[Chem. Pharm. Bull. 20(9)1890—1897(1972)]

UDC 547.597.02 : 581.192 : 615.322.011.5

# Chemical Studies on the Oriental Plant Drugs. XXIX.[1] Saponins and Sapogenins of Ginseng: Further Study on the Chemical Properties of the Side Chain of Dammarane Type Triterpenes

Tomihiko Ohsawa,[2a] Nobutoshi Tanaka,[2b] Osamu Tanaka,[2c] and Shoji Shibata[2]

*Faculty of Pharmaceutical Sciences, University of Tokyo*[2]

(Received February 3, 1972)

The chemical properties of the side chain of dammarane type triterpenes are discussed. Dehydrochlorination of the chloro compounds (II and IV) derived from ginsenosides $Rb_1$, $Rb_2$ and Rc or their prosapogenins by the conc. HCl hydrolysis afforded the compounds having the side chain with isopropylidene (I or III) and isopropenyl double bond (VII or V). The ratio of the occurrence of the two types of double bond systems depends on the dehydrochlorination reagents used.

On treating with $BF_3$ etherate in ether, 20(*R*)-protopanaxadiol (III) gave isodehydroprotopanaxadiol (VIII), which was also obtained as an artifact from the crude hydrolysate of Ginseng saponins.

On treating with NBS betulafolienetriol (VI) yielded a bromo compound, $C_{30}H_{51}O_3Br$, whose stereochemical structure was finally established to be XVI by X-ray crystallographic analysis. A similar compound (XVIII) was obtained from 20(*R*)-protopanaxadiol (III) with NBS. The mechanism of the bromination reaction is elucidated.

In relation to the chemical studies on the Ginseng saponins having dammarane type triterpenes as their sapogenins, the chemical reactivities of the side chain of the triterpenes of this type have been investigated.[1,3] The present paper deals with some other remarkable chemical properties of the side chain.

20(*S*)-Protopanaxadiol (I), the genuine sapogenin of Ginseng saponins, ginsenosides-$Rb_1$, -$Rb_2$ and -Rc, was obtained by Smith's degradation of these saponins or by the base treatment of the ether-more soluble fraction of the conc. HCl-hydrolysate of prosapogenin,[1] which would possibly contain the chloride (II). 20(*R*)-Protopanaxadiol (III) was yielded by the base treatment[4] from the chloride (IV) isolated from the ether-less soluble fraction of this hydrolysate. As already mentioned[4] an isomer in respect to the double bond (V) was also yielded to some extent by the dehydrochlorination reaction. The orientation of this elimination reaction must depend upon the base used as the reagent.

The samples of 20(*S*)-protopanaxadiol (I) obtained by dehydrochlorination with N,N-diethylaniline,[5] with potassium (or sodium) *tert*-butoxide, and by Smith's degradation are tentatively named I-DEA, I-Bu and I-SM, respectively. A distinct difference between these

1) Part XXVIII: M. Nagai, T. Ando, N. Tanaka, O. Tanaka, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **20**, 1212 (1972).

2) Location: *Hongo, Tokyo*; Present address: *a) Institute for Chemical and Physical Research, Yamatomachi, Saitama-ken*; *b) Kyorin Chemical Laboratory, Ukima 1-3-32, Kita-ku, Tokyo*; *c) Pharmaceutical Institute, School of Medicine, Hiroshima University, Kasumi 1-2-3, Hiroshima-shi.*

3) O. Tanaka, M. Nagai, T. Ohsawa, N. Tanaka, K. Kawai and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **20**, 1204 (1972).

4) S. Shibata, O. Tanaka, T. Ando, M. Sado, S. Tsushima, and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 595 (1966).

5) The elimination with the reagent was reported to give mainly the isopropenyl double bond. M. C. Damson, T.G. Halsall, E.R.H. Jones and P.A. Robins, *J. Chem. Soc.*, **1953**, 586.

