAc (5 : 95) gave 45 mg of crystals, which was recrystallized from EtOAc, mp 253-254℃. The ^1H NMR spectrum of the product was identical with that of **40**.

GX-3β, 5, 6β, 14R, 15β-pentaol (**41**). To a solution of **40** (50 mg) in THF (5 ml) was added $LiAlH_4$ (20 mg) at room temperature and the mixture was stirred for 1 day. Addition of MeOH and working up as usual gave a solid, which was purified by silica gel column chromatography. Elution with EtOAc afforded **41** (30 mg), which was recrystallized from EtOAc, mp 232-234℃. ^1H NMR δ (CD_3OD) : 1.01 (3H, d, J = 7.6 Hz, 17-H_3), 1.06 (3H, s, 19-H_3), 1.24 (3H, s, 18-H_3), 1.26 (3H, d, J = 6.8 Hz, 20-H_3), 1.53 (1H, m, 10-H), 1.87 (1H, dd, J = 5.0, 14.7 Hz, 2β-H), 1.94 (1H, dd, J = 4.5, 13.6 Hz, 7a-H), 1.94 (1H, br. s, 13-H), 2.06 (1H, dd, J = 11.0, 13.8 Hz, 7b-H), 2.21 (1H, dd, J = 48, 14.7, 18.6 Hz, 2α-H), 2.62 (2H, m, 1-H and 16-H), 3.62 (1H, d, J = 4.8 Hz, 3-H), 3.92 (1H, dd, J = 4.5, 11.4 Hz, 6-H), 3.99 (1H, s, 14-H), 4.10 (1H, d, J = 10.7 Hz, 15α-H). Found : C, 67.50 ; H, 9.81. Calcd. for $C_{20}H_{34}O_5$: C, 67.76 ; H, 9.67 %. Activity : 1.5 and 2.6 mV at 1.1×10^{-3} M.

GX-3β, 5, 6β, 14R, 15α, 16-hexaol (**42**). To a solution of **35** (100 mg) in THF (6 ml) was added a solution of mercuric acetate (200 mg) in water (2 ml) at room temperature and left for 1 day. After addition of 5 % NaOH (3 ml) and then $NaBH_4$ (20 mg), the mixture was diluted with water and worked up as usual. The product was chromatographed on silica gel column. Elution with n-hexane/EtOAc (10 : 90) gave **42** (60 mg), which was recrystallized from EtOAc, mp 136-138℃. The IR spectrum and ^1H NMR of **42** were identical with those of the compound obtained by OsO_4 oxidation of **2**.[14] ^1H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.24 (3H, d, J = 6.5 Hz, 20-H_3), 1.25 (3H, s, 18-H_3), 1.36 (3H, s, 17-H_3), 1.56 (1H, dd, J = 12.2, 13.9 Hz, 7b-H), 1.87 (1H, dd, J = 5.0, 14.7 Hz, 2β-H), 2.05 (1H, d, J = 3.7 Hz, 13-H), 2.21 (1H, ddd, J = 5.0, 12.0, 14.7 Hz, 2α-H), 2.37 (1H, dd, J = 4.2, 13.9 Hz, 7a-H), 2.59 (1H, ddd, J = 5.3, 6.3, 12.0 Hz, 1-H), 3.52 (1H, s, 15β-H), 3.62 (1H, d, J = 5.0 Hz, 3-H), 3.91 (1H, dd, J = 4.2, 12.2 Hz, 6-H), 3.95 (1H, s, 14-H). Activity : EC_{50} 3.40×10^{-5} M ; Max. 54.6 mV.

3β, 14R-Diacetoxy-GX-15- and 16-ene-5, 6β-diol cyclic 5, 6-(1-methylethylidene acetal) (**43a**). To a solution of α-dihydro GTX-II (**1**, 1.4 g) in acetone (300 ml) was added 0.3 ml of perchloric acid (60 %) with stirring at 0℃ and the stirring was continued for 3 hr at 0-5℃. After neutralization with sat. aq. $NaHCO_3$, the reaction mixture was evaporated and the residue was extracted with benzene. The solution was worked up as usual to yield a solid, which was recrystallized from n-hexane/EtOAc to give 950 mg of isopropylidene-α-dihydro GTX-II, mp 197-200℃. A mixture of the product (400 mg) in acetic anhydride (1.5 ml) and pyridine (1.5 ml) was kept at room temperature for 2 days. The mixture was worked up as usual to give an oily product, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (50 : 50) yielded a solid, which was recrystallized from n-hexane/EtOAc to give an isopropylidene-diacetate (900 mg), mp 221-222℃. To a solution of the product (700 mg) in pyridine

(10 ml) was added $POCl_3$ (1.5 ml) at room temperature and kept for 2 hr, which was then poured onto ice. Working up as usual gave a solid, which was recrystallized from *n*-hexane to afford 570 mg of **43a**, mp 116-118℃. IR ν_{max} (KBr) cm^{-1} : 3030 (-CH=C-), 1740 (AcO). Found : C, 70.22 ; H, 8.71. Calcd. for $C_{27}H_{40}O_6$: C, 70.41 ; H, 8.75 %.

16-Epi-GX-3β, 5, 6β, 14R-tetraol (**44**). A solution of **43a** (540 mg) in EtOH (20 ml) was hydrogenated over Pd-C (10 %) for 5 hr. The product was refluxed with 2*N* KOH (5 ml)-EtOH (10 ml) for 1 hr. The hydrolyzate was separated by silica gel column chromatography. Elution with *n*-hexane/EtOAc (50 : 50) gave two compounds, one (180 mg) showed a spot at Rf 0.30 on silica gel TLC [developing solvent : *n*-hexane/EtOAc (50 : 50)] and the other (240 mg) that at Rf 0.40. Each was treated with CF_3COOH (0.5 ml)-CH_2Cl_2 (15 ml) for 1 hr at room temperature. After recrystallization from EtOAc, the lower fraction gave crystals (160 mg), mp 222-223℃, whose ^1H NMR spectrum was identical with that of **23**. The higher fraction was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (50 : 50) gave a solid, which was recrystallized to yield 110 mg of **44**, mp 247-249℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH). ^1H NMR δ ($CDCl_3$-D_2O) : 1.01 (3H, s, 19-H_3), 1.15 (3H, d, J = 7.0 Hz, 17-H_3), 1.17 (3H, d, J = 6.6 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.26 (1H, m, 9-H), 1.35 (1H, dd, J = 4.5, 12.8 Hz, 15β-H), 1.66 (1H, m, 16-H), 1.81 (1H, dd, J = 12.0, 13.3 Hz, 7b-H), 1.82 (1H, dd, J = 5.1, 14.9 Hz, 2β-H), 1.89 (1H, br. d, J = 4.5 Hz, 13-H), 1.91 (1H, d, J = 12.8 Hz, 15α-H), 1.95 (1H, dd, J = 4.7, 9.0 Hz, 7a-H), 2.17 (1H, ddd, J = 4.7, 12.2, 14.9 Hz, 2α-H), 2.51 (1H, ddd, J = 5.2, 5.4, 12.2 Hz, 1-H), 3.62 (1H, d, J = 5.1 Hz), 3-H), 3.83 (1H, dd, J = 4.7, 11.4 Hz, 6-H), 3.87 (1H, s, 14-H). Found : C, 70.26 ; H, 10.11. Calcd. for $C_{20}H_{34}O_4$: C, 70.97 ; H, 10.12 %. Activity : EC_{50} 5.84×10^{-5} M ; Max. 58.7 mV.

