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# Syntheses of Betulafolienetriol and the Ginseng Sapogenin, 20(*S*)-Protopanaxadiol[1]

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In an attempt toward the synthesis of 20(*S*)-protopanaxadiol (I) from dammarenediol-II(V), the introduction of a hydroxy function to C-12 of the dammarane skeletone has been studied. A solution of *p*-nitrobenzoate (IX) of 3-*epi*-dammaranediol-I(VIII) in *tert*-BuOH was irradiated for 40 hr and the products were saponified to give 17-octakisnordammarane-3$\alpha$,17$\beta$-diol (X). From the crude irradiation products, 6-methyl-2-heptanone (XII) was isolated and identified. Whereas, the irradiation of *p*-nitrophenylacetate (XIX) of 3-*epi*-dammaranediol-II(XVI) under the similar condition followed by saponification yielded the 12-hydroxy compound (XX). This was converted into betulafolienetriol (XXI) and 20(*S*)-protopanaxadiol (I) furnishing the synthesis of the Ginseng sapogenin.

The isolation and the structural elucidation of most of the Ginseng saponins, ginsenosides have been performed.[3-5] The common sapogenin of ginsenosides-$Rb_1$, -$Rb_2$, -Rc, and -Rd is represented by 20(*S*)-protopanaxadiol(12$\beta$-hydroxydammarenediol-II) (I)[6] and that of ginsenosides-Re, -Rf, -$Rg_1$, and -$Rg_2$ is formulated as 20(*S*)-protopanaxatriol(6$\alpha$,12$\beta$-dihydroxydammarenediol-II) (II).[3] In an attempt toward the synthesis of the Ginseng sapogenin, 3$\beta$-acetoxyhexakisnordammaran-20-one (IV) was prepared from hydroxyhopanone (III)[7] which has already been synthesized from $\alpha$-onocerin by Tsuda, *et al.*[8] Recently, the preparation of dammarenediol-II (V) from IV has also been reported.[9]

On the basis of the biomimetic consideration, Breslow and his co-workers have reported the novel idea, "Remote Oxidation" and succeeded the selective introduction of an oxygen function to the unactivated carbon atoms such as C-12 of the steroid nucleus.[10] Their procedure generally consisted of the condensation of the benzophenone phototriplet followed by the dehydration and the subsequent cleavage of the resulted double bond. We have been seeking

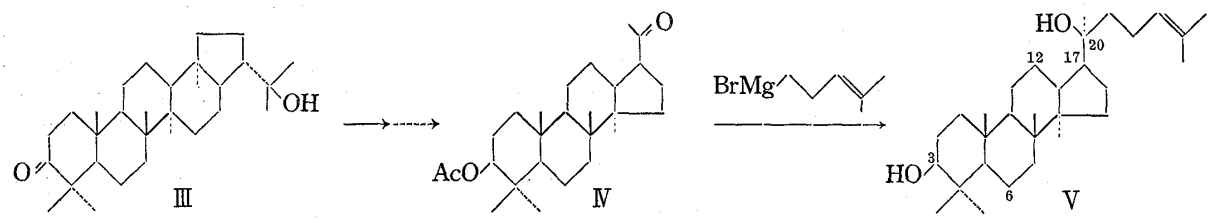
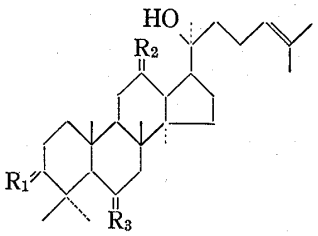



Chart 1

1) This paper was read at 18th Symposium on the Chemistry of Natural Products (October 1974, Kyoto). The preliminary communication of a part of this work was appeared in *Chem. Pharm. Bull.* (Tokyo), **22**, 1213 (1974).
2) Location: *Kasumi 1-2-3, Hiroshima-shi.*
3) Y. Nagai, O. Tanaka, and S. Shibata, *Tetrahedron*, **27**, 881 (1971).
4) S. Sanada, N. Kondo, J. Shoji, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **22**, 421 (1974).
5) S. Sanada, N. Kondo, J. Shoji, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **22**, 2407 (1974).
6) M. Nagai, T. Ando, N. Tanaka, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **20**, 1212 (1972).
7) H. Fujimoto and O. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **18**, 1440 (1970).
8) Y. Tsuda and M. Hattori, *Chem. Pharm. Bull.* (Tokyo), **15**, 1073 (1967).
9) R. Kasai, K. Shinzo, O. Tanaka, and K. Kawai, *Chem. Pharm. Bull.* (Tokyo), **22**, 1213 (1974).
10) R. Breslow, *Chem. Soc. Review*, **1**, 553 (1972) and the references cited therein.