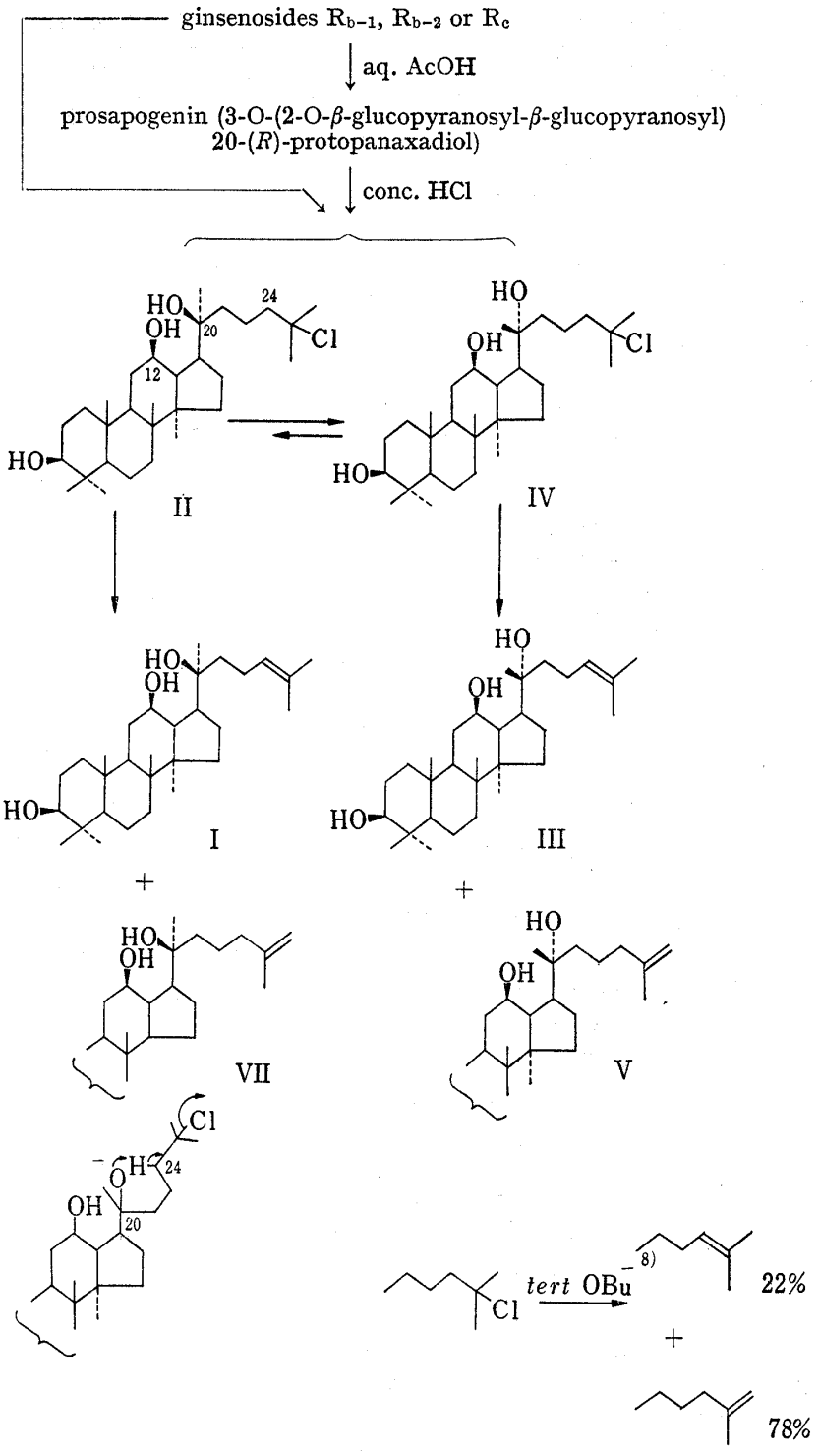


Chart 1

samples was observed in the spectral pattern at the double bond region of their nuclear magnetic resonance (NMR) and infrared (IR) spectra as illustrated in Fig. 1.

The NMR signal at $\delta$ 4.68 ppm must be attributable to a terminal methylene of the isopropenyl double bond and the broad signal (triplet-like) near $\delta$ 5.13 ppm should be assigned to the olefinic proton of the isopropylidene double bond. As expected, I-SM like betulafolienetriol (VI)[3,6] exhibited only the characteristic signal of the isopropylidene double bond,

6) F.G. Fischer and N. Seiler, *Ann*, **626**, 185 (1959); *idem*, *ibid.*, **644**, 146 (1961); S. Shibata, M. Nagai, and O. Tanaka, *Shoyakugaku Zasshi*, **18**, 27 (1964).