3β, 14R-Diacetoxy-5, 6β-dihydroxy-17-nor-GX-16-one cyclic 5, 6-(1-methylethylidene acetal) (**45a**). To a solution of **43a** (2. 34 g) in EtOAc (30 ml) surrounded by a Dry Ice-MeOH bath was passed through a stream of oxygen containing ozone for 30 min. After reduction with zinc dust-50% AcOH followed by filtration of zinc dust and then neutralization with sat. aq. $NaHCO_3$, the mixture was evaporated. The residue was worked up as usual to give an oily product, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (1 : 2) yielded a solid, which was recrystallized from *n*-hexane/EtOAc to give 910 mg of **45a**, mp 236-238℃. IR ν_{max} (KBr) cm^{-1} : 1740(C=O). ^1H NMR δ ($CDCl_3$) : 0.92 (3H, s, 19-H_3), 0.97 (3H, s, 18-H_3), 1.17 (3H, d, J = 6.9 Hz,20-H_3), 1.33 (3H, s, -CCH_3), 1.55 (3H, s. -CCH_3), 2.01 (1H, d, J = 2.0 Hz, 12β-H), 2.05 (3H, s, AcO), 2.08 (3H, s, AcO), 2.29 (1H, d, J = 18.6 Hz, 15β-H), 2.45 (1H, br. s, 13-H), 2.58 (1H, d, J = 18.6 Hz, 15α-H), 2.90 (1H, dd, J = 5.8, 11.8 Hz, 9-H), 4.20 (1H, d, J = 4.4 Hz, 3-H), 4.82 (1H, dd, J = 6.5, 7.8 Hz, 6-H), 5.18 (1H, s, 14-H). Found : C, 67.48 ; H, 8.44. Calcd. for $C_{26}H_{38}O_7$: C, 67.51 ; H, 8.28%.

3β, 5, 6β, 14R-Tetrahydroxy-17-nor-GX-16-one 3, 6, 14-triacetate (**45b**). A solution of **45a** (630 mg) in CH_2Cl_2 (15 ml) was treated with CF_3COOH (2 ml) for 4 hr at room temperature with stirring. Neutralization with sat. aq. $NaHCO_3$ and working up as usual gave an oil, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (30 : 70) yielded an oily product (530 mg). A mixture of the product in acetic anhydride (5 ml) and pyridine (5 ml) was kept at room temperature for 1 day. The mixture was worked up as usual to give a solid, which was recrystallized from *n*-hexane/EtOAc to afford 430 mg of **45b**, mp 188-189℃. IR ν_{max} (KBr) cm^{-1} : 3560 (OH), 1740 (C=O), ^1H NMR δ ($CDCl_3$-D_2O) : 0.93 (3H, s, 19-H_3), 1.08 (3H, s, 18-H_3), 1.16 (3H, d, J = 6.8 Hz, 20-H_3), 1.45 (1H, dd, J = 4.3, 15.0 Hz, 9-H), 2.06 (3H, s, AcO), 2.08 (3H,

s, AcO), 2.18 (3H, s, AcO), 2.22 (2H, d, J = 2.0 Hz, 15-H_2), 2.36 (1H, ddd, J = 5.2, 12.0, 15.7 Hz, 2α-H), 2.46 (1H, br. s, 13-H), 2.79 (1H, ddd, J = 5.2, 6.3, 12.0 Hz, 1-H), 4.80 (1H, ddd, J = 1.3, 4.5, 11.5 Hz, 6-H), 4.84 (1H, d, J = 5.2 Hz, 3-H), 5.42 (1H, s, 14-H).

3β, 5, 6β, 14R-Tetrahydroxy-17-nor-GX-16-one (**45**). A solution of **45a** (520 mg) in EtOH (10 ml) was refluxed 2N KOH (5 ml) for 1 hr. Evaporation followed by working up as usual gave an oily product. The product was dissolved to CH_2Cl_2 (20 ml) and treated with CF_3COOH (3 ml) at room temperature for 1.5 hr with stirring. Neutralization with sat. aq. $NaHCO_3$ followed by working up as usual afforded a solid, which was recrystallized from EtOAc to yield 290 mg of **45**, mp 310-312℃. IRν_{max} (KBr) cm^{-1} : 3400 (OH), 1730 (C=O). ^1H NMR δ (CD_3OD) : 1.09 (3H, s, 19-H_3), 1.26 (3H, s, 18-H_3), 1.27 (3H, d, J = 6.7 Hz, 20-H_3), 1.46 (1H, dd, J = 4.9, 14.5 Hz, 9-H), 1.89 (1H, m, 11β-H), 1.89 (1H, dd, J = 4.7, 14.8 Hz, 2β-H), 2.01 (1H, d, J = 11.2, 13.4 Hz, 7b-H), 2.08 (1H, d, J = 4.7, 13.4 Hz, 7a-H), 2.11 (1H, d, J = 17.2 Hz, 15β-H), 2.24 (1H, d, J = 17.2 Hz, 15α-H), 2.26 (1H, ddd, J = 4.7, 12.3, 14.8 Hz, 2α-H), 2.38 (1H, br. s, 13-H), 2.65 (1H, ddd, J = 4.7, 5.1, 12.3 Hz, 1-H), 3.65 (1H, d, J = 4.7 Hz, 3-H), 3.98 (1H, dd, J = 4.6, 11.2 Hz, 6-H), 4.20 (1H, s, 14-H). CI-MS m/z : 338 (M^+). Activity : EC_{50} 3.89×10^{-4} M ; Max. 52.4 mV.

16-Epi-GX-3β, 5, 6β, 14R, 16β-pentaol (**46**). Compound **45a** (830 mg) was added to a solution prepared from Mg (1.0 g) and CH_3Br in dry THF (30 ml) at room temperature with stirring, and the mixture was then kept for 2 hr. After addition of aq. NH_4Cl, the reaction mixture was extracted with ether and then worked up as usual to give an oily product, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (30 : 70) gave a solid, which was recrystallized from EtOAc, mp 120-122℃ (490 mg). To a solution of the product (300 mg) in CH_2Cl_2 (10 ml) was added CF_3COOH (0.5 ml) at room temerature and kept for 1 hr with stirring. Working up as usual gave an oily product, which was purified by sillica gel column chromatography. Elution with n-hexane/EtOAc (10 : 90) yielded a solid, which was recrystallized from EtOAc to afford 80 mg of **46**, mp 302-303℃. IRν_{max} (KBr) cm^{-1} : 3400 (OH). ^1H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.20 (1H, d, J = 4.5 Hz, 9-H), 1.23 (3H, s, 18-H_3), 1.24 (3H, d, J = 5.4 Hz, 20-H_3), 1.56 (3H, s, 17-H_3), 1.76 (1H, d, J = 14.3 Hz, 15α-H). 1.78 (1H, dd, J = 11.4, 13.7 Hz, 7b-H), 1.86 (1H, dd, J = 4.7, 14.3 Hz, 2β-H), 1.87 (1H, d, J = 14.3 Hz, 15β-H), 1.92 (1H, br. s, 13-H), 1.94 (1H, dd, J = 4.5, 13.7 Hz, 7a-H), 2.20 (1H, m, 11β-H), 2.20 (1H, ddd, J = 4.7, 12.1, 14.3 Hz, 2α-H), 2.59 (1H, ddd, J = 5.3, 5.9, 12.1 Hz, 1-H), 3.61 (1H, d, J = 4.7 Hz, 3-H), 3.92 (1H, dd, J = 4.5,11.4 Hz, 6-H), 3.97 (1H, s, 14-H). Found : C. 67.56 ; H, 9.82. Calcd. for $C_{20}H_{34}O_5$: C, 67.77 ; H, 9.67%. Activity : EC_{50} 2.70×10^{-3} M ; Max. 58.6 mV.