I: $R_1=\langle^{OH}_{H}$, $R_2=\langle^{OH}_{H}$, $R_3=H_2$

II: $R_1=\langle^{OH}_{H}$, $R_2=\langle^{OH}_{H}$, $R_3=\langle^{H}_{OH}$

XVII: $R_1=O$, $R_2=H_2$, $R_3=H_2$

XVIII: $R_1=\langle^{H}_{OH}$, $R_2=H_2$, $R_3=H_2$

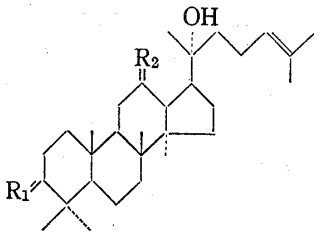
XXI: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{OH}_{H}$, $R_3=H_2$

XXIV: $R_1=\langle^{H}_{OAc}$, $R_2=\langle^{OH}_{H}$, $R_3=H_2$

XXV: $R_1=\langle^{H}_{OAc}$, $R_2=O$, $R_3=H_2$

XXVI: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{H}_{OH}$, $R_3=H_2$

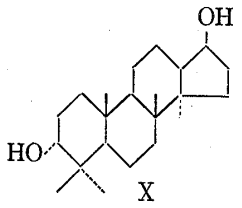
XXXVII: $R_1=O$, $R_2=\langle^{OH}_{H}$, $R_3=H_2$



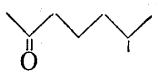
VI: $R_1=O$, $R_2=H_2$

VII: $R_1=\langle^{H}_{OH}$, $R_2=H_2$

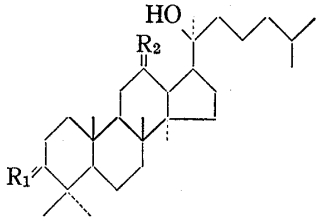
XXXV: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{OH}_{H}$



X



XII



XVI: $R_1=\langle^{H}_{OH}$, $R_2=H_2$

XIX: $R_1=\langle^{H}_{OOCCH_2}$–C$_6$H$_4$–$NO_2$, $R_2=H_2$

XX: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{H}_{OH}$

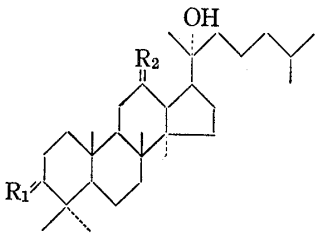
XXXI: $R_1=\langle^{H}_{OAc}$, $R_2=O$

XXXII: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{OH}_{H}$

XXXIII: $R_1=\langle^{H}_{OAc}$, $R_2=\langle^{OAc}_{H}$

XXIX: $R_1=\langle^{H}_{OOCCH_2CH_2}$–C$_6$H$_4$–$NO_2$, $R_2=H_2$

XXX: $R_1=\langle^{H}_{OAc}$, $R_2=\langle^{H}_{OH}$



VIII: $R_1=\langle^{H}_{OH}$, $R_2=H_2$

IX: $R_1=\langle^{H}_{OOC}$–C$_6$H$_4$–$NO_2$, $R_2=H_2$

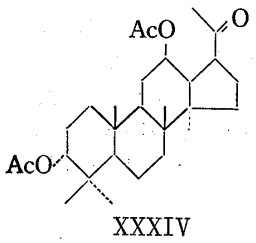
XI: $R_1=\langle^{OH}_{H}$, $R_2=H_2$

XIII: $R_2=\langle^{H}_{OAc}$, $R_2=H_2$

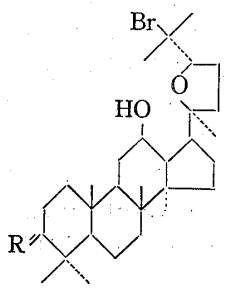
XXVII: $R_1=\langle^{H}_{OOCCH_2}$–C$_6$H$_4$–$NO_2$, $R_2=H_2$

XXXVI: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{OH}_{H}$

XXVIII: $R_1=\langle^{H}_{OH}$, $R_2=\langle^{H}_{OH}$



XXXIV



XXII: $R=\langle^{H}_{OH}$ XXIII: $R=\langle^{H}_{OAc}$

Chart 2

simpler remote oxidizing agents for the purpose of preparation of I from V. The recent publication[11-13] about the photooxidation of unactivated carbon atoms with aromatic nitro groups have prompted us to undertake the direct hydroxylation of the C-12 methylene of dammarane nucleus by the remote oxidation with photoexcited nitrobenzene derivatives.

Meerwein-Pondorf reduction of hydroxydammarenone-I (VI) yielded 3-*epi*-dammarenediol-I (VII), which was hydrogenated to give 3-*epi*-dammaranediol-I (VIII). The *p*-nitrobenzoate (IX) of VIII was irradiated in a various solvent, *i.e.* *n*-hexane, iso-PrOH and $CH_2Cl_2$. In no case, remarkable reaction was observed. However, the irradiation of IX in *tert*-BuOH for 40 hr followed by alkaline saponification afforded a crystalline compound (X) in a yield of 12% along with the parent diol (VIII) (recovery 70%) and its epimer (XI) (5%). The gas-liquid chromatography (GLC) of the volatile fraction of this irradiated mixture (before saponification) indicated the formation of 6-methyl-2-heptanone (XII), whichwas finally identifiad by the derivation to the 2,4-dinitrophenylhydrazone. The structure of X was assigned as 17-octakisnordammarane-3α,17β-diol by its spectral data and finally confirmed by its preparation from VIII *via* XIII, XIV and XVa, b (Chart 3). Although the mechanism of the formation of X in this reaction remains to be solved, the irradiation of the acetate (XIII) with methyl *p*-nitrobenzoate in *tert*-BuOH gave only unchanged starting material, suggesting the intramolecular nature of this anomalous cleavage-reaction.