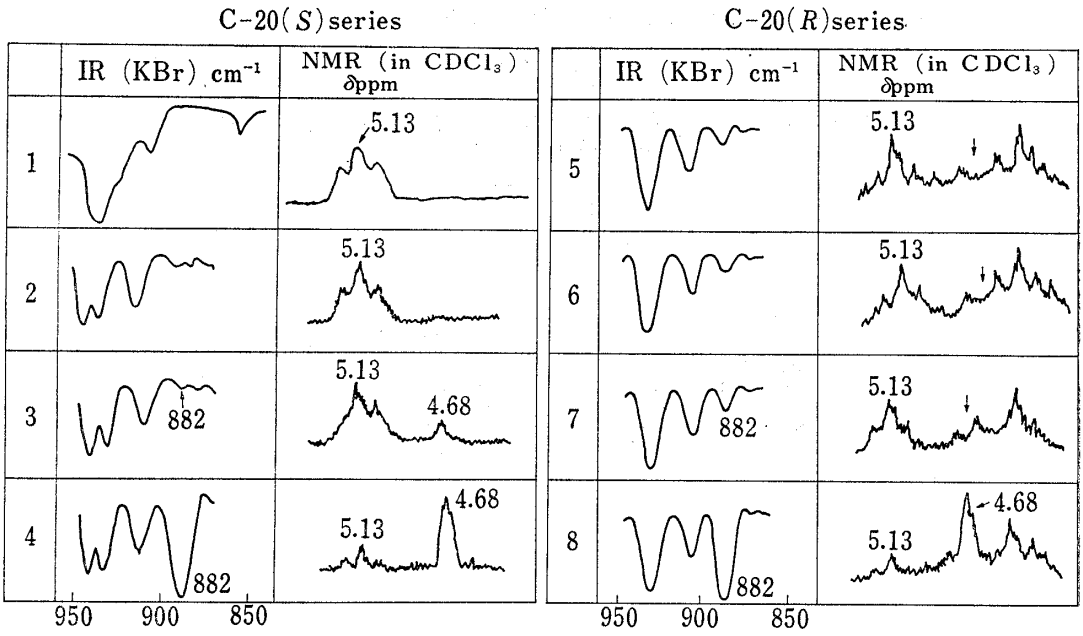


Fig. 1

1) betulafolienetriol (VI) 2) I-SM 3) I-Bu 4) I-DEA 5) 3,12-diacetate of III prepared from XVIII
6) 3,12-diacetate of III prepared from the prosapogenin by the mild hydrolysis[1] 7) 3,12-diacetate of III-Bu
8) 3,12-diacetate of III-DEA

proving that I-SM must be homogeneous with regard to the type of the double bond. The NMR spectrum of I-Bu indicated that this sample mainly consisted of I, and the integration study of the signals revealed that the contamination of VII (isopropenyl double bond) in I-Bu was less than 10%. Contrary to this, the spectrum of I-DEA showed a fairly strong signal due to the isopropenyl double bond, demonstrating the presence of the considerable amount of VII in this sample, which was supported by the remarkable IR absorption at 882 $cm^{-1}$ due to the isopropenyl double bond. The NMR signal near $\delta$ 1.7 attributable to the allylic methyl group of I-DEA was also somewhat different from that of I-SM and I-Bu. The integration of the olefinic proton signals indicated that I-DEA was an about fifty-fifty mixture of I and VII.

The similar conclusion was obtained in the samples of 20(*R*)-series——III-Bu prepared with *tert*-$BuO^-$ and III-DEA with N,N-diethylaniline——, though the NMR spectra of these samples were taken as their diacetate because of the low solubility of the original diols in $CDCl_3$, resulting that the olefinic proton signals were overlapped with the signals of the protons on the carbon atoms bearing the acetoxyl and could not be integrated.

It has been reported that in the dehydrochlorination of the tertiary alkyl halide with *t*-$BuO^-$, the elimination occurred preferentially to produce the less substituted olefine such as isopropenyl type rather than the more substituted one such as isopropylidene type (see Chart 1).[7] The unusual orientation in the elimination shown in the present study would be rationalized in term of the abstraction of the proton at $C_{(24)}$ with $C\text{-}O^-$ at $C_{(20)}$.

In our preceding papers,[1,3] the acid catalyzed reactions of the side chain of the dammarane type triterpenes, *i.e.*, the epimerization of the tertiary hydroxyl group at $C_{(20)}$ and the formation of the trimethyltetrahydropyrane ring were reported.

On treating with $BF_3$ etherate in ether, 20(*R*)-protopanaxadiol (III) gave a crystalline compound (VIII), $C_{30}H_{50}O_2$ (=III ($C_{30}H_{52}O_3$)-$H_2O$), named isodehydroprotopanaxadiol in a yield of 29% along with panaxadiol (IX) and other minor products. Isodehydroprotopanaxadiol (VIII) showed an IR absorption of free OH at 3620 $cm^{-1}$ (in $CCl_4$) but did not exhibit

7) H.C. Brown and R.L. Klimisch, *J. Am. Chem. Soc.*, **88**, 1425 (1966).

the concentration-independent OH band near 3350 $cm^{-1}$, which was observed in the spectra of III as well as IX being attributable to the intramolecularly hydrogen bonding between 12$\beta$-hydroxyl group and the oxygen function at $C_{(20)}$. On acetylation under the usual condition, VIII afforded a mono-acetate (X) giving no OH band, and oxidation of VIII with Jones' reagent yielded a monoketone (XI), IR $\nu_{max}^{CCl_4}$ 1710 $cm^{-1}$ and no OH band.