17-Nor-GX-3β, 5, 6β, 14R, 16β-pentaol 3, 6, 14-triacetate (**47a**).To a solution of **45b** (430 mg) in EtOH (20 ml) was added $NaBH_4$ (400 mg) and the mixture was kept at 0-5℃ for 30 min. Acidification with 1% HCl followed by working up as usual gave an oily product, which was purified by silica gel column chromatography. Elution with n-hexane/EtOAc (50 : 50) yielded 260 mg of **47a** as a viscous oil. ^1H NMR δ ($CDCl_3$-D_2O) : 0.89 (3H, s, 19-H_3), 1.06 (3H, s, 18-H_3), 1.13 (3H, d, J = 6.8 Hz, 20-H_3), 1.78 (1H, dd, J = 4.7, 13.3 Hz, 7a-H), 1.83 (1H, dd, J = 4.8, 15.9 Hz, 2β-H), 1.87 (1H,dd, J = 11.4, 13.3 Hz, 7b-H), 2.04 (3H, s, AcO), 2.07 (3H, s, AcO), 2.17 (3H, s, AcO), 2.22 (1H, br. s, 13-H), 2.32 (1H, ddd, J = 5.3, 12.2, 15.7 Hz, 2α-H), 2.76 (1H, ddd, J = 5.0, 5.5, 13.2 Hz, 1-H), 4.58 (1H, ddd, J = 4.9, 5.3, 11.1 Hz, 16-H), 4.69 (1H, dd, J = 4.6, 11.3 Hz, 6-H), 4.81 (1H, d, J = 5.2 Hz, 3-H), 5.23 (1H, s, 14-H).

17-Nor-GX-3β, 5, 6β, 14R, 16β-pentaol (**47**). A solution of **47a** (40 mg) in EtOH (5 ml) was

treated with 2*N* KOH (1 ml) at room temperature over night. Working up as usual gave a solid, which was recrystallized from EtOAc to give 20 mg of **47**, mp 276-278℃. IRν_{max} (KBr) cm^{-1} : 3400 (OH). ^{1}H NMR δ (CD_3OD) : 1.03 (3H, s, 19-H_3), 1.23 (3H, s, 18-H_3), 1.24 (3H, d, J = 5.3 Hz, 20-H_3), 1.82 (1H, dd, J = 11.3, 13.5 Hz, 7b-H), 1.87 (1H, dd, J = 4.8, 14.8 Hz, 2β-H), 1.94 (1H, dd, J = 4.5, 13.5 Hz, 7a-H), 2.03 (1H, m, 11β-H), 2.04 (1H, dd, J = 10.7, 13.7 Hz, 15β-H), 2.17 (1H, br. s, 13-H), 2.21 (1H, ddd, J = 5.0, 12.2, 14.8 Hz, 2α-H), 2.58 (1H, ddd, J = 5.0, 5.9, 12.2 Hz, 1-H), 3.62 (1H, d, J = 4.8 Hz, 3-H), 3.88 (1H, dd, J = 4.5, 11.3 Hz, 6-H), 3.98 (1H, s, 14-H), 4.59 (1H, ddd, J = 5.0, 5.5, 10.7 Hz, 16-H). Found : C, 66.77 ; H 9.43. Calcd. for $C_{19}H_{32}O_5$: C, 67.03 ; H, 9.48%. X-ray measurement : the crystal data was shown in Table 1 and the stereoscopic view in Fig. 5. Activity : 6.0 and 6.2 mV at 2.0×10^{-3} M.

16β-Methoxy-17-nor-GX-3β, 5, 6β, 14R-tetraol (**48**). To a solution of **47a** (260 mg) in CH_2Cl_2 (20 ml) was added a solution of diazomethane in CH_2Cl_2. A boron trifluoride-etherate (0.2 ml)-ether (5 ml)-CH_2Cl_2 (5 ml) solution was added in small quantities (0.2 ml) to the mixture with stirring at room temperature. The reaction was complete in a short time. Working up as usual gave an oily product, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (65 : 35) afforded a viscous oil (200 mg), which was treated with 2*N* KOH (1.5 ml)-EtOH (10 ml) over night at room temperature. Working up as usual gave a solid, which was recrystallized from EtOAc to yield 110 mg of **48**, mp 251-252℃. IRν_{max} (KBr) cm^{-1} : 3400 (OH). ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.22 (3H, d, J = 5.4 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.83 (1H, dd, J = 11.3, 13.3 Hz, 7b-H), 1.87 (1H, dd, J = 4.9, 14.8 Hz, 2β-H), 1.93 (1H, dd, J = 4.5, 13.3 Hz, 7a-H), 2.00 (1H, dd, J = 10.7, 13.7 Hz, 15β-H), 2.00 (1H, m, 11β-H), 2.21 (1H, ddd, J = 4.9, 12.2, 14.8 Hz, 2α-H), 2.33 (1H, br. s, 13-H), 2.58 (1H, ddd, J = 4.9, 5.3, 12.2 Hz, 1-H), 3.62 (1H, d, J = 4.9 Hz, 3-H), 3.87 (1H, dd, J = 4.5, 11.3 Hz, 6-H), 3.99 (1H, s, 14-H), 4.14 (1H, ddd, J = 5.0, 5.4, 10.7 Hz, 16-H), δ (acetone-d_6) : 3.24 (3H, s, OCH_3). Found : C, 67.53 ; H, 9.55. Calcd. for $C_{20}H_{34}O_5$: C, 67.77 ; H, 9.67%. Activity : 8.1 and 8.3 mV at 3×10^{-3} M.