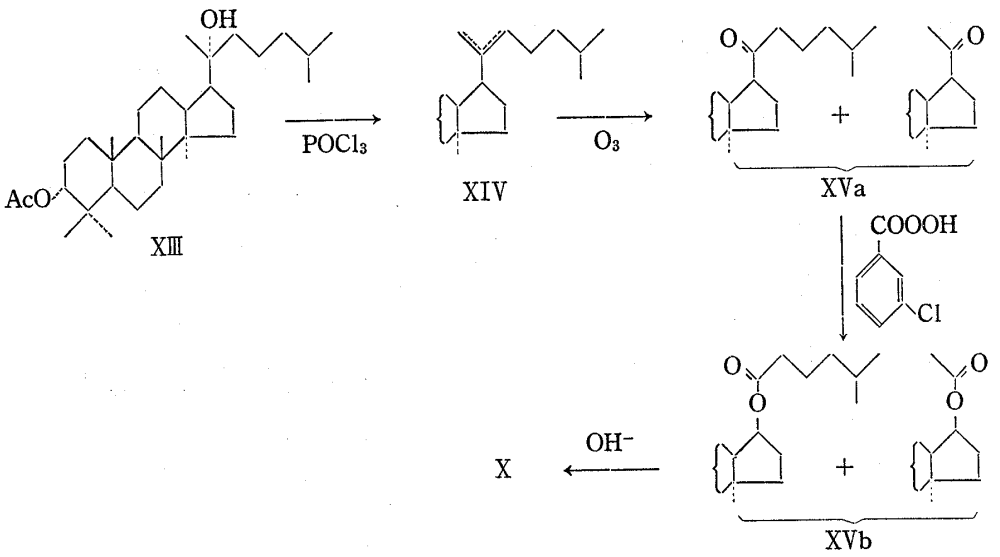



Chart 3

The direct hydroxylation of the C-12 carbon atom was achieved by the remote oxidation of the *p*-nitrophenylacetyl derivatives. 3-*epi*-Dammaranediol-II (XVI) was prepared from the dipterocarpol(hydroxydammarenone-II) (XVII) *via* 3-*epi*-dammarenediol-II (XVIII) in the same way as that of VIII from VI. A solution of the *p*-nitrophenylacetate (XIX) of XVI in *tert*-BuOH was irradiated for 60 hr and the crude products were subjected to alkaline saponification to give a triol (XX) in a yield of 13% along with the parent diol (XVI) (recovery 44%). The nuclear magnetic resonance (NMR) spectrum of the triol (XX) exhibited the signal at $\delta$ 4.30 ppm (1H, $1/2W=8$ Hz) which was very similar in the value of the chemical shift and the shape of the coupling pattern to that of the 12β-proton of 12α-hydroxydammarane derivative,[14] suggesting the introduction of an axial hydroxyl group to C-12 carbon atom of XVI. The structure of this triol (XX) was confirmed by its independent preparation

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12) J.W. Weller and G.A. Hamilton, *Chem. Comm.*, **1970**, 1390.
13) P.C. Scholl and M.R. Van de Mark, J. Org. Chem., **38**, 2376 (1973).
14) O. Tanaka, M. Nagai, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **14**, 1150 (1966).

from betulafolienetriol (XXI), the constituent of Betula leaves.[15] For the purpose of the inversion of the 12$\beta$-hydroxyl group of XXI, the selective protection of the 3$\alpha$-hydroxyl group of XXI was achieved through the bromo-compound (XXII). Treatment of XXI with N-bromosuccinimide (NBS) in $CCl_4$ resulted in the stereospecific cyclization of the side chain to give XXII in a high yield.[16] Because the 12$\beta$-hydroxyl group of XXII was sterically hindered by its cyclized side chain, the acetylation of XXII under the usual condition afforded only the 3-monoacetate (XXIII). Treatment of XXIII with zinc dust regenerated the original side chain to give XXIV quantitatively. 3-O-Acetylbetulafolienetriol (XXIV) was oxidized to the 12-ketone (XXV) which was reduced with $LiAlH_4$ affording 12-*epi*-betulafolienetriol (XXVI). Catalytic hydrogenation of XXVI gave 12-*epi*-betulafolianetriol which was identical with the triol (XX).

The *p*-nitrophenylacetate (XXVII) of VIII, the C-20 epimer of XVI, was demonstrated also to yield 12$\alpha$-hydroxylated compound (XXVIII) by the same sequence of the remote oxidation as above in the similar yield. Recently, Scholl, *et al.* reported the remote oxidation of 5$\alpha$-androstan-3$\alpha$-yl $\beta$-(*p*-nitrophenyl)propionate.[13] The present authors prepared the $\beta$-(*p*-nitrophenyl)propionate (XXIX) of XVI which in turn was subjected to the irradiation followed by the alkaline saponification. The thin-layer chromatography (TLC) of the crude reaction mixture indicated that the products were more complicated than the case of XIX, though the formation of XX was also observed.

