Introduction of Several Groups to the D-ring of Grayanotoxin

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Summary

Grayanotoxin (GTX), one of the lipid-soluble Na\textsuperscript{+} 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 \(\alpha\)-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\textsuperscript{13)}, the Ericaceae toxins, exerts a depolarizing action upon a variety of electrically excitable cells, through a specific increase in the membrane permeability to Na\textsuperscript{+} ion.\textsuperscript{18} A systematic study of the structure-activity relationship for GTX\textsuperscript{48)} has demonstrated that the essential groups for the pharmacological action included 3\(\beta\)-OH, 5-OH, 6\(\beta\)-OH and 10-CH\textsubscript{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.\textsuperscript{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 pharmacological 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\textsubscript{50} and the maximum value of depolarization for these new compounds as well as the previously synthesized GTXs were evaluated. \(\alpha\)-Dihydro GTX-II (I)\textsuperscript{11)}, obtained from hydrogenation of GTX-II, was found to have the highest

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activity (EC₅₀ 2.19 × 10⁻⁸M) among all analogs tested, while the other 23 analogs showed very low activity (EC₅₀ < 10⁻⁴M). 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:

C-16  A. dissociative groups, such as NH₂, CH₂NH₂, CH₂NHR, CO₂H.
      B. electronegative groups, such as β-OH, β-OCH₃, >C=O, >C=NOH.
      C. others, such as CO₂R, CH₂NHOCH₃.
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-14R 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, 14R, 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).¹³ Compound 1a lost one mol. of acetic acid on heating at 230°C to yield 2a. The ¹H 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=CH₂, 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, 14R-tetraol (2).¹⁵

Briggs et al.¹⁵ reported that on treatment with N-bromosuccinimide (NBS), (–)-isokaurene was converted to 17-bromokaure-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/H₂O (1 : 3) yielding 4a, which was converted to 4 on alkaline hydrolysis. The ¹H NMR spectra of 4 and 4a showed a two-proton singlet due to 17-H₂ 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-tetrahydropyranoyloxybutanoic acid or 6-tetrahydropyranoyloxyhexanoic acid in the presence of potassium carbonate and subsequent heating with 50%
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-methylamine (12), N-ethylamine (13), N-propylamine (14), N-isopropylamine (15) and N-benzylamine (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, 14R-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-methylene 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=CH-C=C-H2-.

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-C₅H₄ : b) 1. THPO(CH₂)₅CO₂H or AcO(CH₂)₅CO₂H, K₂CO₃, 2. 50% AcOH ; c) NaOAc ; d) NH₃ ; e) RNH₂ ; f) 1. Ac₂O-Py, 2. OH⁻ ; g) HEDPPT ; h) 1. PCC, 2. OH⁻ ; i) 1. Jones oxd., 2. OH⁻ ; j) CH₂N₂ or EtOH/ HCl ; k) 1. Amberlite-N₃, 2. H₂, PtO₂ ; l) H₂, 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 1H 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-CH₃ 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-CH₃ signal in 44 and 16-H signal in 23 were caused by the 1, 3-diaxial effect 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 NaN₃-DMSO reduction and subsequent saponification. Hydrogenation of 4 gave however an epimeric mixture of 24 and 25 in which the former predominated. The 1H 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-azole 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) according to the method reported by Briggs et al. Alkaline hydrolysis of 35a yielded 35. The 1H 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 H₂O₂-OH oxidation gave also 37.

In deuteriomethanol the 1H NMR signals (doublets) of 17-CH₃ 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 stereo-structural 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 5-0H 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
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, 14\( R \)-tetrahydroxy-16-epi-GX-15-one (39) and 3β, 5, 6β, 14\( R \)-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

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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-CH₃ signal in 39 and 16-H signal in 40 were caused by 14R-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, 14R, 15β-pentaol (41). In comparison of the ¹H 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, 14R, 15α, 16-hexaoxol (42), which was obtained previously by osmium tetraoxide oxidation of 2a. Alkaline epoxy-ring opening of 34a was attempted, but the product was GX-16-ene-3β, 5, 6β, 14R, 15α-pentaol (35).

**Modification of 16-ketone (Fig. 6)**

α-Dihydro GTX-II (1) was converted with acetone-perchloric acid at 0-5°C 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). The ¹H NMR spectrum of 43a exhibited two singlets due to 15-H of the 15-ene and 17-H₂ 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, 14R-tetraol (44), the former predominated. A comparison of ¹H 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. The ¹H 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 14R-OH. Reduction of 45b with sodium borohydride gave 47a, which was hydrolyzed to 17-nor-GX-3β, 5, 6β, 14R, 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 followed by alkaline hydrolysis yielded the corresponding 16β-methoxy compound (48). The ¹H 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, 14R-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-benzyloxy-carbonyl (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 ¹H 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 14R-OH.
Chemical Modification of Grayanotoxin

Fig. 6  a) Me₃CO, HClO₄, 0-5°C; b) Ac₂O-Py; c) POCl₃-Py; d) H₂, Pd-C; e) 1. O₂, 2. Zn-AcOH; f) CF₃CO₂H – CH₂Cl₂; g) OH⁻; h) MeMgBr; i) NaBH₄; j) CH₂N₂- BF₃; k) NH₂NH₂, KOH, 200°C; l) NH₂OH; m) H₂, PtO₂, AcOH.

Syntheses of 14-Substituted Analogs (Fig. 7)

α-Dihydro GTX-II 3, 6, 14, 16-tetraacetate (1a) was hydrolyzed partially with potassium carbonate-methanol to give 14, 16-diacetate (53). 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
anhydride-pyridine followed by hydrogenolysis to give $\alpha$-dihydro GTX-II 14-acetate (54). Along with the similar way, $\alpha$-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°C yielded 3, 6-diacetate 69, which was hydrogenated over Pd-C to 3, 6-diacetyl-\alpha-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. 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 $\alpha$-dihydro GTX-II (1) and GX-3β, 5, 6β, 14S, 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 $\delta$ 3.98 in 1 was shifted to $\delta$ 4.34 (a doublet, $J = 4.4$ Hz) in 60. The splitting and the downward shift of the signal support the structure of 60. On treatment with hydroxylamine hydrochloride
in pyridine at 100 °C, 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 14R-amine (62) and 14S-amine (63) as previously reported. The 1H 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 14R-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 14R-NH2 caused a diamagnetic shift of 1H NMR signals due to 1-H, 2α-H, 14-H and 19-H2 in 61 (1–H: δ 2.51→1.64→1.68; 2α-H: 2.20→1.82; 14–H: 3.30→2.83; 19–H2: 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-H2SO4 and then heating. IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer and 1H NMR spectra on a Varian VXR-500 Instrument. The coupled NMR signals were assigned with 1H-1H 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-D300. Biological activities (EC50 and Max. mV of depolarization) were determined using squid giant axons by means of the method described in the previous paper11. 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).** 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 resin and crystals, to which EtOAc was added for dissolving the resin. Filtration and recrystallization of the crystals from EtOAc gave 6.2 g of GTX-II, mp 206-207°C.

**GX-3β, 5, 6β, 14R, 16-pentaol (α-dihydro GTX-II) (1).** 1H-NMR δ (CD3OD) : 1.06 (3H, s, 19-H3), 1.22 (3H, d, J = 6.5 Hz, 20-H1), 1.24 (3H, s, 18-H3), 1.36 (3H, s, 17-H3), 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, 7β-H2), 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, 7α-H2), 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: EC50 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).** α-Dihydro GTX-II (1) in acetic anhydride-pyridine was heated at 100°C for 20 hr to give the tetraacetate (Ia). 1H-NMR δ (CDCl3-D2O) : 0.85 (3H, s, 19-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3), 1.05 (3H, s, 18-H3).
1.10 (3H, d, J = 6.5 Hz, 20-H3), 1.60 (3H, s, 17-H3), 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°C for 7 min. An EtOAc solution of the product was washed with sat. aq. NaHCO3 and sat. aq. NaCl followed by dehydration with anhydrous Na2SO4. 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°C. IR νmax (KBr) cm⁻¹: 3560 (OH), 3040 (-CH=CH-), 1735 (AcO). ¹H NMR δ (CDCl3-D2O): 0.85 (3H, s, 19-H3), 1.05 (3H, s, 18-H3), 1.10 (3H, d, J = 5.5 Hz, 20-H3), 1.68 (1H, dd, J = 5.5, 6.5 Hz, 10-H), 1.70 (3H, d, J = 1.5 Hz, 17-H3), 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), 2.20 (1H, ddd, J = 5.0, 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 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°C. The IR spectrum was identical with that of the 15-ene in the previous paper. ¹H NMR δ (CD2OD): 1.05 (3H, 19-H3), 1.23 (3H, d, J = 7.3 Hz, 20-H3), 1.24 (3H, s, 18-H3), 1.24 (3H, d, J = 11.3, 13.3 Hz, 7b-H), 1.50 (1H, dd, J = 11.3, 13.3 Hz, 7-a-H), 1.85 (1H, dd, J = 4.8, 12.3, 14.3 Hz, 2α-H), 2.15 (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: EC50 6.78 × 10⁻⁶ M: Max. 65.7 mV.