17-Nor-GX-3β, 5, 6β, 14R-tetraol (**49**). To a solution of **45** (230 mg) in DMSO (5 ml) was added KOH (180 mg) and hydrazine hydrate (150 μl) and the mixture was heated at 200℃ in a flask fitted with a take-out condenser for 2 hr. The reaction mixture was poured into ice water and then worked up as usual to give a solid, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (10 : 90) gave a solid, which was recrystallized from EtOAc to yield 135 mg of **49**, mp 198-200℃. IRν_{max} (KBr) cm^{-1} : 3400 (OH). ^{1}H NMR δ ($CDCl_3$-D_2O) : 1.02 (3H, s, 19-H_3), 1.18 (1H, m, 9-H), 1.18 (3H, d, J = 6.6 Hz, 20-H_3), 1.26 (3H, s, 18-H_3), 1.82 (1H, dd, J = 11.1, 13.8 Hz, 7b-H), 1.83 (1H, dd, J = 5.2, 15.1 Hz, 2β-H), 1.91 (1H, dd, J = 4.7, 13.8 Hz, 7a-H), 2.16 (1H, br. s, 13-H), 2.19 (1H, ddd, J = 5.1, 12.4, 15.1 Hz, 2α-H), 2.55 (1H, ddd, J = 5.4, 5.5, 12.4 Hz, 1-H), 3.63 (1H, d, J = 4.9 Hz, 3-H), 3.83 (1H, dd, J = 4.7, 11.1 Hz, 6-H), 3.87 (1H, s, 14-H). EI-MS m/z : 306 (M^+-H_2O), 288 (M^+-2H_2O). Activity : EC_{50} 4.59×10^{-5} M ; Max. 44.1 mV.

3β, 5, 6β, 14R-Tetrahydroxy-17-nor-GX-16-oxime (**50**). A solutino of **45** (200 mg) was treated with a solution of hydroxylamine hydrochloride (200 mg) in water (10 ml) at room temperature over night. Working up as usual gave a solid, which was recrystallized from EtOAc to yield 190 mg of **50**, mp 230-231℃. IRν_{max} (KBr) cm^{-1} : 3400 (OH), 1630 (C=N). ^{1}H NMR δ (CD_3OD) : 1.07 (3H, s, 19-H_3), 1.25 (3H, s, 18-H_3), 1.27 (3H, d, J = 7.1 Hz, 20-H_3), 1.35 (1H, dd, J = 3.7, 12.6 Hz, 9-H), 1.88 (1H, dd, J = 4.7, 14.7 Hz, 2β-H), 1.95 (1H, dd, J = 11.2, 13.5 Hz, 7b-H), 2.03 (1H, dd,

J = 4.7, 13.5 Hz, 7a-H), 2.24 (1H, ddd, J = 4.9, 12.3, 14.7 Hz, 2α-H), 2.42 (2H, s, 15-H_2), 2.61 (1H, ddd, J = 5.1, 6.0, 12.3 Hz, 1-H), 2.67 (1H, d, J = 3.1 Hz, 13-H), 3.63 (1H, d, J = 4.7 Hz, 3-H), 3.92 (1H, dd, J = 4.7, 11.2 Hz, 6-H), 4.03 (1H, s, 14-H). Found : C, 64.07 ; H, 9.20 ; N, 4.15. Calcd. for $C_{19}H_{31}NO_5 \cdot 1/2H_2O$: C, 64.41 ; H, 9.04 ; N, 3.95%. Activity : 6.70×10^{-4} M ; Max. 47.0 mV.

16α-Amino-17-nor-GX-3β, 5, 6β, 14R-tetraol (**51**) and *16β-Amino-17-nor-GX-3β, 5, 6β, 14R-tetraol* (**52**). A solution of **50** (540 mg)in AcOH (10 ml) was hydrogenated over PtO_2 (30 mg) for 2 hr. Removal of the catalyst and then evaporation of the filtrate gave a residue, which was diluted with water (10 ml) and acidified with 2N HCl. The solution was extracted continuously with ether for 12 hr. The residual aqueous solution was made alkaline with 10N NaOH and extracted continuously with the same solvent to afford a mixture of two basic compounds (360mg, mp 248-253℃). To a suspension of the mixture (300 mg) in $NaHCO_3$ (600 mg)-H_2O (20 ml) was added benzylchloroformate (3 ml) with vigorous stirring and the stirring was continued for 30 min. Working up as usual gave an oily product, whose silica gel TLC showed two spots at Rf = 0.3 and 0.5 [developing solvent : n-hexane/EtOAc (1 : 4)] . The mixture was separated by silica gel column chromatography. Elution with n-hexane/EtOAc (1 : 3) yielded **51**-N-Z (Rf 0.5, 230 mg, mp 245-246℃) and **52**-N-Z (Rf 0.3, 90 mg, a viscous oil). **51**-N-Z : ^{1}H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.22 (3H, d, J = 6.2 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.86 (2H, m, 2β- and 7b-H), 2.04 (1H, dd, J = 4.5, 13.7 Hz, 7a-H), 2.12 (1H, br. s, 13-H), 2.21 (1H, ddd, J = 5.0, 12.2, 14.7 Hz, 2α-H), 2.57 (1H, ddd, J = 5.4, 6.8, 12.2 Hz, 1-H), 3.62 (1H, d, J = 5.0 Hz, 3-H), 3.88 (1H, m, 16β-H), 3.90 (1H, dd, J = 4.5, 13.7 Hz, 6-H), 3.94 (1H, s, 14-H), 5.09 (2H, s, -CH_2Ph), 7.32 -7.38 (5H, m, aromatic H). Found : C, 68.17 ; H, 8.58 ; N, 2.88. Calcd. for $C_{27}H_{39}NO_6$: C, 68.47 ; H, 8.30 ; N, 2.96%.

52-N-Z : ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.23 (3H, d, J = 5.9 Hz, 20-H_3), 1.23 (3H, s, 18-H_3), 1.62 (1H, d, J = 12.8 Hz, 15β-H), 1.83 (1H, dd, J = 11.2, 12.6 Hz, 7b-H), 1.87 (1H, dd, J = 4.4, 14.1 Hz, 2β-H), 1.97 (1H, dd, J = 4.0, 12.6 Hz, 7a-H), 2.09 (1H, d, J = 12.8 Hz, 15α-H), 2.20 (1H, m, 2α-H), 2.35 (1H, br. s, 13-H), 2.58 (1H, m, 1-H), 3.62 (1H, d, J = 4.4 Hz, 3-H), 3.89 (1H, dd, J = 3.9, 11.2 Hz. 6-H), 4.02 (1H, s, 14-H), 4.33 (1H, ddd, J = 5.5, 5.8, 11.2 Hz, 16α-H), 5.11 (2H, s, -CH_2-Ph), 7.30-7.41 (5H, m, aromatic H).