On the basis of an assumption that the irradiation of *p*-nitrophenylacetate of 3-*epi*-dammarenediol-II (XVIII) would result in an addition of the photoexcited nitro group to the double bond of the side chain[17] in preference over hydroxylation of the C-12 carbon atom, the present authors prepared betulafolienetriol (XXI) from XX by the following sequence of reactions. Acetylation of XX at 4° afforded 3-monoacetate (XXX). Oxidation of XXX with Jones' reagent gave the 12-ketone (XXXI). On reduction with $NaBH_4$ followed by the alkaline saponification, XXXI yielded a triol (XXXII), which was identical with the betulafolianetriol. The diacetate (XXXIII) of XXXII was dehydrated with $POCl_3$ and successively degradated with $O_3$ to give 3$\alpha$,12$\beta$-diacetoxyhexakisnordammaran-20-one (XXXIV). The modified Grignard reaction[18] of XXXIV with 4-methyl-3-pentenyl bromide and Li in tetrahydrofuran (THF) afforded two triols with mp 196—198.5° and 245—247°. The former triol was proved to be identical with natural betulafolienetriol (XXI) and the latter with its C-20 epimer (XXXV), the structure of which was proved by its conversion into known 20-*epi*-betulafolianetriol (XXXVI).[19] The 3-ketone (XXXVII) prepared from XXI[20] was reduced with $NaBH_4$ to give 20(*S*)-protopanaxadiol (I), which accomplished the synthesis of the Ginseng sapogenin.

## Experimental

All melting points were determined on a micro-hot stage and uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethyl silane (TMS) as internal standard (1 OOMHz). Photooxidation employed a 200W or 400W high pressure mercury lamp with a Pyrex filter and 250 ml reaction vessel.

**Preparation of 3-*epi*-Dammaranediol-I(VIII)**——i) Meerwein-Pondorf Reduction of Hydroxydammarenone-I(VI): To a fresh iso-PrOH solution (200 ml) of VI (5 g) which was isolated from dammar resin was added Al(iso-PrO)$_3$ (10 g) and a mixture was heated under reflux for 5 hr with magnetical stirring. After evaporation of the solvent under reduced pressure, the residue was treated with dil. HCl (100 ml), stirred

15) F.G. Fischer and N. Seiler, *Liebigs Ann. Chem.*, **644**, 146 (1960).
16) O. Tanaka, N. Tanaka, T. Ohsawa, Y. Iitaka, and S. Shibata, *Tetrahedron Letters*, **1968**, 4235; T. Ohsawa, N. Tanaka, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **20**, 1890 (1972).
17) J.L. Charlton and P.de Mayo, *Canad. J. Chem.*, **46**, 1041 (1968).
18) P.J. Pearce and D.H. Richards, *J. Chem. Soc. Perkin* I, **1972**, 1655.
19) O. Tanaka, M. Nagai, T. Ohsawa, N. Tanaka, K. Kawai, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo,) **20**, 1204 (1972).
20) F.G. Fischer and N. Seiler, *Liebigs Ann. Chem.*, **626**, 185 (1959).

under ice cooling and then extracted with $(C_2H_5)_2O$. The ethereal layer was washed with 5%–$NaHCO_3$ and $H_2O$ and dried. After evaporation of the solvent, the residue was chromatographed on silica gel. From the fractions eluted with $C_6H_6$–$(CH_3)_2CO$(20: 1), VII (3.2 g) was obtained as colourless needles from EtOH–$H_2O$, mp 73—74°. $[\alpha]_D^{24}$ +15.5° ($c$=2.96, $CHCl_3$), IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3640 (OH). NMR ($CDCl_3$): $\delta$ 0.84 (3H, s), 0.86 (3H, s), 0.88 (3H, s), 0.96 (3H, s), 1.12 (3H, s), 1.16 (3H, s), 1.61 (3H, s), 1.67 (3H, s), 3.38 (1H, triplet-like, $1/2W$=6 Hz), 5.10 (1H, m). Mass Spectrum Calcd. for $C_{30}H_{52}O_2$: $M^+$, 444.397. Found: $M^+$, 444.395.

ii) Catalytic Hydrogenation of 3-*epi*-Dammarenediol-I(VII): Compound VII (3.2 g) was catalytically hydrogenated on $PtO_2$ in EtOH and the reaction mixture was filtered. The filtrate was evaporated *in vacuo* and the residue was recrystallised from EtOH–$H_2O$ to give VIII (2.8 g) as colourless needles, mp 65—65.5°. $[\alpha]_D^{24}$ +16.9° ($c$=2.78, $CHCl_3$). NMR ($CDCl_3$): $\delta$ 0.84—0.97 (3H×7), 1.11 (3H, s), 3.38 (1H, triplet-like, $1/2W$=6 Hz). Mass Spectrum Calcd. for $C_{30}H_{54}O_2$: $M^+$, 446.412. Found: $M^+$, 446.412.

***p*-Nitrobenzoate (IX) of 3-*epi*-Dammaranediol-I(VIII)**——A solution of *p*-nitrobenzoyl chloride (3 g) in $C_5H_5N$ (50 ml) was added to a solution of VIII (3 g) in $C_5H_5N$ (50 ml) and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water. The precipitates were collected by filtration, washed with $H_2O$ and recrystallised from *n*–hexane giving IX (3.9 g) as colourless needles, mp 141°. $[\alpha]_D^{16}$ 0° ($c$=1.16, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3640 (OH), 1723 (C=O), 1606 (arom), 1530, 1350 ($NO_2$). NMR ($CDCl_3$): $\delta$ 0.84 (3H, s), 0.91—1.00 (3H×6), 1.12 (3H, s), 4.90 (1H, triplet-like, $1/2W$=6 Hz), 8.16 (2H, d, $J$=9 Hz), 8.32 (2H, d, $J$=9 Hz). *Anal.* Calcd. for $C_{37}H_{57}O_5N$: C, 74.85; H, 9.64; N, 2.35. Found: C, 74.70; H, 9.61; N, 2.28.