**GX-16-ene-3β, 5, 6β, 14R-tetraol**. ¹H NMR δ (CDCl3-D2O): 1.00 (3H, s, 19-H3), 1.18 (3H, d, J = 6.8 Hz, 20-H3), 1.20 (3H, s, 18-H3), 1.32 (1H, dd, J = 11.3, 13.3 Hz, 7b-H), 1.34 (1H, dd, J = 4.9, 15.0 Hz, 2β-H), 1.36 (1H, dd, J = 4.6, 13.0 Hz, 7a-H), 1.94 (1H, d, J = 5.1, 12.3, 15.0 Hz, 2α-H), 2.18 (1H, dd, J = 5.3, 6.4, 12.7 Hz, 1-H), 2.58 (1H, d, J = 4.8 Hz, 13-H), 3.63 (3H, d, J = 4.9 Hz, 3-H), 3.82 (1H, d, J = 4.5, 11.3 Hz, 6-H), 3.88 (1H, s, 14-H), 4.90 (2H, d, J = 13.3 Hz, 17-H2). Activity: EC50 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 CCl4 (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 νmax (KBr) cm⁻¹: 3650 (OH), 3030 (-CH=CH-), 1740 (AcO), 630 (Br). ¹H NMR δ (CDCl3-D2O): 0.87 (3H, s, 19-H3), 1.05 (3H, s, 18-H3), 1.10 (3H, d, J = 6.5 Hz, 20-H3), 1.60 (3H, s, 17-H3), 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).

b) "Worked up as usual" means extraction with EtOAc and the extract was washed with sat. aq. NaCl, dried over Na2SO4, followed by evaporation of the solvent under reduced pressure. In case of using solvent other than EtOAc for the extraction, the solvent was described.
11.11 (3H, d, J = 6.5 Hz, 20-H3), 1.80 (1H, dd, J = 5.0, 15.5 Hz, 2β-H), 1.88 (1H, dd, J = 5.0, 13.5 Hz, 7α-H), 1.93 (1H, dd, J = 11.5, 13.5 Hz, 7β-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-H2), 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°C. IR νmax (KBr) cm⁻¹: 3440 (OH), 3030 (–CH=C–), 630 (Br).

1H NMR δ (CDCl₃-D₂O) : 1.01 (3H, s, 19-H3), 1.20 (3H, d, J = 6.7 Hz, 20-H3), 1.21 (3H, s, 18-H3), 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⁺(4²Br)], 414 [M⁺(3²Br)], 380 [M⁺(4²Br)-2H₂O], 378 [M⁺(4²Br)-2H₂O]. Activity: EC₉⁰ 5.47 × 10⁻⁷ 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/H₂O (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°C. IR νmax (KBr) cm⁻¹: 3400 (OH), 3030 (–CH=C–), 1740 (AcO). 1H NMR δ (CDCl₃-D₂O) : 0.89 (3H, s, 19-H3), 1.07 (3H, s, 18-H3), 1.17 (3H, d, J = 6.5 Hz, 20-H3), 1.83 (1H, ddd, J = 4.6, 15.7 Hz, 2β-H), 1.91 (1H, dd, J = 5.0, 13.3 Hz, 7α-H), 1.97 (1H, dd, J = 11.5, 13.3 Hz, 7β-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-H₂), 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 C₃₈H₅₈O₈: 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°C. IR νmax (KBr) cm⁻¹: 3400 (OH), 3030 (–CH=C–). 1H NMR δ (CD₃OD) : 1.05 (3H, s, 19-H3), 1.22 (3H, d, J = 5.0 Hz, 20-H3), 1.23 (3H, s, 18-H3), 1.71 (1H, m, 10-H), 1.87 (1H, ddd, J = 4.7, 14.6 Hz, 2β-H), 1.92 (1H, ddd, 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-H₂), 5.26 (1H, s, 15-H). Found : C, 68.33; H, 9.07. Calcd. for C₃₈H₅₈O₈: C, 68.15; H, 9.15%. Activity: EC₉₀ 7.01 × 10⁻⁷ 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°C. IR ν_{max} (KBr) cm⁻¹: 3400 (OH), 3020 (‐CH=‐C‐). 1H NMR δ (CDCl₃/D₂O): 1.00 (3H, s, 19-H₃), 1.19 (3H, d, J = 6.7 Hz, 20-H₂), 1.21 (3H, s, 18-H₃), 1.83 (1H, dd, J = 4.7, 15.0 Hz, 2β-H), 1.88 (2H, m, 7-H₂), 2.18 (1H, dd, J = 5.0, 12.2, 14.8 Hz, 2α-H), 2.51 (1H, dd, J = 5.0, 5.5, 12.2 Hz, 1-H), 2.66 (1H, d, J = 3.3 Hz, 13-H), 3.37 (3H, s, OCH₃), 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 C₂₃H₄₀O₅: C, 68.82; H, 9.35 %. Activity: EC₅₀ 3.98 × 10⁻⁸ 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°C) via 6-triacetate (6a). IR ν_{max} (KBr) cm⁻¹: 3400 (OH), 3020 (‐CH=‐C‐). 1H NMR δ (CDCl₃/D₂O): 1.01 (3H, s, 19-H₃), 1.19 (3H, d, J = 6.6 Hz, 20-H₂), 1.21 (3H, s, 18-H₃), 1.22 (3H, t, J = 7.0 Hz, OCH₂CH₃), 1.83 (1H, dd, J = 4.7, 14.8 Hz, 2β-H), 1.89 (2H, m, 7-H₂), 2.18 (1H, dd, J = 5.0, 13.2, 15.0 Hz, 2α-H), 2.51 (1H, dd, 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, OCH₂CH₃), 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), 5.30 (1H, s, 15-H). Found: C, 69.08; H, 9.65. Calcd. for C₂₃H₄₀O₅: C, 69.44; H, 9.54 %. Activity: EC₅₀ 7.00 × 10⁻⁸ 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 dihydropyran (1 eq.) in the presence of pyridinium p-toluenesulfonate, which was oxidized with Jones reagent at -10°C 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°C), 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°C. IR ν_{max} (KBr) cm⁻¹: 3400 (OH), 3020 (‐CH=‐C‐), 1740 (‐COO‐). 1H NMR δ (CDCl₃/D₂O): 1.01 (3H, s, 19-H₃), 1.19 (3H, d, J = 6.8 Hz, 20-H₂), 1.21 (3H, s, 18-H₃), 1.84 (1H, dd, J = 5.0, 14.5 Hz, 2β-H), 1.89 (3H, m, 7-H and OCOCH₂C₂H₅OH), 2.19 (1H, dd, J = 5.0, 12.5, 15.0 Hz, 2α-H), 2.48 (2H, t, J = 7.0 Hz, OCOCH₂C₂H₅OH), 2.51 (1H, dd, 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, OCOCH₂C₂H₅OH), 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 C₂₃H₄₀O₅: C, 67.90; H, 9.50 % Activity: EC₅₀ 2.06 × 10⁻⁸ 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 °C) 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
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(–CH=–C–), 1740 (–COO–). 1H NMR δ (CDCl3-D2O) : 1.01 (3H, s, 19–H3), 1.20 (3H, d, J = 6.8 Hz, 20–H3), 1.22 (3H, s, 18–H3), 1.84 (1H, dd, J = 4.8, 15.0 Hz, 2β–H), 1.89 (2H, d, J = 7.6 Hz, 7–H3), 2.20 (1H, ddd, J = 4.9, 12.4, 14.9 Hz, 2α–H), 2.31 (2H, t, J = 7.4 Hz, OCOCHE2(CH3)2CH2OH), 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, OCOCHE2(CH3)2CH2OH), 3.67 (1H, d, J = 5.0 Hz, 3–H), 3.83–3.90 (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 C26H44O9 : C, 70.55 ; H, 10.02 %. Activity : EC50 = 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°C. IR νmax (KBr) cm–1 : 3400 (OH), 3020 (–CH=–C–), 1740 (–COO–). 1H NMR δ (CDCl3-D2O) : 1.02 (3H, s, 19–H3), 1.20 (3H, d, J = 6.8 Hz, 20–H3), 1.22 (3H, s, 18–H3), 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, –OCOCHE2CH2CHOOC2H5), 2.05 (3H, s, –OCOCHE2CH2 CH2OCOC2H5), 2.20 (1H, ddd, J = 4.8, 11.3, 14.9 Hz, 2α–H), 2.44 (2H, t, J = 7.4 Hz, –OCOCHE2CH2 CH2OCOC2H5), 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, –OCOCHE2CH2CH2OCOC2H5), 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 C32H42O7 : C, 66.93 ; H, 9.08 %. Activity : EC50 = 1.00×10–4 M ; Max. 22.1 mV.