51-N-Z (150 mg) in EtOH (20 ml) was treated with hydrogen over Pd-C (10%, 50 mg) for 1 day. The product was recrystallized from MeOH to give 16 mg of **51** (mp 296-298℃). ^{1}H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.21 (3H, d, J = 6.0 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.50 (1H, dd, J = 3.0, 12.2 Hz, 15β-H), 1.85 (1H, dd, J = 4.8, 13.4 Hz, 2β-H), 1.87 (1H, dd, J = 11.2, 13.4 Hz, 7b-H), 2.08 (1H, s, 13-H), 2.10 (1H, dd, J = 4.4, 13.7 Hz, 7a-H), 2.15 (1H, dd, J = 8.2, 14.0 Hz, 15β-H), 2.21 (1H, ddd, J = 4.8, 12.1, 14.6 Hz, 2α-H), 2.59 (1H, ddd, J = 5.0, 5.6, 11.8 Hz, 1-H), 3.13 (1H, dd, 16β-H), 3.62 (1H, d, J = 4.9 Hz, 3-H), 3.92 (1H, dd, J = 4.6, 11.6 Hz, 6-H), 3.94 (1H, s, 14-H). Found : C, 65.99 ; H, 9.93 ; N, 3.91. Calcd. for $C_{19}H_{33}NO_4 \cdot 1/2H_2O$: C, 65.52 ; H, 9.77 ; N, 4.02 %. Activity : 0.5 and 0.6 mV at 0.9×10^{-3} M.

Hydrogenolysis of **52**-N-Z (90 mg) gave 50 mg of the corresponding amine (**52**) as a viscous oil. ^{1}H NMR δ (CD_3OD) : 1.06 (3H, s, 19-H_3), 1.24 (3H, s, 18-H_3), 1.24 (3H,d, J = 6.3 Hz, 20-H_3), 1.44 (1H, dd, J = 6.0, 13.7 Hz, 15α-H), 1.60 (1H, m, 10-H), 1.86 (1H, dd, J = 11.2, 15.4 Hz, 7b-H), 1.88 (1H, dd, J = 4.8, 15.9 Hz, 2β-H), 1.98 (1H, dd, J = 4.4, 13.7 Hz, 7a-H), 2.04 (1H, dd, J = 11.7, 13.2 Hz, 15β-H), 2.10 (1H, d, J = 4.2 Hz, 13-H), 2.22 (1H, ddd, J = 4.8, 11.2, 13.6 Hz, 2α-H), 2.60 (1H, ddd, J = 5.3, 5.9, 11.2 Hz, 1-H), 3.64 (1H, d, J = 4.8 Hz, 3-H), 3.70 (1H, ddd, J = 5.5, 5.8, 11.4 Hz,

16α-H), 3.89 (1H, dd, J = 4.4, 11.3 Hz, 6-H), 4.00 (1H, s, 14-H). Found : C, 65.93 ; H, 9.68 ; N, 3.78. Calcd. for $C_{19}H_{33}NO_4 \cdot 1/2H_2O$: C, 65.52 ; H, 9.77 ; N, 4.02%. Activity : -3.3 and 4.2 mV at 1.6×10^{-3} M.

GX-3β, 5, 6β, 14R, 16-pentaol 14, 16-diacetate (α-dihydro GTX-II 14, 16-diacetate)[14] (**53**). ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.95 (3H, s, 19-H_3), 1.18 (3H, s, 18-H_3), 1.18 (3H, d, J = 6.5 Hz, 20-H_3), 1.27 (1H, dd, J = 4.8, 14.1 Hz, 9-H), 1.60 (3H, s, 17-H_3), 1.79 (2H, m, 2β-H and 7b-H), 1.95 (3H, s, AcO), 1.97 (1H, d, J = 15.0 Hz, 15β-H), 1.98 (1H, dd, J = 4.4, 13.6 Hz, 7a-H), 2.05 (3H, s, AcO), 2.20 (1H, ddd, J = 4.9, 12.3, 15.6 Hz, 2α-H), 2.35 (1H, d, J = 15.0 Hz, 15α-H), 2.54 (1H, ddd, J = 5.1, 5.3, 11.9 Hz, 1-H), 2.72 (1H, br. s, 13-H), 3.49 (1H, dd, J = 4.8, 11.4 Hz, 6-H), 3.66 (1H, d, J = 4.8 Hz, 3-H), 5.03 (1H, s, 14-H), Activity : EC_{50} 1.51×10^{-4} M ; Max. 40.6 mV.

GX-3β, 5, 6β, 14R, 16-pentaol 14-acetate (**54**). α-Dihydro GTX-II 14, 16-diacetate (**53**, 220 mg) was added in small quantities to a mixture of NaH (200 mg) in THF (5 ml) with stirring. After keeping the reaction mixture at room temperature for 1 hr, benzyl bromide (700 mg) was added to the mixture with stirring and the stirring was continued for 6 hr. The reaction mixture was diluted with benzene and washed with sat. aq. NaCl. Evaporation of the solvent gave an oily product, which was purified by silica gel column chromatography. Elution with benzene/EtOAc (80 : 20) yielded 200 mg of 3, 6-dibenzyl-14, 16-diacetyl-α-dihydro GTX-II. To a cooled (0-5℃) solution of the dibenzyldiacetate in THF (5 ml) was added large excess of $LiAlH_4$ with stirring and the stirring was continued for 6 hr. Addition of MeOH followed by evaporation the solvent gave a solid, which was recrystallized from EtOAc to yield 160 mg of 3, 6-dibenzyl-α-dihydro GTX-II (mp 203℃). The mixture of the dibenzyl compound in acetic anhydride (1 ml) and pyridine (1 ml) was kept at 40℃ for 1 day. Addition of MeOH followed by working up as usual afforded a viscous oil, which was purified by silica gel column chromatography. Elution with benzene/EtOAc (95 : 5) gave 112 mg of 3, 6-dibenzyl-α-dihydro GTX-II 14-acetate. A solution of the dibenzylacetate in EtOH (5 ml) was hydrogenated over Pd-C (10 %) for 20 hr. Removal of the catalyst followed by working up as usual gave a solid, which was purified by silica gel column chromatography. Elution with benzene/EtOAc (60 : 40) afforded a solid, which was recrystallized from n-hexane/EtOAc to yield 41 mg of **54**, mp 189℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 1735 (COO). ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.97 (3H, s, 19-H_3), 1.19 (3H, s, 18-H_3), 1.19 (3H, d, J = 6.4 Hz, 20-H_3), 1.34 (3H, s, 17-H_3), 1.78 (1H, dd, J = 4.6, 14.5 Hz, 2β-H), 1.81 (1H, dd, J = 10.7, 14.7 Hz, 7b-H), 1.89 (1H, d, J = 15.2 Hz, 15β-H), 1.94 (1H, dd, J = 5.0, 14.0 Hz, 7a-H), 2.07 (1H, br. s, 13-H), 2.07 (1H, d, J = 15.2 Hz, 15α-H), 2.13 (3H, s, AcO), 2.23 (1H, ddd, J = 5.0, 12.4, 15.1 Hz, 2α-H), 2.63 (1H, ddd, J = 4.9, 4.9, 12.1 Hz, 1-H), 3.48 (1H, dd, J = 5.0, 11.3 Hz, 6-H), 3.68 (1H, d, J = 4.9 Hz, 3-H), 5.29 (1H, s, 14-H). Found : C, 66.63 ; H, 9.20. Calcd. for $C_{22}H_{36}O_6$: C, 66.64 ; H, 9.15 %. Activity : EC_{50} 7.54×10^{-6} M ; Max. 67.9 mV.