**Preparation of 3-*epi*-Dammaranediol-II(XVI)**——Compound XVI was prepared from XVII (4.5 g), which was extracted from capolwood, by way of XVIII in the similar way to that for the preparation of VIII described above. Compound XVIII was recrystallised from *n*–hexane as colourless needles (2.1 g), mp 80—85°. $[\alpha]_D^{24}$ +16.4° ($c$=2.08, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3640 (OH). NMR ($CDCl_3$): $\delta$ 0.78 (3H, s), 0.86 (3H, s), 0.88 (3H, s), 0.94 (3H, s), 0.96 (3H, s), 1.15 (3H, s), 1.63 (3H, s), 1.69 (3H, s), 3.39 (1H, triplet-like, $1/2W$=6 Hz), 5.12 (1H, m). Mass Spectrum Calcd. for $C_{30}H_{52}O_2$: $M^+$, 444.397. Found: $M^+$ 444.398. Compound XVI was recrystallised from EtOH–$H_2O$ as colourless needles (2.0 g), mp 77—78°. $[\alpha]_D^{24}$ +15.9° ($c$=1.07, $CHCl_3$). NMR ($CDCl_3$): $\delta$ 0.84—0.98 (3H×7), 1.12 (3H, s), 3.38 (1H, triplet-like, $1/2W$=6 Hz). Mass Spectrum Calcd. for $C_{30}H_{54}O_2$: $M^+$, 446.412. Found: $M^+$, 446.413.

***p*-Nitrophenylacetate (XIX) of 3-*epi*-Dammaranediol-II(XVI)**——To a solution of XVI (0.7 g) in dry $C_6H_6$ (30 ml) containing $C_5H_5N$(0.2 ml) was gradually added a solution of *p*-nitrophenylacetyl chloride (0.35 g) in dry $C_6H_6$ (5 ml) with magnetical stirring. After 2 hr, the reaction mixture was washed with 5%–$NaHCO_3$ and $H_2O$ and dried. After evaporation of the solvent, the yellow oily product was purified by chromatography on silica gel with *n*–hexane–$(CH_3)_2CO$ (20: 1) to give XIX (0.65 g) as colourless syrup. $[\alpha]_D^{24}$ −7.5° ($c$=2.04, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3630 (OH), 1730 (C=O), 1603 (arom), 1545, 1350 ($NO_2$). NMR ($CDCl_3$): $\delta$ 0.71 (3H, s), 0.84—0.95 (3H×6), 1.14 (3H, s), 3.77 (2H, s), 4.64 (1H, triplet-like, $1/2W$=6 Hz), 7.45 (2H, d, $J$=9.5 Hz), 8.18 (2H, d, $J$=9.5 Hz). Mass Spectrum Calcd. for $C_{38}H_{59}O_5N$: $M^+$, 609.439. Found: $M^+$, 609.436.

**Irradiation of IX**——A solution of IX (1 g) in *tert*–BuOH–$H_2O$ (95: 5, 250 ml) was irradiated for 40 hr under a stream of $N_2$ with magnetical stirring at room temperature. The solvent was removed by distillation and the residue was saponified by refluxing with 5%–KOH in a mixture of MeOH (50 ml) and $C_6H_6$ (10 ml) for 1 hr. After cooling, the reaction mixture was diluted with $H_2O$ and extracted with $(C_2H_5)_2O$. The organic layer was dried and evaporated *in vacuo*. The crude photooxidation products were chromatographed on silica gel with *n*–hexane–$(CH_3)_2CO$ (10: 1) to afford VIII (404 mg), XI (28 mg) and X (70 mg). X: colourless needles from *n*–hexane–$(CH_3)_2CO$, mp 194—195°. $[\alpha]_D^{19}$ +11.0° ($c$=1.18, EtOH). NMR ($CDCl_3$): $\delta$ 0.85 (3H×3, s), 0.93 (3H, s), 0.98 (3H, s), 3.37 (1H, triplet-like, $1/2W$=6 Hz), 3.86 (1H, d-t). Mass Spectrum $m/e$: 334 ($M^+$), 190 (base peak). A part of the irradiation mixture without saponification treatment was evaporated to a small volume. To the residue was added an excess of 2,4-dinitrophenylhydrazine to yield precipitates which were recrystallised from EtOH, giving the 2,4-dinitrophenylhydrazone as yellow needles, mp 73—74°. $[\alpha]_D^{24}$ −1.9° ($c$=2.64, $CHCl_3$). Mass Spectrum Calcd. for $C_{14}H_{20}O_4N_4$: $M^+$, 308.148. Found: $M^+$, 308.147. This was identified with an authentic 2,4-dinitrophenylhydrazone of 6-methyl-2-heptanone (XII).