**GX–15–ene–3β, 5, 6β, 14R, 17–pentaol 17–acetaete** (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 10 mg of 10, mp 163–165°C. IR νmax (KBr) cm–1 : 3400 (OH), 3030 (–CH=–C–), 1730 (AcO). 1H NMR δ (CDCl3-D2O) : 1.05 (3H, s, 19–H3), 1.23 (3H, d, J = 6.6 Hz, 20–H3), 1.23 (3H, s, 18–H3), 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 C32H42O7 : C, 66.98 ; H, 8.69 %. Activity : EC50 = 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°C), dried NH3 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 1N HCl and extracted continuously with ether. The aqueous layer was made alkaline with 1N 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°C. IR νmax (KBr) cm–1 : 3400 (OH, NH), 3030 (–CH=–C–), 1665 (NH2). 1H NMR δ (CD2OD) : 1.06 (3H, s, 19–H3), 1.23 (3H, d, J = 5.5 Hz, 20–H3), 1.24 (3H, s, 18–H3), 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), 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 C25H33NO4·1/2H2O: C, 66.67; H, 9.44; N, 3.89 %. Activity: 5.8 and 6.0 mV at 9.0×10⁻³ M.

17-N-Methylimino-GX-15-ene-3β, 5, 6β, 14R-tetraol (12). To a cooled (−78°C) 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°C. IR νmax (KBr) cm⁻¹: 3420 (OH, NH), 3020 (–CH=–C–). ¹H NMR δ (CD3OD): 1.05 (3H, s, 19-H), 1.23 (3H, d, J = 6.3 Hz, 20-H), 1.24 (3H, s, 18-H), 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, 7α-H), 2.05 (1H, s, –NHCH3), 2.22 (1H, ddd, J = 4.8, 12.2, 14.6 Hz, 2α-H), 2.49 (3H, s, –NHCH2), 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 C21H33NO4·1/2H2O: C, 67.38; H, 9.63; N, 3.74 %. Activity: negative at 1×10⁻³ M.

17-N-Ethylamino-GX-15-ene-3β, 5, 6β, 14R-tetraol (13). Compound 13 (680 mg, mp 165-167°C) was obtained from 3 (750 mg) and dried ethylamine gas by the similar method to the above. IR νmax (KBr) cm⁻¹: 3420 (OH, NH), 3030 (–CH=–C–). ¹H NMR δ (CD3OD): 1.05 (3H, s, 19-H), 1.19 (3H, t, J = 7.2 Hz, –NHCH2CH3), 1.23 (3H, d, J = 6.7 Hz, 20-H), 1.24 (3H, s, 18-H), 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, 7α-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, –NHCH2CH3), 3.28 (2H, d, J = 6.4 Hz, 17-H), 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 C22H37NO4·1/2H2O: C, 68.04; H, 9.79; N, 3.61 %. Activity: EC₅₀ 1.05×10⁻³ M: Max: 47.9 mV.

17-N-Propylamino-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°C. IR νmax (KBr) cm⁻¹: 3420 (OH, NH), 3020 (–CH=–C–). ¹H NMR δ (CD3OD): 0.88 (3H, s, 19-H), 1.04 (3H, s, 18-H), 1.18 (3H, d, J = 6.5 Hz, 20-H), 1.08 (3H, t, –NHCH2CH2CH3), 1.70 (2H, m, –NHCH2CH2CH3), 2.80 (2H, t, –NHCH2CH2CH3), 3.76 (2H, m, 17-H), 5.21 (1H, m, 15-H). Found: C, 69.53; H, 10.07; N, 3.32. Calcd. for C22H39NO4: C, 70.19; H, 9.99; N, 3.56 %. Activity: EC₅₀ 3.55×10⁻⁴ M: Max. 19.0 mV.

17-N-Isopropylamino-GX-15-ene-3β, 5, 6β, 14R-tetraol (15). Compound 15 (54 mg, mp 180-182°C) was obtained from 3 (120 mg) and isopropylamine (2 ml) by the similar method to the above. IR νmax (KBr) cm⁻¹: 3400 (OH, NH), 3030 (–CH=–C–). ¹H NMR δ (CD3OD): 1.05 (3H, s, 19-H), 1.13 (3H, d, J = 6.3 Hz, –NHCH2CH3), 1.15 (3H, d, J = 6.3 Hz, –NHCH2CH3), 1.23 (3H, d, J = 6.6 Hz, 20-H), 1.23 (3H, s, 18-H), 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, 2a-H), 2.57 (1H, d, $J = 4.6, 6.5, 12.2$ Hz, 1-H), 2.65 (1H, d, $J = 3.4$ Hz, 13-H), 2.91 (1H, m, $J = 6.3$ Hz, -NHCH(CH$_2$)$_3$), 3.26 (2H, s, 17-H$_2$), 3.63 (1H, d, $J = 4.6$ Hz, 3-H), 3.88 (1H, ddd, $J = 4.8, 11.4$ 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$_{35}$NO$_3$: C, 70.19; H, 9.99; N, 3.56%. Activity: EC$_{50}$ 3.10 x 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$_2$CO$_3$ (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 the 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°C. 'H NMR $δ$ (CD$_3$OD) : 1.05 (3H, s, 19-H$_3$), 1.24 (3H, d, $J = 6.0$ Hz, 20-H$_2$), 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, d, $J = 4.4, 13.5$ 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$_{35}$NO$_3$: C, 73.43; H, 8.90; N, 3.17%. Activity: 3.0 and 5.9 mV at 1.4 x 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°C. 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°C. IR $ν_{\text{max}}$ (KBr) cm$^{-1}$: 3400 (OH), 3280, 3080 (NH), 3020 (–CH=C–), 1650, 1580 (NHCO). 'H NMR $δ$ (CD$_3$OD) : 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, d, $J = 4.4, 14.6$ 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, ddd, $J = 4.8, 11.2$ 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$_{23}$H$_{35}$NO$_3$·1/2H$_2$O: C, 65.67; H, 8.96; N, 3.48%. Activity: 3-5 mV at 1 x 10$^{-2}$ 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°C. IR $ν_{\text{max}}$ (KBr) cm$^{-1}$: 3400 (OH), 3030 (–CH=C–). 'H NMR $δ$ (CD$_3$OD) : 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, s, 14-H).
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 $C_{25}H_{23}O_5$: C, 65.18; H, 8.75 %. Activity: $EC_{50} 3.75 \times 10^{-5}$ 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 2N K$_2$CO$_3$ (10 ml)-MeOH (20 ml) for 1 day at room temperature. After neutralization with 2N 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 $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3380 (OH), 2870 (CHO), 1680 (CHO), 1610 (C=O).$^1$H NMR $\delta$ (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, ddd, $J = 5.2, 14.2$ 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 $C_{25}H_{30}O_5$: C, 68.64; H, 8.63 %. Activity: $EC_{50} 7.31 \times 10^{-5}$ M; Max. 57.1 mV.