GX-3β, 5, 6β, 14R, 16-pentaol 14-propionate (**55**). A mixture of 3, 6-dibenzyl-α-dihydro GTX-II (78 mg) in propionic anhydride (0.4 ml) and pyridine (2 ml) was kept at 40℃ for 3 days. The product (55 mg) was treated with hydrogen in the presence of Pd-C (10 %) to give 20 mg of **55**, mp 134-135℃. IR υ_{max} (KBr) cm^{-1} : 3400 (OH), 1735 (COO). ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.96 (3H, s, 19-H_3), 1.18 (3H, t, J = 7.8 Hz, $COCH_2CH_3$), 1.19 (3H, d, J = 6.4 Hz, 20-H_3), 1.19 (3H, s, 18-H_3), 1.34 (3H, s, 17-H_3), 1.80 (1H, dd, J = 4.0, 15.1 Hz, 2β-H), 1.81 (1H, dd, J = 11.2, 13.7 Hz, 7b-H), 1.90 (1H, d, J = 15.2 Hz, 15β-H), 1.93 (1H, dd, J = 5.0, 13.6 Hz, 7a-H), 2.07 (1H, br. s, 13-H), 2.07 (1H, d, J = 15.2 Hz, 15α-H), 2.23 (1H, ddd, J = 4.8, 12.2, 15.2 Hz, 2α-H), 2.40 (2H, t, J = 7.8 Hz,

$COCH_2CH_3$), 2.64 (1H, ddd, J = 4.8, 5.4, 11.6 Hz, 1-H), 3.45 (1H, dd, J = 4.8, 11.7 Hz, 6-H), 3.68 (1H, d, J = 4.8 Hz, 3-H), 5.32 (1H, s, 14-H). Found : C, 66.82 ; H, 9.24. Calcd. for $C_{23}H_{38}O_6$: C, 67.29 ; H, 9.33 %. Activity : EC_{50} 3.99×10^{-6} M ; Max. 67.9 mV.

GX-3β, 5, 6β, 14R, 16-pentaol 14-isobutyrate (**56**). A mixture of 3, 6-dibenzyl-α-dihydro GTX-II (165 mg) in isobutyric anhydride (1 ml) and pyridine (5 ml) was kept at 40℃ for 80 hr. The product (76 mg) was derived to 25 mg of **56**, mp 210-211℃, by the similar method to the above. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 1735 (COO).^{1}H NMR δ ($CDCl_3$-D_2O) : 0.95 (3H, s, 19-H_3), 1.17-1.21 (12H, m, 18-H_3, 20-H_3 and COCH (CH_3)$_2$), 1.34 (3H, s, 17-H_3), 1.79 (1H, dd, J = 4.8, 14.9 Hz, 2β-H), 1.82 (1H, dd, J = 11.0, 14.8 Hz, 7b-H), 1.91 (1H, d, J = 15.2 Hz, 15β-H), 1.93 (1H, dd, J = 4.9, 13.8 Hz, 7a-H), 2.06 (1H, br. s, 13-H), 2.08 (1H, d, J = 15.2 Hz, 15α-H), 2.23 (1H, ddd, J = 4.9, 12.2, 15.0 Hz, 2α-H), 2.61 (1H, septet, J = 7.0 Hz, $COCH(CH_3)_2$), 2.64 (1H, ddd, J = 5.0, 5.0, 12.1 Hz, 1-H), 3.43 (1H, dd, J = 4.7, 12.3 Hz, 6-H), 3.67 (1H, d, J = 5.0 Hz, 3-H), 5.32 (1H, s, 14-H). Found : C, 67.89 ; H, 9.55. Calcd. for $C_{24}H_{40}O_6$: C, 67.90 ; H, 9.50 %. Activity : EC_{50} 9.44×10^{-6} M ; Max. 58.0 mV.

GX-3β, 5, 6β, 14R, 16-pentaol 14-benzoate (**57**). A mixture of 3, 6-dibenzyl-α-dihydro GTX-II (100 mg) in benzoic anhydride (1 ml) and pyridine (5 ml) was kept at 40℃ for 60 hr. The product (55 mg) was derived to 20 mg of **57**, mp 136-137℃, through the similar route to the above. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 1735 (COO). ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.92 (3H, s, 19-H_3), 1.15 (3H, s, 18-H_3), 1.22 (3H, d, J = 6.4 Hz, 20-H_3), 1.38 (3H, s, 17-H_3), 1.82 (1H, dd, J = 4.8, 15.0 Hz, 2β-H), 1.89 (1H, dd, J = 11.6, 13.7 Hz, 7b-H), 2.06 (1H, d, J = 14.7 Hz, 15β-H), 2.06 (1H, dd, J = 5.0, 13.7 Hz, 7a-H), 2.16 (1H, d, J = 14.7 Hz, 15α-H), 2.22 (1H, br. s, 13-H), 2.27 (1H, ddd, J = 4.8, 12.2, 15.0 Hz, 2α-H), 2.72 (1H, ddd, J = 5.2, 5.2, 11.3 Hz, 1-H), 3.52 (1H, dd, J = 4.8, 11.4 Hz, 6-H), 3.67 (1H, d, J = 4.8 Hz, 3-H), 5.53 (1H, s, 14-H), 7.4-8.0 (5H, m, aromatic H). Found : C, 70.64 ; H, 8.32. Calcd. for $C_{27}H_{38}O_6$: C, 70.72 ; H, 8.35 %. Activity : EC_{50} 9.80×10^{-6} M ; Max. 58.0 mV.

3β, 5, 6β, 16-Tetrahydroxy-GX-14-one 3, 6-diacetate (**58a**). A mixture of GTX-II (4.00 g) in acetic anhydride (10 ml) and pyridine (10 ml) was kept for 12 hr at 5℃. Addition of MeOH followed by working up as usual gave an oily product, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (40 : 60) afforded 3.46 g of GTX-II 3, 6-diacetate as a viscous oil. A solution of the diacetate (2.68 g) in EtOH (25 ml) was hydrogenated over Pd-C (10 %) for 6 hr. Removal of the catalyst and working up as usual gave a solid, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (30 : 70) afforded a solid, which was recrystallized from EtOAc to yield 1.95 g of α-dihydro GTX-II 3, 6-diacetate, mp 240-241℃. To a cooled (0℃) solution of the diacetate (1.13 g) in acetone (20 ml) added Jones reagent with stirring and the stirring was continued for 30 min. Addition of isopropyl alcohol, evaporation and working up as usual gave a solid, which was recrystallized from EtOAc to afford 1.06 g of **58a**, mp 242-245℃. ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.95 (3H, s, 19-H_3), 1.05 (3H, s, 18-H_3), 1.08 (3H, d, J = 6.8 Hz, 20-H_3), 1.40 (3H, s, 17-H_3), 1.70 (1H, dd, J = 4.8, 15.5 Hz, 2β-H), 1.76 (1H, d, J = 14.3 Hz, 15β-H), 1.82 (1H, dd, J = 10.7, 13.6 Hz, 7b-H), 1.93 (1H, dd, J = 5.3, 13.6 Hz, 7a-H), 2.04 (3H, s, AcO), 2.05 (3H, s, AcO), 2.12 (1H, br. s, 13-H), 2.17 (1H, ddd, J = 5.3, 12.4, 15.5 Hz, 2α-H), 2.27 (1H, d, J = 14.3 Hz, 15α-H), 2.88 (1H, ddd, J = 4.8, 5.3, 11.2 Hz, 1-H), 4.75 (1H, d, J = 5.1 Hz, 3-H), 5.66 (1H, dd, J = 5.3, 10.7 Hz, 6-H).