**Preparation of 17-Octakisnordammarane-3$\alpha$,17$\beta$-diol (X)**——A solution of VIII (650 mg) in $Ac_2O$ (10 ml) and $C_5H_5N$ (10 ml) was allowed to stand at room temperature overnight. After an usual work up, the monoacetate (XIII) was obtained as colourless syrup. To a solution of XIII in $C_5H_5N$ (5 ml) was added $POCl_3$ (1.5 ml) and heated at 70° for 15 min. After cooling, the reaction mixture was poured into ice-water and the mixture was extracted with $(C_2H_5)_2O$. The ethereal layer was washed with 5%–$NaHCO_3$, 1N $H_2SO_4$ and $H_2O$ and dried. After evaporation, the residue (XIV) was dissolved in $CH_2Cl_2$ (50 ml) and treated by $O_3$ under dry ice–$(CH_3)_2CO$ cooling. The reaction mixture was reduced with zinc dust (20 g) in AcOH (59 ml) at 80—90° for 5 min and then allowed to stand overnight at room temperature with stirring. The residue was extracted with $(C_2H_5)_2O$ to remove insoluble substance and the ethereal solution was washed with $H_2O$, dried and evaporated. The residue (XVa) (210 mg) was dissolved in $CH_2Cl_2$ (25 ml) and to this was added a solution of *m*-chloroperbenzoic acid (900 mg) in $CH_2Cl_2$ (25 ml). The reaction mixture was allowed to stand at room temperature for 24 hr and then refluxed for 1.5 hr. After cooling, 5%–$Na_2CO_3$ (50 ml) was added with stirring to decompose an excess of reagent. The organic layer was washed successively with 5%–$NaHCO_3$ and $H_2O$, dried and evaporated. To a solution of the residue (XVb) in $(C_2H_5)_2O$ (9 ml) was added 1N KOH in

EtOH (1 ml) and refluxed for 1.5 hr. The reaction mixture was diluted with $H_2O$ and extracted with $(C_2H_5)_2O$. The organic layer was washed with $H_2O$, dried and evaporated. The crude products were purified by preparative TLC on silica gel (solvent, $C_6H_6$–$(CH_3)_2CO$, 10: 3) to give the 17-octakisnordammarane-3$\alpha$,17$\beta$-diol (32 mg) as colourless needles from $(CH_3)_2CO$–*n*-hexane, mp 197.5—198°. $[\alpha]_D^{24}$ +9.0° ($c$=0.67, EtOH). *Anal.* Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 79.04; H, 11.61. This was proved to be identical with X by admixture and comparisons of their infrared (IR) spectra and TLC.

**Irradiation of XIX**——A solution of XIX (495 mg) in *tert*-BuOH–$H_2O$ (95: 5, 250 ml) was irradiated for 60 hr under a stream of $N_2$ with magnetical stirring. After evaporation *in vacuo*, the residue was saponified by refluxing in 5%–KOH solution of MeOH (50 ml) and $C_6H_6$ (10 ml). After cooling, the reaction mixture was diluted with $H_2O$ and extracted with $(C_2H_5)_2O$. The organic layer was washed with $H_2O$, dried and evaporated. The crude products were chromatographed on silica gel with *n*-hexane–$(CH_3)_2CO$ (10: 1) to give XVI (165 mg) and colourless needles (XX) (50 mg) from AcOEt, mp 157—158°. $[\alpha]_D^{20}$ +3.0° ($c$=1.00, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3620 (free OH), 3420 (H-bonded OH). NMR ($CDCl_3$): $\delta$ 0.84—0.94 (3H×6), 1.09 (3H, s), 1.14 (3H, s), 3.40 (1H, triplet-like, 1/2W=6 Hz), 4.30 (1H, 1/2$W$=8 Hz).

**Preparation of 12-*epi*-Betulafolianetriol (XX)**——i) Partial acetylation of Betulafolienetriol (XXI): A solution of XXI (1 g) (extracted from the leaves of Japanese White birch) and NBS (0.4 g) in $CH_2Cl_2$ (200 ml) was heated under reflux for 30 min. After cooling, the resulting precipitate was removed by filtration and the filtrate was washed with $H_2O$, dried and concentrated to dryness. The residue (XXII) was acetylated with $Ac_2O$ (5 ml) in $C_5H_5N$ (5 ml) at room temperature for 24 hr. After working up in the usual way, XXIII (1.2 g) was obtained as colourless needles from $(C_2H_5)_2O$, mp 188° (decomp.). $[\alpha]_D^{20}$ −9.1° ($c$=2.54, $CHCl_3$). NMR ($CDCl_3$): $\delta$ 0.84 (3H, s), 0.89 (3H, s), 0.92 (3H, s), 0.96 (3H, s), 1.03 (3H, s), 1.33 (3H, s), 1.68 (3H, s), 1.72 (3H, s), 2.08 (3H, s), 3.54 (1H, m), 3.95 (1H, q), 4.63 (1H, triplet-like, 1/2$W$=6 Hz). *Anal.* Calcd. for $C_{32}H_{53}O_4Br$: C, 66.07; H, 9.18; Br, 13.74. Found: C, 66.28; H, 9.61; Br, 13.94. To a solution of XXIII (1.2 g) in a mixture of $(C_2H_5)_2O$ (60 ml) and AcOH (15 ml) was gradually added zinc dust (10 g) under ice cooling. The reaction mixture was stirred at room temperature for 12 hr. After filtration, the filtrate was washed with $H_2O$, dried and evaporated to dryness *in vacuo*. The residue was recrystallised from $(CH_3)_2CO$ affording XXIV (0.54 g) as colourless needles, mp 216—218°. $[\alpha]_D^{19}$ −8.9° ($c$=1.47, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 3420 (OH), 1730 (C=O). NMR ($CDCl_3$): $\delta$ 0.84 (3H, s), 0.89 (3H×2, s), 0.92 (3H, s), 1.01 (3H, s), 1.20 (3H, s), 1.55 (3H, s), 1.62 (3H, s), 2.06 (3H, s), 3.60 (1H, m), 4.62 (1H, triplet-like, 1/2$W$=6 Hz), 5.15 (1H, m). *Anal.* Calcd. for $C_{32}H_{54}O_4$: C, 76.44; H, 10.83. Found: C, 76.40; H, 10.59.