3β, 5, 6β, 14R-Tetrahydroxy-GX-15-ene-17-oic acid (20). To a cooled (0°C) 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 used as usual to give a solid, which was recrystallized from $n$-hexane/EtOAc, mp 220-223°C (240 mg). To a solution of the product (110 mg) in MeOH (2 ml), 2N KOH (2 ml) was added and the mixture was refluxed for 3 hr. After acidification with 2N HCl, the reaction mixture was evaporated and worked up as usual to give a solid, which was recrystallized from CH$_3$CN to yield 57 mg of 20, mp 269-271°C. IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3500-3200 (COOH), 3380 (OH), 3030 ($\sim$CH=), 1680 (COOH), 1610 (C=O). $^1$H NMR $\delta$ (CD$_2$OD): 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 $C_{25}H_{30}O_4 \cdot 1/2$H$_2$O: 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°C. IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3500, 3400 (OH), 1700 (C=O), 1620 ($\sim$C=O). $^1$H NMR $\delta$ (CD$_2$OD): 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 $C_{21}H_{25}O_5 \cdot 1/2$H$_2$O: 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 2N 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°C. IR νmax (KBr) cm⁻¹: 3500, 3400 (OH), 1700 (C=O), 1620 (C=C=O). ¹H NMR δ (CDCl₃): 1.00 (3H, s, 19-H₃), 1.19 (3H, d, J = 6.5 Hz, 20-H₃), 1.20 (3H, s, 18-H), 1.28 (3H, t, J = 7.0 Hz, COOCH₂CH₃), 1.83 (1H, dd, J = 5.0, 15.0 Hz, 2β-H), 2.19 (1H, dd, J = 5.5, 12.5, 15.0 Hz, 2α-H), 2.33 (1H, d, J = 5.3 Hz, 13-H), 2.48 (1H, dd, 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, COOCH₂CH₂), 6.40 (1H, s, 15-H). Found: C, 65.28; H, 8.65. Calcd. for C₂₅H₂₄O₅ • 1/2H₂O: 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°C. IR νmax (KBr) cm⁻¹: 3400 (OH). ¹H NMR δ (CDCl₃-D₂O): 1.01 (3H, s, 19-H₃), 1.04 (3H, d, J = 7.1 Hz, 17-H₂), 1.18(3H, d, J = 6.2 Hz, 20-H₃), 1.21 (3H, s, 18-H), 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, dd, J = 5.1, 12.3, 15.0 Hz, 2α-H), 2.43 (1H, m, 16-H), 2.54 (1H, dd, 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 C₃₉H₄₁O₇: C, 70.97; H, 10.12 %. Activity: EC₅₀ 9.01×10⁻⁴ 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 column chromatography yielding 24 (140 mg) and its 16-epimer (25, 30 mg) eluted with EtOAc. Each was recrystallized from EtOAc, mp 188–190°C (24) and mp 232–234°C (25), respectively. 24: IR νmax (KBr) cm⁻¹: 3580, 3400 (OH). ¹H NMR δ (CD₃OD): 1.06 (3H, s, 19-H), 1.22 (3H, d, J = 6.3 Hz, 20-H₃), 1.23 (3H, s, 18-H), 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), 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 C₃₉H₄₁O₇ • 1/2H₂O: C, 66.12; H, 9.64 %. Activity: EC₅₀ 6.72×10⁻⁴ M: Max. 43.2 mV.

25: ¹H NMR δ (CD₃OD): 1.05 (3H, s, 19-H), 1.24 (3H, d, J = 6.5 Hz, 20-H₃), 1.24 (3H, s, 18-H), 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), 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 C₃₉H₄₁O₇: C, 67.76; H, 9.67 %. Activity: EC₅₀ 5.70×10⁻⁴ 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°C. IR νmax (KBr) cm⁻¹: 3400 (OH), 1740 (AcO). ¹H NMR δ (CDCl₃-D₂O): 0.87 (3H, s, 19-H₃), 1.05 (3H, s, 18-H₃), 1.11 (3H, d, J = 6.5 Hz, 20-H₃), 1.73 (2H, dd, J = 11.8, 14.0 Hz, 15-H₂), 1.80 (1H, dd, J = 5.0, 15.7 Hz, 2β-H), 1.87-1.90 (2H, m, 7-H₂), 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-H₂), 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 2N KOH in ETOH to give a solid, which was recrystallized from ETOAc, mp 188-190°C. 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°C over night. The reaction mixture was poured onto ice and the resulting precipitate (480 mg) was collected, which was recrystallized from ETOAc, mp 208°C. ¹H NMR δ (CDCl₃-D₂O): 0.88 (3H, s, 19-H₃), 1.05 (3H, s, 18-H₃), 1.08 (3H, d, J = 6.6 Hz, 20-H₃), 1.69 (2H, dd, J = 11.7, 13.8 Hz, 15-H₂), 1.80 (1H, dd, J = 5.0, 16.1 Hz, 2β-H), 1.80 (1H, dd, J = 5.0, 13.3 Hz, 7α-H), 1.85 (1H, dd, J = 11.0, 13.5 Hz, 7β-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-CH₃), 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-H₂), 4.67 (1H, ddd, 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 C₁₃H₁₄O₁₁S·C, 62.33; H, 7.28%. To a solution of the tosylate (50 mg) in DMSO (1.5 ml) was added NaBH₄ (15 mg) and the mixture was heated at 90°C 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 product, 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°C, 130 mg) and 28 (mp 197-198°C, 40 mg) by silica gel column chromatography eluted with n-hexane/ETOAc (70:30). 26: IR νmax (KBr) cm⁻¹: 3400 (OH). ¹H NMR δ (CDCl₃-D₂O): 1.01 (3H, s, 19-H₃), 1.17 (3H, d, J = 6.7 Hz, 20-H₃), 1.21 (3H, s, 18-H₃), 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, OCH₃), 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 C₁₃H₁₉O₃S·C, 68.44; H, 9.85%. Activity: EC₅₀ 7.81×10⁻⁶ M; Max. 43.7 mV.

28: ¹H NMR δ (CDCl₃-D₂O): 1.00 (3H, s, 19-H₃), 1.19 (3H, d, J = 6.8 Hz, 20-H₃), 1.20 (3H, s, 18-H₃), 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, OCH₃), 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,
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°C) and 29 (40 mg, mp 130-132°C) were obtained from 6 (150 mg) by the similar way to the above. 27 : IR \( \nu_{\text{max}} \) (KBr) cm\(^{-1}\) : 3400 (OH). \( ^1H \) NMR \( \delta \) (CDCl\(_3\) : D\(_2\)O) : 0.99 (3H, s, 19-H\(_3\)), 1.16 (3H, d, \( J = 6.5 \) Hz, 20-H\(_2\)), 1.17 (3H, t, \( J = 6.3 \) Hz, OCH\(_2\)CH\(_3\)), 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), 2.02 (1H, br, s, 13-H), 2.14 (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, dddd, \( J = 6.0, 7.4, 12.3 \) Hz, 16-H), 3.47 (2H, dq, \( J = 2.5, 7.0 \) Hz, OCH\(_2\)CH\(_3\)), 3.52 (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\(_{25}\)H\(_{34}\)O\(_3\) : 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°C. IR \( \nu_{\text{max}} \) (KBr) cm\(^{-1}\) : 3600-2500 (COOH, OH), 1680 (COOH). \( ^1H \) NMR \( \delta \) (CD\(_3\)OD) : 1.06 (3H, s, 19-H\(_3\)), 1.21 (3H, d, \( J = 6.7 \) Hz, 20-H\(_2\)), 1.23 (3H, s, 18-H\(_3\)), 1.74 (1H, dd, \( J = 12.0, 13.6 \) Hz, 15α-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, ddd, \( J = 4.6, 11.4 \) Hz, 6-H), 4.00 (1H, s, 14-H). Found : C, 64.75 ; H, 8.86. Calcd. for C\(_{29}\)H\(_{33}\)O\(_5\) : 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°C. IR \( \nu_{\text{max}} \) (KBr) cm\(^{-1}\) : 3520, 3400 (OH), 1740 (COO). \( ^1H \) NMR \( \delta \) (CD\(_3\)OD) : 1.06 (3H, s, 19-H\(_3\)), 1.21 (3H, d, \( J = 6.7 \) Hz, 20-H\(_2\)), 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, COOC\(_3\)H), 3.88 (1H, ddd, \( J = 4.4, 11.3 \) Hz, 6-H), 3.99 (1H, s, 14-H). Found : C, 65.54 ; H, 9.05. Calcd. for C\(_{29}\)H\(_{33}\)O\(_5\) : 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 CH₂Cl₂ (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°C. 1H NMR δ (CDCl₃-D₂O): 0.89 (3H, s, 19-H₂), 1.06 (3H, s, 18-H₂), 1.09 (3H, d, J = 6.8 Hz, 20-H₃), 1.81 (1H, dd, J = 4.9, 15.1 Hz, 2β-H), 1.84 (1H, dd, J = 4.6, 13.2 Hz, 7α-H), 1.95 (1H, dd, J = 11.5, 13.4 Hz, 7β-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°C. IR νmax (KBr) cm⁻¹: 3380 (OH), 2870 (CHO), 1730 (C=O). 1H NMR δ (CDCl₃): 1.00 (3H, s, 19-H₂), 1.20 (3H, s, 18-H₂), 1.20 (3H, d, J = 6.5 Hz, 20-H₃), 1.80 (1H, dd, J = 5.0, 15.5 Hz, 7β-H), 1.88 (1H, dd, J = 5.0, 13.5 Hz, 7α-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, d, J = 5.0, 14.0 Hz, 6-H), 4.90 (1H, d, J = 7.0 Hz, 14-H), 9.70 (1H, s, CHO). Found: C, 68.12; H, 9.10. Calcd. for C₂₀H₂₆O₅: 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 filtered and the filtrate was evaporated to dryness. The residue was dissolved in EtOH (5 ml) and the solution was hydrogenated over PtO₂. 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 CHCl₃/MeOH/proplyamine (80:5:15) gave pure 33 (60 mg), mp 181-185°C. Compound 33 was also obtained by hydrogenation of 11 over Pd-C (10%). IR νmax (KBr) cm⁻¹: 3400 (OH), 1630 (NH₂). 1H NMR δ (CD₂OD): 1.06 (3H, s, 19-H₂), 1.25 (3H, d, J = 6.8 Hz, 20-H₃), 1.24 (3H, s, 18-H₂), 1.86 (1H, dd, J = 9.8, 13.7 Hz, 7β-H), 1.87 (1H, dd, J = 4.8, 14.7 Hz, 2β-H), 2.01 (1H, dd, J = 4.4, 13.6 Hz, 7α-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-H₂), 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⁺-2H₂O). Activity at 3×10⁻³ M.