In the series of the dammarane type triterpenes, it has been reported that the 3-ketone showed optical rotatory dispersion (ORD) (CD) curve with positive Cotton effect,[8] whereas the 12-ketone exhibited the characteristic negative Cotton effect.[9] Positive Zimmermann test[10] and the ORD (CD) curve (in MeOH) with positive Cotton effect of XI as well as the NMR spectra of VIII and X revealed that the 3$\beta$-hydroxyl group of III still remained unreacted in VIII. The NMR signal of VIII near $\delta$ 3.65 ppm (1H sextet) which was left almost unshifted even after acetylation or oxidation indicated that the 12$\beta$-hydroxyl group of III participated to form an ether linkage in this reaction.

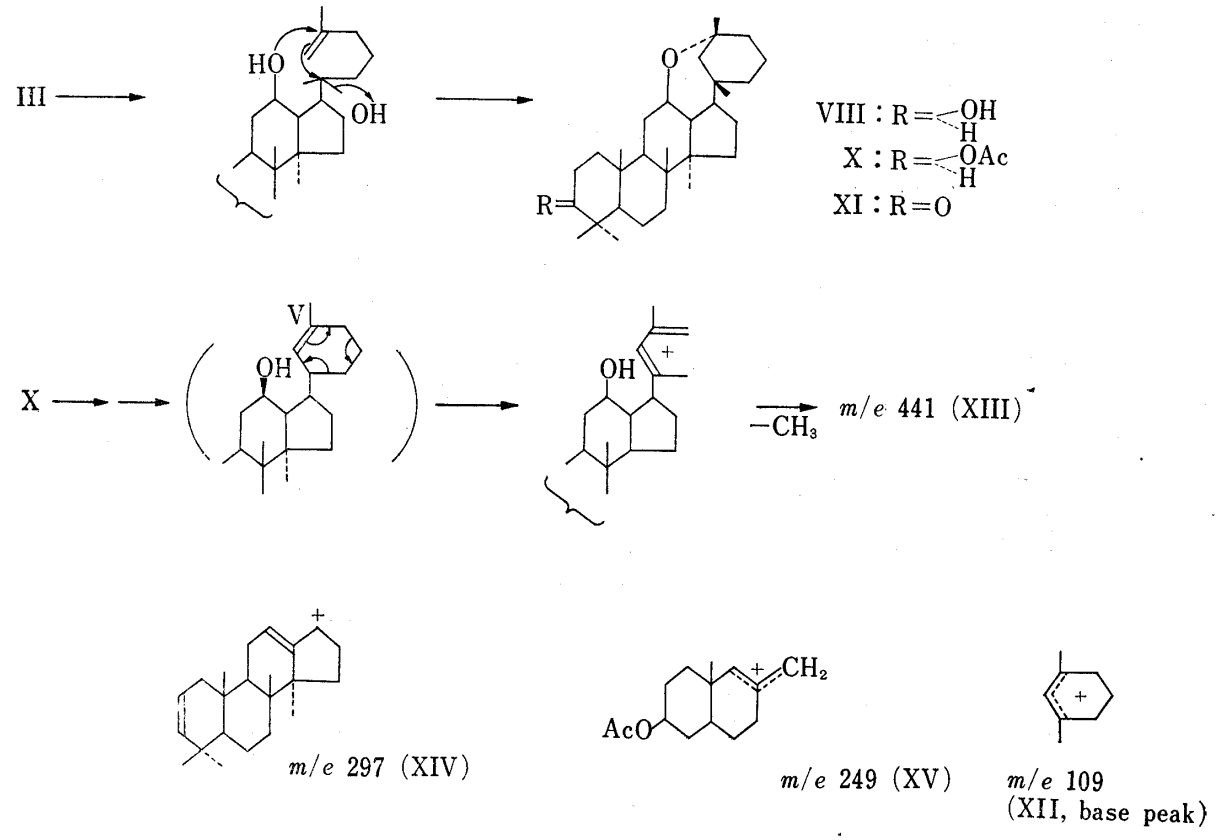


Chart 2

The absence of a double bond in VIII was proved by the negative nitromethane test and its NMR spectrum which exhibited no signal due to olefinic proton and allylic methyl. The NMR spectra of VIII and its derivative taken in benezne[11] at 60 Mc as well as those taken at 100 Mc disclosed the absence of the secondary methyl and the presence of seven tertiary methyl, indicating the participation of one of eight methyl groups of III in this reaction.