3β, 5, 6β, 16-Tetrahydroxy-GX-14-one (**58**).[14] A solution of **58a** (1.10 g) in MeOH (20 ml) was refluxed with 5 % K_2CO_3 (15 ml) for 6 hr. The reaction mixture was evaporated and then working

up as usual gave a solid, which was purified by silica gel column chromatography. Elution with *n*-hexane/EtOAc (20 : 80) afforded a solid, which was recrystallized from EtOAc to yield 0.66 g of **58**, mp 205℃. ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.92 (3H, s, 19-H_3), 1.08 (3H, d, J = 6.7 Hz, 20-H_3), 1.08 (3H, s, 18-H_3), 1.33 (3H, s, 17-H_3), 1.61 (1H, dd, J = 5.0, 14.9 Hz, 2β-H), 1.68 (1H, dd, J = 10.5, 14.0 Hz, 7b-H), 1.71 (1H, d, J = 14.2 Hz, 15β-H), 1.85 (1H, dd, J = 4.9, 14.0 Hz, 7a-H), 2.00 (1H, d, J = 4.1 Hz, 13-H), 2.03 (1H, ddd, J = 5.3, 12.1, 15.0 Hz, 2α-H), 2.23 (1H, d, J = 14.2 Hz, 15α-H), 2.66 (1H, ddd, J = 5.1, 6.2, 11.7 Hz, 1-H), 3.54 (1H, d, J = 4.5 Hz, 3-H), 4.41 (1H, dd, J = 5.0, 10.2 Hz, 6-H). Activity : EC_{50} 1.62×10^{-5} M ; Max. 68.6 mV.

GX-3β, 5, 6β, 16-tetraol (**59**). To a solution of **58** (200 mg) in DMSO (5 ml) was added KOH (180 mg) and hydrazine-hydrate (150 μl), and then the mixture was heated at 200℃ for 2 hr. The mixture was poured onto ice and then worked up as usual to give a viscous oil, which was chromatographed on silica gel column. Elution with *n*-hexane/EtOAc (50 : 50) yielded a solid (150 mg), which was recrystallized from EtOAc to give **59**, mp 195℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH). ^{1}H NMR δ ($CDCl_3$-D_2O) : 1.00 (3H, s, 19-H_3), 1.17 (3H, d, J = 6.5 Hz, 20-H_3), 1.20 (3H, s, 18-H_3), 1.36 (3H, s, 17-H_3), 1.66 (1H, dd, J = 4.7, 13.4 Hz, 7a-H), 1.83 (1H, dd, J = 5.0, 14.9 Hz, 2β-H), 1.98 (1H, dd, J = 11.0, 13.4 Hz, 7b-H), 2.17 (1H, ddd, J = 5.0, 12.2, 14.9 Hz, 2α-H), 2.56 (1H, ddd, J = 5.0, 6.2, 12.2 Hz, 1-H), 3.63 (1H, d, J = 5.0 Hz, 3-H), 3.65 (1H, dd, J = 4.7, 11.0 Hz, 6-H). Found : C, 70.55 ; H, 10.01. Calcd. for $C_{20}H_{34}O_4$: C, 70.97 ; H, 10.12 %. Activity : EC_{50} 4.32×10^{-6} M ; Max. 61.9 mV.

GX-3β, 5, 6β, 14S, 16-pentaol (**60**). To a solution of **58** (300 mg) in MeOH (10 ml) was added $NaBH_4$ (150 mg) and the mixture was left for 2 hr at room temperature. Neutralization with 50 % AcOH and evaporation followed by working up as usual gave a solid, whose silica gel TLC (developing solvent : EtOAc) showed two spots at Rfs 0.20 and 0.15. Silica gel column chromatography eluted with EtOAc gave 80 mg of the higher Rf fraction and 150 mg of the lower fraction. The former was recrystallized from EtOAc to give α-dihydro GTX-II (**1**), mp 262-264℃. The latter was recrystallized from the same solvent to yield **60**, mp 218-219℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH). ^{1}H NMR δ (CD_3OD) : 1.03 (3H, s, 19-H_3), 1.16 (3H, d, J = 6.8 Hz, 20-H_3), 1.21 (3H, s, 18-H_3), 1.36 (3H, s, 17-H_3), 1.60 (1H, d, J = 14.6 Hz, 15β-H), 1.65 (1H, dd, J = 4.3, 13.7 Hz, 7a-H), 1.80 (1H, br. s, 13-H), 1.86 (1H, d, J = 14.6 Hz, 15α-H), 2.06 (1H, dd, J = 11.3, 13.5 Hz, 7b-H), 2.11 (1H, ddd, J = 5.0, 12.4, 14.5 Hz, 2α-H), 3.44 (1H, ddd, J = 6.4, 6.5, 12.8 Hz, 1-H), 3.58 (1H, d, J = 4.8 Hz, 3-H), 4.00 (1H, dd, J = 4.3, 11.3 Hz, 6-H), 4.38 (1H, d, J = 4.4 Hz, 14-H). Found : C, 67.35 ; H, 9.85. Calcd. for $C_{20}H_{34}O_5$: C, 67.76 ; H, 9.67 %. Activity : EC_{50} 4.24×10^{-5} M ; Max. 64.9 mV.

3β, 5, 6β, 16-Tetrahydroxy-GX-14-oxime (**61**). A solution of **58** (250 mg) and hydroxylamine hydrochloride (490 mg) in pyridine (9 ml) was heated for 1 day at 100℃. Evaporation followed by working up as usual gave a solid, which was recrystallized from EtOAc to yield 180 mg of **61**, mp 243-245℃. IR ν_{max} (KBr) cm^{-1} : 3400 (OH), 1630 (C=N). ^{1}H NMR δ ($CDCl_3$) : 0.98 (3H, s, 19-H_3), 1.16 (3H, d, J = 6.5 Hz, 20-H_3), 1.18 (3H, s, 18-H_3), 1.38 (3H, s, 17-H_3), 1.67 (1H, d, J = 14.2 Hz, 15β-H), 1.71 (1H, dd, J = 4.8, 19.7 Hz, 2β-H), 1.85 (1H, dd, J = 10.7, 19.5 Hz, 7b-H), 1.97 (1H, dd, J = 5.4, 13.8 Hz, 7a-H), 2.11 (1H, d, J = 14.2 Hz, 15α-H), 2.11 (1H, ddd, J = 5.4, 12.3, 16.8 Hz, 2α-H), 3.07 (1H, ddd, J = 4.8, 6.7, 10.5 Hz, 1-H), 3.62 (1H, d, J = 5.4 Hz, 3-H), 4.41 (1H, ddd, J = 5.4, 8.0, 10.8 Hz, 6-H). Found : C, 64.97 ; H, 9.13 ; N, 3.65. Calcd. for $C_{20}H_{33}NO_5$: C, 65.37 ; H, 9.05 ; N, 3.81 %. Activity : EC_{50} 1.46×10^{-5} M ; Max. 53.5 mV.