15a, 16a-Epoxy-GX-3β, 5, 6β, 14R-tetraol 3, 6, 14-triacetate (34a). To a solution of 2a (1.2 g) in CH₂Cl₂ (20 ml) was added MCPBA (1.0 g) and left for 4 hr at room temperature. Excess peracid was decomposed by addition of 10% Na₂SO₃ 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°C. IR νmax (KBr) cm⁻¹: 3500 (OH), 1740 (AcO). On alkaline hydrolysis, 34a was converted to 34, mp 234°C, which was identical with the compound described previously. Activity: EC₅₀ 9.30×10⁻⁸ M; Max. 60.5 mV.

GX-16ene-3β, 5, 6β, 14R, 15a-pentatol 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 atmosphere with stirring and the mixture was
then refluxed for 3 hr. The reaction mixture was poured onto ice and acidified with 2N 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°C. IR u_{max} (KBr) cm^{-1} : 3550 (OH), 3070 (CH=,C-), 1740 (AcO). ^1H NMR δ (CDCl₃-D₂O) : 0.92 (3H, s, 19-H₃), 1.07 (3H, s, 18-H₃), 1.13 (3H, d, = 6.8 Hz, 20-H₃), 1.76 (1H, dd, J = 11.7, 13.8 Hz, 7b-H), 1.80 (1H, dd, J = 5.5, 15.8 Hz, 2b-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 2N 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°C. IR u_{max} (KBr) cm^{-1} : 3370 (OH), 3050 (CH₃=C), 1665 (C=C). ^1H NMR δ (CDCl₃-D₂O) : 1.03 (3H, s, 19-H₃), 1.21 (3H, d, J = 6.8 Hz, 20-H₃), 1.23 (3H, s, 18-H₃), 1.72 (1H, dd, J = 11.2, 14.0 Hz, 7b-H), 1.83 (1H, dd, J = 5.5, 15.0 Hz, 2b-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^+-H₂O), 316 (M^+-2H₂O), 298 (M^+-3H₂O). Activity : EC₅₀ 4.02×10^{-9} 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 PtO₂ (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°C (36) and mp 221–222°C (37), respectively. 36 : IR u_{max} (KBr) cm^{-1} : 3560, 3380 (OH). ^1H NMR δ (CD₃OD) : 1.06 (3H, s, 19-H₃), 1.17 (3H, d, J = 7.7 Hz, 17-H), 1.24 (3H, s, 18-H₃), 1.25 (3H, d, J = 4.6 Hz, 20-H₃), 1.68 (1H, dd, J = 11.5, 13.8 Hz, 7b-H), 1.83 (1H, dd, J = 5.5, 14.5 Hz, 2b-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-δ₃) : 1.14 (3H, s, 19-H₃), 1.47 (6H, d, J = 6.9 Hz, 17-H and 20-H₃), 1.68 (3H, s, 18-H₃). EI-MS m/z : 336 (M^+-H₂O), 318 (M^+-2H₂O), 300 (M^+-3H₂O). 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). Activity : EC₅₀ 2.01×10^{-4} M; Max. 49.7 mV.

37 : ^1H NMR δ (CD₃OD) : 1.07 (3H, s, 19-H₃), 1.20 (3H, d, J = 7.2 Hz, 17-H), 1.23 (3H, d, J = 6.7 Hz, 20-H₃), 1.25 (3H, s, 18-H₃), 1.54 (1H, dd, J = 11.2, 13.7 Hz, 7b-H), 1.86 (1H, dd, J = 4.9, 14.6 Hz, 2b-H), 1.93 (1H, br, s, 13-H), 2.18–2.28 (2H, m, 2α-H and 16β-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-δ₃) : 1.17 (3H, s, 19-H₃), 1.29 (3H, d, J = 7.3 Hz, 17-H), 1.47 (3H, d, J = 6.8 Hz, 20-H₃), 1.70 (3H, s, 18-H₃). Found : C, 67.48; H, 9.75. Calcd. for C₂₅H₃₅O₅ : C, 67.76; H, 9.67 %. Activity : EC₅₀ 4.60×10^{-4} M; Max. 33.2 mV.

A solution of 35a (150 mg) in AcOH (5 ml) was hydrogenated over PtO₂ (30 mg) for 3 hr to give an epimeric mixture of 36-triacetate (130 mg) and 37-triacetate (10 mg).
To a cooled (0 °C) solution of 2a (50 mg) in dry THF (10 ml) was added slowly BH₃–THF (1 ml) with stirring in an atmosphere of argon. After the mixture had been stirred for 1 hr, 2N NaOH (2 ml) and 30 % H₂O₂ (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°C. The 1H 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 CH₂Cl₂ (5 ml) was added a solution of PCC (250 mg) in CH₂Cl₂ (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°C). IR υmax (KBr) cm⁻¹ : 3580, 3500 (OH), 3080 (-CH=CH-), 1740 (C=O), 1650 (-NH=CHCO-). 1H NMR δ (CDCl₃-D₂O) : 0.95 (3H, s, 19-H₃), 1.07 (3H, s, 18-H₃), 1.12 (3H, d, J = 6.8 Hz, 20-H₃), 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, 7β-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 2N KOH (2 ml) for 4 hr. Working up as usual gave a solid, which was recrystallized from EtOAc to yield 38 (mp 285-288°C). IR υmax (KBr) cm⁻¹ : 3550, 3400 (OH), 3070 (CH=CH), 1730 (C=O), 1650 (-NH=CHC-). 1H NMR δ (CD₂OD) : 1.07 (3H, s, 19-H₃), 1.24 (3H, d, J = 6.5 Hz, 20-H₃), 1.25 (3H, s, 18-H₃), 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, 7β-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 C₂₀H₂₀O₄ : C, 68.54; H, 8.63 %. Activity : EC₅₀ 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 PtO₂ (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°C (39) and mp 240-242°C (40), respectively. 39 : IR υmax (KBr) cm⁻¹ : 3400 (OH), 1730 (C=O). 1H NMR δ (CD₂OD) : 1.05 (3H, s, 19-H₃), 1.23 (3H, d, J = 6.8 Hz, 20-H₃), 1.24 (3H, s, 18-H₃), 1.33 (3H, d, J = 7.7 Hz, 17-H₃), 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, 7β-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 C₂₀H₂₀O₄ : C, 68.54; H, 8.63 %. Activity : EC₅₀ 5.55 × 10⁻⁴ M : Max. 33.8 mV.

40 : IR υmax (KBr) cm⁻¹ : 3400 (OH), 1720 (C=O). 1H NMR δ (CD₂OD) : 1.06 (3H, s, 19-H₃), 1.14 (3H, d, J = 7.0 Hz, 17-H₃), 1.21 (3H, d, J = 6.6 Hz, 20-H₃), 1.24 (3H, s, 18-H₃), 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, ddd, J = 11.0, 13.7 Hz, 7β-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_{26}H_{42}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 NaNH$_4$ (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°C. The $^1$H 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°C.

$^1$H NMR δ (CD$_3$OD): 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, 7α-H), 1.94 (1H, br. s, 13-H), 2.06 (1H, dd, J = 11.0, 13.8 Hz, 7β-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$_{26}$H$_{44}$O$_5$: C, 67.76; H, 9.67 %. Activity: 1.5 and 2.6 mV at 1.1 × 10^{-5} M.