ii) Oxidation of 3$\alpha$-Acetoxybetulafolienetriol (XXIV): A mixture of $CrO_3$ (680 mg) and $C_5H_5N$ (30 ml) was added to a solution of XXIV (340 mg) in $C_5H_5N$ (30 ml) and the reaction mixture was allowed to stand at room temperature for 15 hr with stirring. A small amount of MeOH was added to the reaction mixture to decompose an excess of $CrO_3$. The precipitates were removed by filtration and washed with $C_5H_5N$. The filtrate and the washing were combined and concentrated *in vacuo* to afford crystalline residue, which was recrystallised from EtOH, giving XXV (280 mg) as colourless leaflets, mp 218—220°. $[\alpha]_D^{19}$ +17.7° ($c$=1.13, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 3420 (OH); 1730 (C=O); 1700 (C=O). NMR ($CDCl_3$): $\delta$ 0.84 (3H×2, s), 0.92 (3H, s), 0.96 (3H, s), 1.12 (3H, s), 1.20 (3H, s), 1.62 (3H, s), 1.68 (3H, s), 2.04 (3H, s), 4.65 (1H, triplet-like, 1/2W=6 Hz). 5.12 (1H, m). *Anal.* Calcd. for $C_{32}H_{52}O_4$: C, 76.75: H, 10.47. Found: C, 77.03; H, 10.37.

iii) $LiAlH_4$ Reduction of 3$\alpha$-Acetoxy-12-Keto-betulafolienetriol (XXV): To a solution of XXV (270 mg) in dry $(C_2H_5)_2O$ (50 ml) was dropwise added a suspension of $LiAlH_4$ (225 mg) in dry $(C_2H_5)_2O$ (25 ml) with stirring and the reaction mixture was heated under reflux for 1 hr. After cooling, a small volume of AcOEt, $H_2O$ and 2N $H_2SO_4$ (100 ml) were added to the reaction mixture to decompose the excess of the reagent and the complexes. The organic layer was washed with $H_2O$ and dried. After evaporation of the solvents, the crystalline residue was recrystallised from AcOEt, affording XXVI (187 mg) as colourless needles, mp 187—189°, $[\alpha]_D^{20}$ +30.5° ($c$=1.67, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$ 3620 (free OH); 3360 (H-bonded OH). NMR ($CDCl_3$): $\delta$ 0.84 (3H, s), 0.88 (3H, s), 0.92 (3H×2, s), 1.12 (3H, s), 1.18 (3H, s), 1.62 (3H, s), 1.68 (3H, s), 3.38 (1H, triplet-like, 1/2$W$=6 Hz), 4.30 (1H, m), 5.14 (1H, m). Mass Spectrum Calcd. for $C_{30}H_{52}O_3$: M$^+$, 460.392. Found: M$^+$, 460.391.

iv) Hydrogenation of 12-*epi*-Betulafolienetriol (XXVI): Compound XXVI (50 mg) was hydrogenated with $PtO_2$ (2.5 mg) in EtOH (30 ml). After working up in the usual way, the product was recrystallised from AcOEt to give 12-*epi*-betulafolianetriol (39 mg), mp 156—158°. $[\alpha]_D^{24}$ +4.3° ($c$=2.45, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 3620 (free OH); 3420 (H-bonded OH). NMR ($CDCl_3$): $\delta$ 0.84—0.95 (3H×6), 1.13 (3H, s), 1.18 (3H, s), 3.38 (1H, triplet-like, 1/2$W$=6 Hz), 4.30 (1H, 1/2$W$=8 Hz). *Anal.* Calcd. for $C_{30}H_{54}O_3$: C, 77.86; H, 11.76. Found: C, 77.86; H, 11.72. This was proved to be identical with XX by mixed melting point and comparisons of their IR spectra and TLC.