14R-Amino-GX-3β, 5, 6β, 16-tetraol (**62**) and *14S-amino-GX-3β, 5, 6β, 16-tetraol* (**63**). A solution of **61** (420 mg) in AcOH (1 ml) was hydrogenated over PtO_2 (120 mg) at 20 kg/cm² of hydrogen for 60 hr at 60℃. The reaction mixture was diluted with 50 % AcOH and removed the catalyst. The filtrate was evaporated and the residue was acidified with 2*N* HCl. The solution was extracted continuously with ether for 1 day. The residual aqueous solution was made alkaline with 2*N* KOH and extracted continuously with the same solvent to give a mixture of two basic compounds, which was separated[10] each other with preparative silica gel TLC detected by spraying of a solution of bromthymol blue (50 mg) in EtOH (10 ml)-H_2O (100 ml) to yield 160 mg of crude **62** and 120 mg of crude **63**. Each was recrystallized from CH_3CN, mp 262-265℃ (**62**) and mp 182℃ (**63**), respectively. **62** : IR ν_{max} (KBr) cm^{-1} : 3400 (OH, NH), 1590 (NH). ^{1}H NMR δ (CD_3OD) : 1.05 (3H, s, 19-H_3), 1.23 (3H, d, J = 6.7 Hz, 20-H_3), 1.24 (3H, s, 18-H_3), 1.33 (3H, s, 17-H_3), 1.56 (1H, d, J = 14.7 Hz, 15β-H), 1.72 (1H, dd, J = 6.5, 13.3 Hz, 2β-H), 1.87 (1H, dd, J = 4.4, 14.4 Hz, 7a-H), 1.92 (1H, d, J = 14.7 Hz, 15α-H), 1.98 (1H, m, 7b-H), 2.20 (1H, ddd, J = 4.7, 13.4, 14.7 Hz, 2α-H), 2.51 (1H, ddd, J = 4.8, 5.4, 11.7 Hz, 1-H), 3.30 (1H, s, 14-H), 3.62 (1H, d, J = 4.5 Hz, 3-H), 3.77 (1H, dd, J = 4.5, 11.5 Hz, 6-H), Found : C, 67.75 ; H, 9.92 ; N, 4.01. Calcd. for $C_{20}H_{35}NO_4$: C, 67.99 ; H, 9.92 ; N, 3.97 %. Activity : EC_{50} 4.87×10^{-6} M ; Max. 40.2 mV.

63 : IR ν_{max} (KBr) cm^{-1} : 3400 (OH, NH), 1590 (NH). ^{1}H NMR δ (CD_3OD) : 1.01 (3H, s, 19-H_3), 1.14 (3H, s, 18-H_3), 1.20 (3H, d, J = 6.5 Hz, 20-H_3), 1.38 (3H, s, 17-H_3), 1.70 (1H, d, J = 14.6 Hz, 15β-H), 1.75 (1H, br. s, 13-H), 1.80 (1H, dd, J = 3.8, 14.6 Hz, 7a-H), 1.88 (1H, dd, J = 6.2, 15.1 Hz, 2β-H), 1.94 (1H, d, J = 14.6 Hz, 15α-H), 2.03 (1H, dd, J = 9.7, 14.6 Hz, 7b-H), 2.19 (1H, ddd, J = 5.4, 11.5, 14.3 Hz, 2α-H), 3.06 (1H, ddd, J = 5.5, 6.0, 11.5 Hz, 1-H), 3.44 (1H, d, J = 4.3 Hz, 14-H), 3.62 (1H, d, J = 5.2 Hz, 3-H), 4.03 (1H, dd, J = 3.6, 9.7 Hz, 6-H). Found : C, 67.20 ; H, 9.87 ; N, 3.68. Calcd. for $C_{20}H_{35}NO_4$: C, 67.99 ; H, 9.92 ; N, 3.97 %. Activity : EC_{50} 2.90×10^{-3} M ; Max. 29.2 mV.

14R-N-Benzylimino-GX-3β, 5, 6β, 16-tetraol (**64**). To a solution of **62** (74 mg) in MeOH (2 ml) was added benzyl bromide (48 mg) and K_2CO_3 (40 mg). The mixture was kept for 18 hr at room temperature and then for 9 hr at 50℃ with stirring. The mixture was diluted with water and the resultant precipitate was filtered. The precipitate was recrystallized from CH_3CN to give 34 mg of **64**, mp 113-115℃. IR ν_{max} (KBr) cm^{-1} : 3420 (OH), 3040, 3030, 3008, 1600 (C_6H_5), 750, 700 (monosubstituted benzene). ^{1}H NMR δ ($CDCl_3$-D_2O) : 0.77 (3H, s, 19-H_3), 1.10 (3H, d, J = 6.5 Hz, 20-H_3), 1.14 (3H, s, 18-H_3), 1.30 (3H, s, 17-H_3), 1.64-1.68 (2H, m, 1-H and 2β-H), 1.82 (1H, m, 2α-H), 1.84 (2H, m, 7-H_2), 1.90 (1H, d, J = 13.8 Hz, 15β-H), 1.98 (1H, d, J = 14.6 Hz, 15α-H), 2.26 (1H, s, 13-H), 2.83 (1H, s, 14-H), 3.34 (1H, dd, J = 6.4, 10.0 Hz, 6-H), 3.58 (1H, d, J = 4.2 Hz, 3-H), 3.62 (1H, d, J = 13.5 Hz, NH-C*H*Ph), 3.98 (1H, d, J = 13.5 Hz, NH-C*H*Ph), 7.35 (5H, m, aromatic H). Found : C, 72.08 ; H, 9.12 ; N, 3.10. Calcd. for $C_{27}H_{41}NO_4$: C, 73.11 ; H, 9.32 ; N, 3.16 %. Activity : EC_{50} 7.67×10^{-4} M ; Max. 27.6 mV. The tested solution was cloudy because of its low solubility.

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グラヤノトキシン D 環の化学修飾

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ツツジ科植物に含まれる毒成分グラヤノトキシン類(GTX)は，神経興奮膜に存在するNaチャンネルに，膜の内側から作用して，電気的刺激なしに膜を脱分極させる．これまでの研究で，脱分極活性発現に必須な部分構造が明らかになっている．そこで，これまで活性発現に余り関与しないと思われているD環部の構造活性相関を調べ，この部分に光親和性標識などをして，既にその一次構造が明らかになっているNaチャンネル蛋白質に対する消息子を開発する基礎を明らかにする目的でこの研究を行なった．

ハナヒリノキ（ツツジ科）から容易に高収率で得られるGTX-IIを出発物として，D環部を化学修飾した新化合物51種を合成した．脱分極活性はイカの巨大軸索内部潅流法により測定した．それぞれのEC_{50}，最大脱分極値及びそれに基づく構造活性相関に対する考察については既に報告したので，ここでは上記の化学修飾法について報告する．