GX-3β, 5, 6β, 14R, 15α, 16-hexao1 (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 NaNH$_4$ (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°C. The IR spectrum and $^1$H NMR of 42 were identical with those of the compound obtained by OsO$_4$ oxidation of 2. $^1$H NMR δ (CD$_3$OD): 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, 7β-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, 7α-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^{-4} 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 (I, 1.4 g) in acetone (300 ml) was added 0.3 ml of perchloric acid (60 %) with stirring at 0°C and the stirring was continued for 3 hr at 0–5°C. 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°C. 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°C. To a solution of the product (700 mg) in pyridine
(10 ml) was added POCls\textsubscript{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 \(\tau\)-hexane to afford 570 mg of 43a, mp 116-118\degree C. IR \(\nu\)\textsubscript{max} (KBr) cm\textsuperscript{-1} : 3030 (-CH=CH-), 1740 (AcO). Found : C, 70.22 ; H, 8.71. Calcd. for C\textsubscript{2}H\textsubscript{4}O\textsubscript{2} : 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 2N KOH (5 ml)-EtOH (10 ml) for 1 hr. The hydrolyzate was separated by silica gel column chromatography. Elution with \(\tau\)-hexane/EtOAc (50 : 50) gave two compounds, one (180 mg) showed a spot at Rf 0.30 on silica gel TLC [developing solvent : \(\tau\)-hexane/EtOAc (50 : 50)] and the other (240 mg) that at Rf 0.40. Each was treated with CF\textsubscript{3}COOH (0.5 ml)-CH\textsubscript{2}Cl\textsubscript{2} (15 ml) for 1 hr at room temperature. After recrystallization from EtOAc, the lower fraction gave crystals (160 mg), mp 222-223\degree C, whose \(^1\)H NMR spectrum was identical with that of 23. The higher fraction was purified by silica gel column chromatography. Elution with \(\tau\)-hexane/EtOAc (50 : 50) gave a solid, which was recrystallized to yield 110 mg of 44, mp 247-249\degree C. IR \(\nu\)\textsubscript{max} (KBr) cm\textsuperscript{-1} : 3400 (OH), \(^1\)H NMR \(\delta\) (CDCl\textsubscript{3}-D\textsubscript{2}O) : 1.01 (3H, s, 19-H\textsubscript{3}), 1.15 (3H, d, \(J = 7.0\) Hz, 17-H\textsubscript{3}), 1.17 (3H, d, \(J = 6.6\) Hz, 20-H\textsubscript{2}), 1.21 (3H, s, 18-H\textsubscript{2}), 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, 7β-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, 7α-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\textsubscript{22}H\textsubscript{36}O\textsubscript{3} : C, 70.97 ; H, 10.12 %. Activity : EC\textsubscript{50} 5.84 x 10\textsuperscript{-8} 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\textsubscript{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 \(\tau\)-hexane/EtOAc (1 : 2) yielded a solid, which was recrystallized from \(\tau\)-hexane/EtOAc to give 910 mg of 45a, mp 236-238\degree C. IR \(\nu\)\textsubscript{max} (KBr) cm\textsuperscript{-1} : 1740(C=O), \(^1\)H NMR \(\delta\) (CDCl\textsubscript{3}) : 0.92 (3H, s, 19-H\textsubscript{3}), 0.97 (3H, s, 18-H\textsubscript{2}), 1.17 (3H, d, \(J = 6.9\) Hz,20-H\textsubscript{2}), 1.33 (3H, s, -CCH\textsubscript{3}), 1.55 (3H, s, -CCH\textsubscript{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\textsubscript{22}H\textsubscript{36}O\textsubscript{3} : 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\textsubscript{2}Cl\textsubscript{2} (15 ml) was treated with CF\textsubscript{3}COOH (2 ml) for 4 hr at room temperature with stirring. Neutralization with sat. aq. NaHCO\textsubscript{3} and working up as usual gave an oil, which was purified by silica gel column chromatography. Elution with \(\tau\)-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 \(\tau\)-hexane/EtOAc to afford 430 mg of 45b, mp 188-189\degree C. IR \(\nu\)\textsubscript{max} (KBr) cm\textsuperscript{-1} : 3560 (OH), 1740 (C=O), \(^1\)H NMR \(\delta\) (CDCl\textsubscript{3}-D\textsubscript{2}O) : 0.93 (3H, s, 19-H\textsubscript{3}), 1.08 (3H, s, 18-H\textsubscript{2}), 1.16 (3H, d, \(J = 6.8\) Hz, 20-H\textsubscript{2}), 1.45 (1H, dd, \(J = 4.3, 15.0\) Hz, 9-H), 2.06 (3H, s, AcO), 2.08 (3H, s, 17-H\textsubscript{2}), 2.11 (3H, s, 18-H\textsubscript{2}), 2.15 (3H, s, 17-H\textsubscript{2}), 2.55 (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\textsubscript{22}H\textsubscript{36}O\textsubscript{3} : C, 67.51 ; H, 8.28 %.
s, AcO), 2.18 (3H, s, AcO), 2.22 (2H, d, J = 2.0 Hz, 15-H2), 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 CH2Cl2 (20 ml) and treated with CF3COOH (3 ml) at room temperature for 1.5 hr with stirring. Neutralization with sat. aq. NaHCO3 followed by working up as usual afforded a solid, which was recrystallized from EtOAc to yield 290 mg of 45, mp 310–312°C. IRmax (KBr) cm⁻¹: 3400 (OH), 1730 (C=O). ¹H NMR δ (CD3OD): 1.09 (3H, s, 19-H3), 1.26 (3H, s, 18-H3), 1.27 (3H, d, J = 6.7 Hz, 20-H3), 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: EC₅₀ 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 CH2Br in dry THF (30 ml) at room temperature with stirring, and the mixture was then kept for 2 hr. After addition of aq. NH4Cl, 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°C (490 mg). To a solution of the product (300 mg) in CH2Cl2 (10 ml) was added CF3COOH (0.5 ml) at room temperature and kept for 1 hr with stirring. Working up as usual gave an oily product, which was purified by silica 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°C. IRmax (KBr) cm⁻¹: 3400 (OH). ¹H NMR δ (CD3OD): 1.05 (3H, s, 19-H3), 1.20 (1H, d, J = 4.5 Hz, 9-H), 1.23 (3H, s, 18-H3), 1.24 (3H, d, J = 5.4 Hz, 20-H3), 1.56 (3H, s, 17-H3), 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, ddd, J = 4.7, 13.4 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 C₂₅H₃₀O₃: C, 67.77; H, 9.67 %. Activity: EC₅₀ 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 NaBH₄ (400 mg) and the mixture was kept at 0–5°C 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 (CDCl₃-D2O): 0.89 (3H, s, 19-H3), 1.06 (3H, s, 18-H3), 1.13 (3H, d, J = 6.8 Hz, 20-H3), 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, ddd, 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 2N KOH (1 ml) at room temperature overnight. Working up as usual gave a solid, which was recrystallized from EtOAc to give 20 mg of 47, mp 276–278°C. IR £max (KBr) cm⁻¹ : 3400 (OH). 1H NMR δ (CDOD) : 1.03 (3H, s, 19-Hs), 1.23 (3H, s, 18-Hs), 1.24 (3H, d, J = 5.3 Hz, 20-Hs), 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 C₁₆H₃₅O₅ : 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 CH₂Cl₂ (20 ml) was added a solution of diazomethane in CH₂Cl₂. A boron trifluoride-etherate (0.2 ml)-ether (5 ml)-CH₂Cl₂ (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 2N 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°C. IR £max (KBr) cm⁻¹ : 3400 (OH). 1H NMR δ (CDCl₃-D₂O) : 1.05 (3H, s, 19-Hs), 1.22 (3H, d, J = 5.4 Hz, 20-Hs), 1.23 (3H, s, 18-Hs), 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-d₆) : 3.24 (3H, s, OCH₃). Found : C, 67.53 ; H, 9.55. Calcd. for C₁₆H₃₅O₅ : 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°C 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°C. IR £max (KBr) cm⁻¹ : 3400 (OH). 1H NMR δ (CDCl₃-D₂O) : 1.02 (3H, s, 19-Hs), 1.18 (1H, m, 9-H), 1.18 (3H, d, J = 6.6 Hz, 20-Hs), 1.26 (3H, s, 18-Hs), 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). El-MS m/z : 306 (M⁺-H₂O), 288 (M⁺-2H₂O). Activity : EC₅₀ 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 overnight. Working up as usual gave a solid, which was recrystallized from EtOAc to yield 190 mg of 50, mp 230–231°C. IR £max (KBr) cm⁻¹ : 3400 (OH), 1630 (C=N). 1H NMR δ (CDOD) : 1.07 (3H, s, 19-Hs), 1.25 (3H, s, 18-Hs), 1.27 (3H, d, J = 7.1 Hz, 20-Hs), 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,
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J = 4.7, 13.5 \text{ Hz}, 7a-H), 2.24 (1H, ddd, J = 4.9, 12.3, 14.7 \text{ Hz}, 2a-H), 2.42 (2H, s, 15-H), 2.61 (1H, ddd, J = 5.1, 6.0, 12.3 \text{ Hz}, 1-H), 2.67 (1H, d, J = 3.1 \text{ Hz}, 13-H), 3.63 (1H, d, J = 4.7 \text{ Hz}, 3-H), 3.92 (1H, dd, J = 4.7, 11.2 \text{ Hz}, 6-H), 4.03 (1H, s, 14-H). \text{ Found: } C, 64.07; H, 9.20; N, 4.15. \text{ Calcd. for } \text{C}_{19}\text{H}_{21}\text{NO}_5 \cdot 1/2\text{H}_2\text{O}: C, 64.41; H, 9.04; N, 3.95\%. \text{ Activity: } 6.70 \times 10^{-4} \text{ M; Max: } 47.0 \text{ mV.}
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\text{16a-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) \text{ in AcOH (10 ml) was hydrogenated over } \text{Pt}_2 \text{O} (30 \text{ mg}) \text{ 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 \text{ HCl. The solution was extracted continuously with ether for 12 hr. The residual aqueous solution was made alkaline with } 10N \text{ NaOH and extracted continuously with the same solvent to afford a mixture of two basic compounds (360 mg, mp 248-253°C). To a suspension of the mixture (300 mg) in } \text{NaHCO}_3 (600 mg) - \text{H}_2\text{O} (20 ml) \text{ 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 silicone gel TLC showed two spots at } \text{Rf = 0.3 and 0.5 [developing solvent: n-hexane/EtOAc (1:4)]. The mixture was separated by silicone gel column chromatography. Elution with n-hexane/EtOAc (1:3) yielded } 51-N-Z (\text{Rf 0.5, 230 mg, mp 245-246°C}) \text{ and } 52-N-Z (\text{Rf 0.3, 90 mg, a viscous oil). 51-N-Z: } ^1\text{H NMR } \delta (\text{CD}_3\text{OD}) : 1.06 (3H, s, 19-H), 1.22 (3H, d, J = 6.2 \text{ Hz}, 20-H), 1.24 (3H, s, 18-H), 1.86 (2H, m, 2β- and 7b-H), 2.04 (1H, dd, J = 4.5, 13.7 \text{ Hz}, 7a-H), 2.12 (1H, br, s, 13-H), 2.21 (1H, ddd, J = 5.0, 12.2, 14.7 \text{ Hz}, 2α-H), 2.57 (1H, ddd, J = 5.4, 6.8, 12.2 \text{ Hz}, 1-H), 3.62 (1H, d, J = 5.0 \text{ Hz}, 3-H), 3.88 (1H, m, 16β-H), 3.90 (1H, dd, J = 4.5, 13.7 \text{ Hz}, 6-H), 3.94 (1H, s, 14-H), 5.09 (2H, s, -CH_2Ph), 7.32 -7.38 (5H, m, aromatic H). \text{ Found: } C, 68.17; H, 8.58; N, 2.88. \text{ Calcd. for C}_{19}\text{H}_{23}\text{NO}_5 : C, 68.47; H, 8.30; N, 2.96\%.
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\text{52-N-Z: } ^1\text{H NMR } \delta (\text{CD}_3\text{OD}) : 1.05 (3H, s, 19-H), 1.23 (3H, d, J = 5.9 \text{ Hz}, 20-H), 1.23 (3H, s, 18-H), 1.62 (1H, d, J = 12.8 \text{ Hz}, 15β-H), 1.83 (1H, dd, J = 11.2, 12.6 \text{ Hz}, 7b-H), 1.87 (1H, dd, J = 4.4, 14.1 \text{ Hz}, 2β-H), 1.97 (1H, dd, J = 4.0, 12.6 \text{ Hz}, 7a-H), 2.09 (1H, d, J = 12.8 \text{ 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 \text{ Hz}, 3-H), 3.89 (1H, dd, J = 3.9, 11.2 \text{ Hz}, 6-H), 4.02 (1H, s, 14-H), 4.33 (1H, ddd, J = 5.5, 5.8, 11.2 \text{ Hz}, 16α-H), 5.11 (2H, s, -CH_2-Ph), 7.30-7.41 (5H, m, aromatic H).
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\text{51-N-Z (150 mg) in EtOH (20 ml) was treated with hydrogen over } \text{Pd-C} (10\%, 50 \text{ mg}) \text{ for 1 day. The product was recrystallized from MeOH to give 16 mg of 51 (mp 296-298°C). } ^1\text{H NMR } \delta (\text{CD}_3\text{OD}) : 1.06 (3H, s, 19-H), 1.21 (3H, d, J = 6.0 \text{ Hz}, 20-H), 1.24 (3H, s, 18-H), 1.50 (1H, dd, J = 3.0, 12.2 \text{ Hz}, 15β-H), 1.85 (1H, dd, J = 4.8, 13.4 \text{ Hz}, 2β-H), 1.87 (1H, dd, J = 11.2, 13.4 \text{ Hz}, 7b-H), 2.08 (1H, s, 13-H), 2.10 (1H, dd, J = 4.4, 13.7 \text{ Hz}, 7a-H), 2.15 (1H, dd, J = 8.2, 14.0 \text{ Hz}, 15β-H), 2.21 (1H, ddd, J = 4.8, 12.1, 14.6 \text{ Hz}, 2α-H), 2.59 (1H, ddd, J = 5.0, 5.6, 11.8 \text{ Hz}, 1-H), 3.13 (1H, dd, 16β-H), 3.62 (1H, d, J = 4.9 \text{ Hz}, 3-H), 3.92 (1H, dd, J = 4.6, 11.6 \text{ Hz}, 6-H), 3.94 (1H, s, 14-H). \text{ Found: } C, 65.99; H, 9.93; N, 3.91. \text{ Calcd. for C}_{19}\text{H}_{23}\text{NO}_5 \cdot 1/2\text{H}_2\text{O}: C, 65.52; H, 9.77; N, 4.02\% \text{. Activity: } 0.5 \text{ and 0.6 mV at } 0.9 \times 10^{-5} \text{ M.}
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\text{Hydrogenolysis of } 52-N-Z (90 mg) gave 50 mg of the corresponding amine (52) as a viscous oil. \text{1H NMR } \delta (\text{CD}_3\text{OD}) : 1.06 (3H, s, 19-H), 1.24 (3H, s, 18-H), 1.24 (3H, d), J = 6.3 \text{ Hz}, 20-H), 1.44 (1H, dd, J = 6.0, 13.7 \text{ Hz}, 15α-H), 1.60 (1H, m, 10-H), 1.86 (1H, dd, J = 11.2, 15.4 \text{ Hz}, 7b-H), 1.88 (1H, dd, J = 4.8, 15.9 \text{ Hz}, 2β-H), 1.98 (1H, dd, J = 4.4, 13.7 \text{ Hz}, 7a-H), 2.04 (1H, dd, J = 11.7, 13.2 \text{ Hz}, 15β-H), 2.10 (1H, d, J = 4.2 \text{ Hz}, 13-H), 2.22 (1H, ddd, J = 4.8, 11.2, 13.6 \text{ Hz}, 2α-H), 2.60 (1H, ddd, J = 5.3, 5.9, 11.2 \text{ Hz}, 1-H), 3.64 (1H, d, J = 4.8 \text{ 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 C₁₉H₂₃NO₄·1/2H₂O: 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)** (53).