**Conversion of 12-*epi*-Betulafolianetriol (XX) into Betulafolienetriol (XXI)**——i) Partial Acetylation of 12-*epi*-Betulafolianetriol (XX): Compound XX (600 mg) was partially acetylated with $Ac_2O$ (2 ml) in $C_5H_5N$ (4 ml) at 4° for 45 hr. After an usual work up, the residue was chromatographed on silica gel with $C_6H_6$–$(CH_3)_2CO$ (10: 1) to give XXX (476 mg) as colourless needles from *n*-hexane, mp 153—155°. $[\alpha]_D^{20}$ +11.1° ($c$=1.62, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 3620 (free OH); 3420 (H-bonded OH); 1730 (C=O). NMR ($CDCl_3$): $\delta$ 0.82—0.96 (3H×6), 1.16 (3H, s), 1.18 (3H, s), 2.06 (3H, s), 4.30 (1H, m, 1/2$W$=8 Hz), 4.60 (1H, triplet-like, 1/2$W$=6 Hz). Mass Spectrum Calcd. for $C_{32}H_{54}O_4$: M$^+$, 502.402. Found: M$^+$, 502.405.

ii) Jones' Oxidation of 3α-Acetoxy-12-*epi*-betulafolianetriol (XXX): Compound XXX (320 mg) in $(CH_3)_2CO$ (50 ml) was oxidized with an excess of Jones' reagent for 20 min in the usual way. To the reaction mixture was added a small volume of MeOH to decompose an excess of reagent, diluted with $H_2O$ and extracted with $(C_2H_5)_2O$. The ethereal layer was washed with $H_2O$, dried and concentrated to dryness. The crystalline residue was recrystallised from AcOEt, giving the XXXI (309 mg) as colourless needles, mp 242—245°. $[\alpha]_D^{20}$ +6.7° ($c$=1.49, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3430 (H-bonded OH); 1735 (C=O); 1700 (C=O). NMR ($CDCl_3$): $\delta$ 0.84—0.97 (3H×6), 1.10 (3H, s), 1.20 (3H, s), 2.06 (3H, s), 4.50 (1H, triplet-like, $1/2W$=6 Hz).

iii) Preparation of Betulafolianetriol (XXXII) from 3α-Acetoxy-12-keto-betulafolianetriol (XXXI): A solution of XXXI (130 mg) in dioxane–$H_2O$ (10 ml) was added to a mixture of $NaBH_4$ (260 mg) in dioxane–$H_2O$ (10 ml) and the mixture was allowed to stand overnight at room temperature with stirring. The reaction mixture after addition of 2N $H_2SO_4$ under ice cooling was diluted with $H_2O$ and extracted with $(C_2H_5)_2O$. The ethereal layer was washed with 5%–$Na_2CO_3$ and $H_2O$ and dried. After evaporation, the residue (118 mg) was dissolved in 5%–KOH–MeOH and refluxed for 30 min. After working up in the usual way, the crystalline product was recrystallised from $(CH_3)_2CO$, affording colourless needles (XXXII) (105 mg), mp 199—202°. $[\alpha]_D^{24}$ +8.4° ($c$=1.07, $CHCl_3$). This was proved to be identical with betulafolianetriol by mixed melting point and comparisons of their IR spectra and TLC.

iv) Ozone Degradation of the Betulafolianetriol (XXXII): Compound XXXII (1.8 g) was acetylated, dehydrated and then degradated with $O_3$ as described above for the preparation of X to give 3α,12β-diacetoxyhexakisnordammaran-20-one (XXXIV) (452 mg) as colourless needles from AcOEt, mp 239—241°. $[\alpha]_D^{20}$ +7.0° ($c$=1.38, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 1730 (C=O); 1710 (C=O). NMR ($CDCl_3$): $\delta$ 0.84 (3H, s), 0.90 (3H×2, s), 1.00 (3H, s), 1.08 (3H, s), 1.92 (3H, s), 2.08 (3H, s), 2.12 (3H, s), 2.88 (1H, m), 4.62 (1H, triplet-like, $1/2W$=6 Hz), 4.78 (1H, m). *Anal.* Calcd. for $C_{28}H_{44}O_5$: C, 72.65; H, 9.21. Found: C, 73.00; H, 9.63.

v) Preparation of XXI from XXXIV: Dry THF (50 ml) and Li Slices (1.2 g) was stirred and to this mixture was gradually added a solution of XXXIV (500 mg) and 4-methyl-3-pentenyl bromide (9.8 g) in dry THF (100 ml). The reaction mixture was allowed to stand at room te mperature for 2 hr with strirring and an excess of Li was filtered off and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel. Elution with $C_6H_6$–$(CH_3)_2CO$ (10: 2) gave colourless needles (XXXV) (129 mg) from $(CH_3)_2CO$, mp 245—247°. $[\alpha]_D^{20}$ +7.1° ($c$=1.88, $CHCl_3$). Compound XXXV was catalytically hydrogenated on $PtO_2$ in AcOEt. After working up in the usual way, the residue was recrystallised from AcOEt as colourless needles (XXXVI), mp 253—255°. $[\alpha]_D^{24}$ −4.3° ($c$=1.62, $CHCl_3$). This was proved to be identical with an authentic sample of 20-*epi*-betulafolianetriol by mixed melting point and comparisons of their IR spectra and TLC. Further elution with the same solvent gave a crystalline compound (XXI) (82 mg), which was identified as betulafolienetriol by mixed melting point, IR and TLC with the authentic sample.

**Preparation of I from XXI**——Compound XXXVII (300 mg), which was derived from XXI, was reduced with $NaBH_4$ in dioxane–$H_2O$. After working up in the usual way, the residue was crystallised from $C_6H_6$ affording colourless needles (280 mg), mp 197—198°, which was proved to be identical with the authentic 20 (*S*)-protopanaxadiol (I) by mixed melting point and comparisons of their IR spectra and TLC.

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