8) C. Djerassi, J. Osiecki, and W. Closson, *J. Am. Chem. Soc.*, **81**, 4587 (1959).
9) O. Tanaka, M. Nagai, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **14**, 1150 (1966).
10) D.H.R. Barton and P. de Mayo, *J. Chem. Soc.*, **1954**, 887. The present authors proved that the 12-ketone fo this type is negative to this test.
11) The better resolution of the tertiary methyl signals was obtained in the spectrum taken in benzene than that in $CDCl_3$.

On the basis of these evidences, the structure shown in Chart 2 was proposed for VIII which would be formed from III *via* its double bond isomer V. It should be noted that the acid catalyzed migration of the isopropylidene type double bond to the isopropenyl type has been shown in some tetracyclic triterpenes.[12] Examination of the Dreiding model demonstrated that the possible stereostructure of VIII was limited only to the $C_{(20)}$-(*R*) and $C_{(25)}$-(*S*) configuration.

The structure of VIII was supported by the mass spectrum of its acetate (X). The base peak at *m/e* 109 can reasonably be assigned to the fragment XII. The peaks at *m/e* 441, 297, and 249 would be corresponding to the fragments XIII, XIV, and XV, respectively.

Isodehydroprotopanaxadiol (VIII) was also isolated from the crude hydrolysate of the Ginseng saponins with dil. mineral acid as one of the minor products along with panaxadiol (IX), the main product. Absence of VIII in the crude hydrolysate of the hydrogenated saponins revealed that VIII should be an artifact formed during the process of the acid hydrolysis like panaxadiol (IX).[1,13]

The other anomalous chemical property of the side chain was encountered when betulafolienetriol (VI) was treated with N-bromosuccinimide (NBS) in $CCl_4$ at room temperature. The crystalline product (XVI), $C_{30}H_{51}O_3Br$, obtained in a good yield showed IR bands (in $CCl_4$) at 3385 (concentration independent, intramolecularly hydrogenbonded OH) and 3635 $cm^{-1}$ (free OH). In the NMR spectrum of XVI, no resonance due to the olefinic proton was observed and beside the characteristic signals of the carbinyl protons at $C_{(3)}$ and $C_{(12)}$, and additional signal appeared at $\delta$ 3.92 ppm (1H, q, $J$=10 Hz, $J$=5 Hz) which would be assignable to the proton attached to the carbon linking the oxygen bridge and having two proton on the adjacent carbon atom. Of the eight tertiary methyl signals of XVI, the signal at $\delta$ 1.31 ppm would be assigned to a methyl on the carbon having an oxygen function, and two methyl signals in the lower field ($\delta$ 1.68 and 1.72 ppm) were too sharp as for the allylic methyl $-CH=C(CH_3)_2$ being rather attributable to the methyls on the carbon atom bearing a halogen atom. Reduction of XVI with zinc dust in AcOH at room temperature reproduced VI in an almost quantitative yield. These evidences revealed that the usual allylic bromination with NBS in non-polar solvent did not take place, and the structure (XVI), except the configuration at $C_{(24)}$, was proposed for XVI. The regeneration of VI from XVI with zinc can be referred to the debromination reaction of the $\alpha$-bromo ether such as XVII in the steroid chemistry.[14] The X-ray crystallographic analysis of XVI finally established its structure including all the stereochemistry.[15]

The same type of the reaction was also confirmed in 20(*R*)-compound. On treatment with NBS in $CCl_4$, 20(*R*)-protopanaxadiol (III) afforded a bromo-compound (XVIII), whose structure was deduced by analogy with XVI. The reduction of XVIII with zinc regenerated III which must be homogeneous with regard to the position of the double bond (see Fig. 1).

It should be noted that the addition of the radical inhibitor such as *m*-dinitrobenzene or hydroquinone gave no remarkable effect on this reaction. Bromination with NBS in the polar solvent, acetone or acidic medium, proceeded more rapidly than in the non-polar solvent, yielding XVI and an amorphous product (XIX) which seemed to be the $C_{(24)}$ isomer of XVI as it gave a similar NMR spectrum to that of XVI. These observations suggest that the concerted ionic reaction mechanism shown in Chart 3 would be operative in the NBS reaction in the non-polar solvent, rationalizing the stereospecificity of this reaction.

12) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publ. N.Y., 1959, p. 397.
13) M. Fujita, S. Itokawa, and S. Shibata, *Yakugaku Zasshi*, **82**, 1638 (1962).
14) J.A. Edwards, M.C. Calzada, L.C. Ibanez and A. Bowers, *Steroids*, **6**, 371 (1965); J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1017 (1963).
15) The NBS reaction of VI including the X-ray analysis of XVI has been reported preliminarily in *Tetrahedron Letters*, **1968**, 4235.

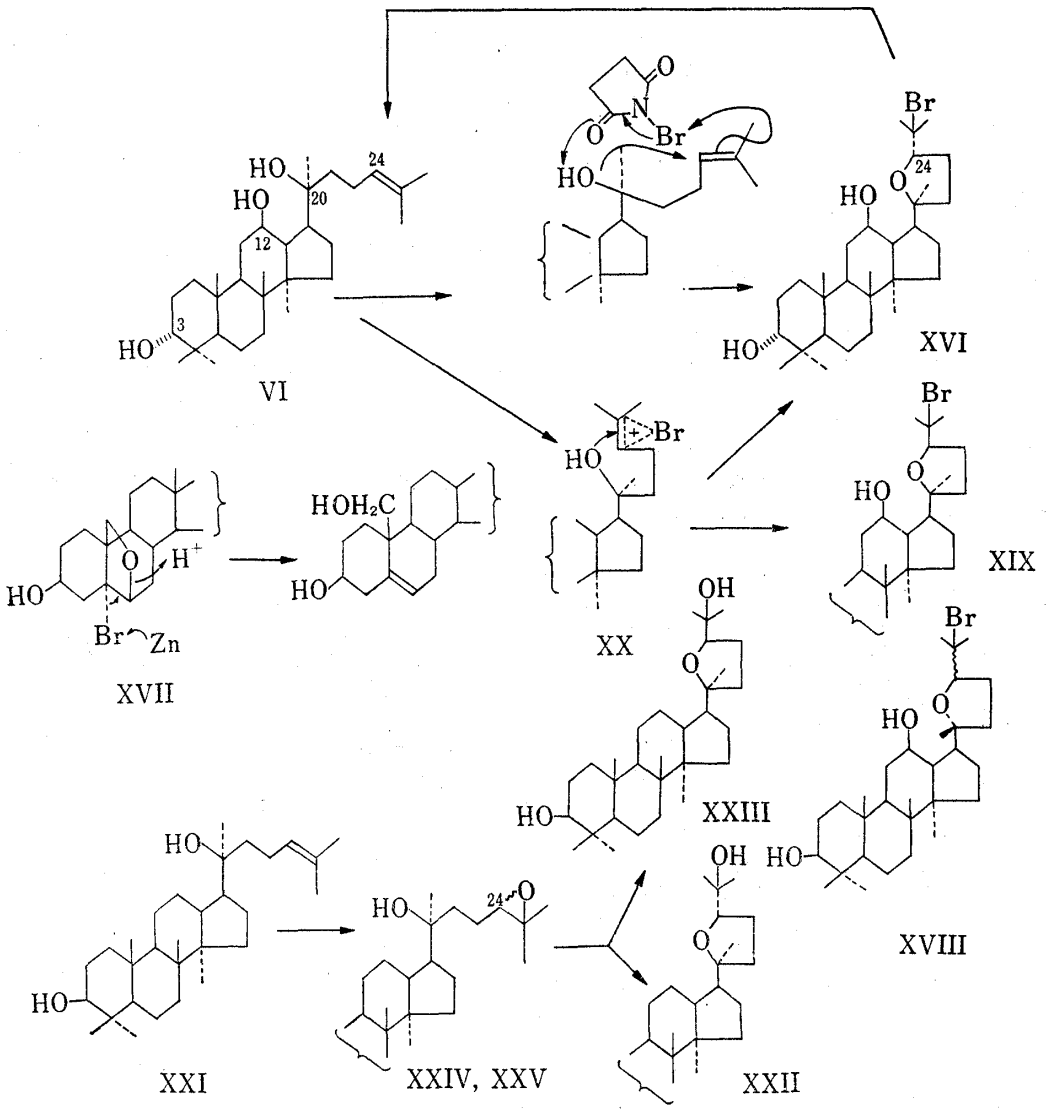


Chart 3

Furthermore, it has been found that the action of molecular bromine to VI in $CHCl_3$ afforded the similar products to those of NBS reaction in acetone. In these cases, the intermediate would be the bromo-cation complex (XX), which was attacked by the 20-hydroxyl group from both sides yielding a pair of the $C_{(24)}$ epimers, XVI and XIX.[16] An analogous reaction has been reported when dammarenediol-II (XXI) was oxidized with the organic peracid, affording a mixture of the epimeric compounds having the hydroxyisopropyl-tetrahydrofuran ring, XXII and XXIII *via* the unstable epoxides, XXIV and XXV.[17] Incidentally, the several triterpenes having such a modified side chain (ocotillol-II (XXIII) *etc.*) have been found in nature, whose chirality at $C_{(24)}$ has been established by the chemical correlation with XVI.[18]