1H NMR δ (CDCl₃-D₂O): 0.95 (3H, s, 19-H₃), 1.18 (3H, s, 18-H₃), 1.18 (3H, d, J = 6.5 Hz, 20-H₃), 1.27 (1H, dd, J = 4.8, 14.1 Hz, 9-H), 1.60 (3H, s, 17-H₃), 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), 3.86 (1H, d, J = 4.8 Hz, 3-H), 5.03 (1H, s, 14-H), Activity: EC₅₀ 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°C) solution of the dibenzylidiacetate in THF (5 ml) was added large excess of LiAlH₄ 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°C). The mixture of the dibenzyl compound in acetic anhydride (1 ml) and pyridine (1 ml) was kept at 40°C 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°C. IR νmax (KBr) cm⁻¹: 3400 (OH), 1735 (COO). 1H NMR δ (CDCl₃-D₂O): 0.97 (3H, s, 19-H₃), 1.19 (3H, s, 18-H₃), 1.19 (3H, d, J = 6.4 Hz, 20-H₃), 1.34 (3H, s, 17-H₃), 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 C₂₃H₂₃NO₄: C, 66.64; H, 9.15 %. Activity: EC₅₀ 7.54×10⁻⁴ 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°C 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°C. IR νmax (KBr) cm⁻¹: 3400 (OH), 1735 (COO). 1H NMR δ (CDCl₃-D₂O): 0.96 (3H, s, 19-H₃), 1.18 (3H, t, J = 7.8 Hz, COCH₂CH₃), 1.19 (3H, d, J = 6.4 Hz, 20-H₃), 1.19 (3H, s, 18-H₃), 1.34 (3H, s, 17-H₃), 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, 2β-H), 2.54 (1H, dd, J = 5.1, 8.9 Hz, 1-H), 2.72 (1H, br. s, 13-H), Activity: EC₅₀ 1.51×10⁻⁴ M; Max. 40.6 mV.
COCH₂CH₃), 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 C₁₉H₂₅NO₆: C, 67.29; H, 9.33%. Activity: EC₉₀ 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°C for 80 hr. The product (76 mg) was isolated and recrystallized from MeOH to 25 mg of 56, mp 210–211°C, by the similar method to the above. IR νmax (KBr) cm⁻¹: 3400 (OH), 1735 (COO). IH NMR δ (CDCl₃-D₂O): 0.95 (3H, s, 19-H), 1.17–1.21 (12H, m, 18-H), 20-H, and COCH (CH₃), 1.34 (3H, s, 17-H), 1.79 (1H, dd, J = 4.8, 14.9 Hz, 2β-H), 1.82 (1H, ddd, 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 = 7.9 Hz, COCH(CH₃), 2.64 (1H, ddd, J = 5.0, 5.0, 12.1 Hz, 1–H), 3.43 (1H, ddd, J = 5.0, 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 C₁₀H₁₄O₅: C, 67.90; H, 9.50%. Activity: EC₉₀ 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°C for 60 hr. The product (55 mg) was isolated and recrystallized from MeOH to 20 mg of 57, mp 136–137°C, through the similar route to the above. IR νmax (KBr) cm⁻¹: 3400 (OH), 1735 (COO). IH NMR δ (CDCl₃-D₂O): 0.92 (3H, s, 19-H), 1.15 (3H, s, 18-H), 1.22 (3H, d, J = 6.4 Hz, 20-H), 1.38 (3H, s, 17-H), 1.82 (1H, dd, J = 4.8, 15.0 Hz, 2β-H), 1.89 (1H, ddd, 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, d, 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 C₁₉H₂₅NO₆: C, 70.72; H, 8.35%. Activity: EC₉₀ 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°C. 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°C. To a cooled (0°C) 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°C. IH NMR δ (CDCl₃-D₂O): 0.95 (3H, s, 19-H), 1.05 (3H, s, 18-H), 1.08 (3H, d, J = 6.8 Hz, 20-H), 1.40 (3H, s, 17-H), 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 (58a). A solution of 58a (1.10 g) in MeOH (20 ml) was refluxed with 5% K₂CO₃ (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°C. 1H NMR δ (CDCl₃-D₂O) : 0.92 (3H, s, 19-H₃), 1.08 (3H, d, J = 6.7 Hz, 20-H₂), 1.08 (3H, s, 18-H₃), 1.33 (3H, s, 17-H₃), 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 : EC₅₀ 1.62×10⁻⁸ M : Max. 68.6 mV.

GX-3β, 5, 6β, 16-tertanol (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°C 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°C. IR νₐₘₙₙ (KBr) cm⁻¹ : 3400 (OH). 1H NMR δ (CDCl₃-D₂O) : 1.00 (3H, s, 19-H₃), 1.17 (3H, d, J = 6.5 Hz, 20-H₂), 1.20 (3H, s, 18-H₃), 1.36 (3H, s, 17-H₃), 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 C₂₅H₄₀O₆ : C, 70.97 : H, 10.12 %. Activity : EC₅₀ 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 NaBH₄ (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°C. The latter was recrystallized from the same solvent to yield 60, mp 218-219°C. IR νₐₘₙₙ (KBr) cm⁻¹ : 3400 (OH). 1H NMR δ (CD₃OD) : 1.03 (3H, s, 19-H₃), 1.16 (3H, d, J = 6.8 Hz, 20-H₂), 1.21 (3H, s, 18-H₃), 1.36 (3H, s, 17-H₃), 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 C₂₅H₃₀O₆ : C, 67.76 : H, 9.67 %. Activity : EC₅₀ 4.24×10⁻⁶ 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°C. Evaporation followed by working up as usual gave a solid, which was recrystallized from EtOAc to yield 180 mg of 61, mp 243-245°C. IR νₐₘₙₙ (KBr) cm⁻¹ : 3400 (OH), 1630 (C=N). 1H NMR δ (CDCl₃) : 0.98 (3H, s, 19-H₃), 1.16 (3H, d, J = 6.5 Hz, 20-H₂), 1.18 (3H, s, 18-H₃), 1.38 (3H, s, 17-H₃), 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 C₅₀H₅₂NO₄ : C, 65.37 : H, 9.05 : N, 3.81 %. Activity : EC₅₀ 1.46×10⁻⁸ 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 PtO₂ (120 mg) at 20 kg/cm² of hydrogen for 60 hr at 60°C. The reaction mixture was diluted with 50 % AcOH and removed the catalyst. The filtrate was evaporated and the residue was acidified with 2N HCl. The solution was extracted continuously with ether for 1 day. The residual aqueous solution was made alkaline with 2N KOH and extracted continuously with the same solvent to give a mixture of two basic compounds, which was separated¹⁰ each with preparative silica gel TLC detected by spraying of a solution of bromothyl blue (50 mg) in EtOH (10 ml)-H₂O (100 ml) to yield 160 mg of crude 62 and 120 mg of crude 63. Each was recrystallized from CH₃CN, mp 262–265°C (62) and mp 182°C (63), respectively. 62 : IR ²νmax (KBr) cm⁻¹ : 3400 (OH, NH), 1590 (NH). ¹H NMR δ (CD₃OD) : 1.05 (3H, s, 19-H₃), 1.23 (3H, d, J = 6.7 Hz, 20-H₃), 1.24 (3H, s, 18-H₃), 1.33 (3H, s, 17-H₃), 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 C₃₆H₅₅NO₄ : C, 67.99 ; H, 9.92 ; N, 3.97 %. Activity : EC₉₀ 4.87×10⁻⁸ M ; Max. 40.2 mV.

63 : IR ²νmax (KBr) cm⁻¹ : 3400 (OH, NH), 1590 (NH). ¹H NMR δ (CD₃OD) : 1.01 (3H, s, 19-H₃), 1.14 (3H, s, 18-H₃), 1.20 (3H, d, J = 6.5 Hz, 20-H₃), 1.38 (3H, s, 17-H₃), 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 C₃₆H₅₅NO₄ : C, 67.99 ; H, 9.92 ; N, 3.97 %. Activity : EC₉₀ 2.90×10⁻³ M ; Max. 29.2 mV.

14R-α-Benzylximino-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 K₂CO₃ (40 mg). The mixture was kept for 18 hr at room temperature and then for 9 hr at 50°C with stirring. The mixture was diluted with water and the resultant precipitate was filtered. The precipitate was recrystallized from CH₃CN to give 34 mg of 64, mp 113–115°C. IR ²νmax (KBr) cm⁻¹ : 3420 (OH), 3040, 3030, 3008, 1600 (C=H), 750, 700 (monosubstituted benzene). ¹H NMR δ (CDCl₃-D₂O) : 0.77 (3H, s, 19-H₃), 1.10 (3H, d, J = 6.5 Hz, 20-H₃), 1.14 (3H, s, 18-H₃), 1.30 (3H, s, 17-H₃), 1.64–1.68 (2H, m, 1-H and 2β-H), 1.82 (1H, m, 2α-H), 1.84 (2H, m, 7-H), 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-CH₂Ph), 3.98 (1H, d, J = 13.5 Hz, NH-CH₂Ph), 7.35 (5H, m, aromatic H). Found : C, 72.08 ; H, 9.12 ; N, 3.10. Calcd. for C₃₇H₄₁NO₄ : C, 73.11 ; H, 9.32 ; N, 3.16 %. Activity : EC₉₀ 7.67×10⁻⁴ M ; Max. 27.6 mV. The tested solution was cloudy because of its low solubility.

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References


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、この部分に光誘導性構造などをして、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灌流法に測定した。それぞれの EC50、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。