16) Very recently, Demole and Enggist reported the similar NBS reaction of linalool referring our preliminary paper[15] and its application to the synthesis of karakaraenone (E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456 (1971)).
17) J.F. Biellmann, *Bull. Soc. Chim. France*, **1967**, 3459.
18) Preliminary communication of this work: M. Nagai, N. Tanaka, S. Ichikawa, and O. Tanaka, *Tetrahedron Letters*, **1968**, 4239.

## Experimental[19]

**The Samples of 20(*S*)- and 20(*R*)-Protopanaxadiols**——I-Bu, I-DEA, I-SM, III-Bu, and III-DEA were prepared by the procedure described in our preceding papers.[1,4] I-Bu, I-DEA, and I-SM were recrystallized from benzene, and III-Bu and III-DEA were recrystallized from EtOAc. The samples of 20(*R*)-proptopanaxadiol prepared from XVI by zinc reduction or from the prosapogenin[1,20] by periodate oxidation followed by the alkaline treatment must be completely homogeneous even with regard to the orientation of the double bond, but III-Bu can, also practically be used as 20(*R*)-protopanaxadiol in the series of our experiments. I-Bu has been also used as 20(*S*)-protopanaxadiol. The qualitative and quantitative separations of I and VII from their mixture, and III and V from their mixture have not been attempted as yet.

**Isodehydroprotopanaxadiol (VIII)**——To a solution of 20(*R*)-protopanaxadiol (III) (5.8 g) in anhyd. ether (500 ml) was added the commercial ethereal solution of $BF_3$ etherate (500 ml), and the mixture was allowed to stand at room temperature for 20 hr. After decomposition of $BF_3$ by stirring with ice water, the ethereal layer was concentrated to dryness giving a mixture of VIII and panaxadiol (IX) and other minor products. Column chromatography of this mixture on silica gel followed by crystallization from MeOH afforded VIII (1.6 g) as colorless prisms, mp 218—219.5°, $[\alpha]_D^{25}$ +45.6° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.16; H, 11.50. NMR: in $CDCl_3$ $\delta$ 0.77 (3H), 0.84 (9H), 0.94 (3H), 0.97 (3H) and 1.12 ppm (3H) (all singlets, tertiary methyls). $\delta$ 3.22 (1H, broad >C<u>H</u>-OH) and 3.65 ppm (1H, sextet, -CH-O-). In benzene $\delta$ 0.77 (6H), 0.80 (3H), 0.85 (3H), 0.95 (3H), 1.01 (3H), and 1.21 ppm (3H) (all singlet, tertiary methyls) at 60 Mc as well as at 100 Mc.

**3-O-Acetylisodehydroprotopanaxadiol (X)**——VIII (100 mg) was acetylated with acetic anhydride (4 ml) in pyridine (2 ml) at room temperature. Working up in the usual way and recrystallization from ethyl acetate of the product yielded X, colorless prisms, mp 252.5—254°, $[\alpha]_D^{25}$ +54.6° ($CHCl_3$). *Anal.* Calcd. for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.41; H, 10.88. NMR: in $CDCl_3$ $\delta$ 0.83 (12H), 0.87 (3H), 0.93 (3H), 1.13 (3H) (all singlets, tertiary methyls), 2.03 (3H, singlet, -OAc), 3.73 (1H sextet) and 4.54 ppm (1H, triplet-like. -C<u>H</u>-OAc).

**The Ketone (XI)**——To a solution of VIII (150 mg) in acetone (60 ml) was added dropwise Jones reagent until the constant orange color was obtained. After working up in the usual way, the product was recrystallized from MeOH giving XI as colorless prisms, mp 195—197°. It contained 1 mol of crystalline MeOH which was removed by heating at 60° for 5 hr *in vacuo*. $[\alpha]_D^{13}$ +71.0° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.01; H, 11.05. NMR: in $CDCl_3$ $\delta$ 0.85 (6H), 0.99 (6H), 1.04 (3H), 1.08 (3H), 1.33 (3H) (all singlets, tertiary methyls), 3.63 ppm (1H, sextet, -C<u>H</u>-O-). in benzene $\delta$ 0.78 (6H), 0.86 (3H), 0.93 (3H), 0.97 (3H), 1.08 (3H) and 1.21 ppm (3H) (all singlets, tertiary methyls).

**Bromination of Betulafolienetriol (VI) (1)**——A suspension of VI (1 g) and NBS (400 mg) in $CCl_4$ (200 ml) was heated under reflux for 25 min. After cooling, the resulted precipitate (succinimide) was removed by filtration and the filtrate was washed with water, dried over anhyd. $Na_2SO_4$, and concentrated to dryness. The residue was recrystallized from a mixture of benzene and *n*-hexane (1:10) giving XVI (500 mg), colorless prisms, mp 170—174° (decomp.), $[\alpha]_D^{19}$ −10.3° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{51}O_3Br$: C, 66.77; H, 9.53; Br, 14.81. Found: C, 66.54; H, 9.41; Br, 14.65. NMR: in $CDCl_3$ 0.82 (3H), 0.86 (3H), 0.90 (6H), 1.02 (3H), 1.31 (3H) (all singlets, tertiary methyls), 1.68 (3H), 1.72 (3H) (both singlets, Br-C=$(CH_3)_2$), 3.35 (1H, triplet, -C<u>H</u>-OH (3-ax.)), 3.54 (1H, sextet, -C<u>H</u>-OH (12-eq.)), and 3.92 ppm (1H, quartet, -C<u>H</u>-O-), no signal more than 4.0 ppm excepting that of OH which was moved by addition of $D_2O$.

No significant effect was observed even by the addition of a small amount of *m*-dinitrobenzene or hydroquinone. The thin-layer chromatography (TLC) (solvent: $CHCl_3$: ether=1:1, on silica gel) indicated that the reaction in $CCl_4$ was completed within 15 min while it took about 1 hr in petroleum ether. In both cases, the product was only XVI.

**Bromination of VI (2)**——VI (800 mg) and NBS (320 mg) was dissolved in acetone (50 ml) and the solution was refluxed for 5 min. After cooling the solution was diluted with excess of water and extracted with ether. The crude reaction mixture obtained from the ethereal layer was chromatographed on silica gel (pretreated with oxalic acid (10% aqueous solution) and reactivated at 110° for 1 hr) afforded XVI and its $C_{(24)}$ isomer XIX in a ratio of 4:1. The latter compound (XIX) which showed the lower *Rf* value than XVI in TLC (solvent: $CHCl_3$: ether=1:1, on silica gel), could not be crystallized as yet. NMR of XIX: in $CDCl_3$ $\delta$ 0.84 (3H), 0.88 (3H), 0.93 (6H), 0.98 (3H), 1.25 (3H) (all singlets, tertiary methyls), 1.73 (3H), 1.78 (3H) (both singlets, Br-C=$(CH_3)_2$), 3.35 (1H, triplet, -C<u>H</u>-OH (3-ax.)), 3.54 (1H, sextet, -C<u>H</u>-OH (12-eq.)), and 3.98 (1H, broad, -C<u>H</u>-O-).

The reaction in a mixture of AcOH and petroleum ether (1:7) also proceeded fast (within 15 min) and TLC of the crude products revealed XVI and a small amount of XIX and other by-products.

To a solution of VI (30 mg) in $CHCl_3$ (8 ml) was added slight excess of bromine gradually at room temperature. TLC of the crude products indicated the formation of XVI and XIX.

19) All melting points were determined on a Kofler block, and remain uncorrected.
20) S. Shibata, T. Ando, and O. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **14**, 1157 (1966).

**Reduction of XVI to VI**——To a solution of XVI (300 mg) in ether (20 ml) and AcOH (5 ml) was gradually added zinc dust (3.3 g) under ice cooling. The mixture was stirred at room temperature for 5.5 hr. After dilution with water, the mixture was extracted with ether and the ethereal layer was washed with water, dried, and evaporated to dryness *in vacuo*. The residue was recrystallized from EtOAc affording VI (150 mg). The identity with authentic sample of VI was established by mixed melting point, TLC (solvent:ether: $CHCl_3$=1:1, on silica gel), and the comparison of the IR spectra.

**Bromination of 20(*R*)-protopanaxadiol (III)**——A mixture of III (370 mg), and NBS (150 mg) in $CCl_4$ (105 ml) was refluxed for 30 min. After working up in the same way as in the case of VI, the products was chromatographed on silica gel pretreated with oxalic acid (loc. cited). On recrystallization from a mixture of benzene and *n*-hexane, XVIII was obtained as colorless needles, decomposed between mp 180—200°, $[\alpha]_D^{28}$ +9.6° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{51}O_3Br$: C, 66.77; H, 9.53; Br, 14.81. Found: C, 66.82; H, 9.42; Br, 15.21. IR $\nu_{max}^{CCl_4}$: 3622 (free OH) and 3420 $cm^{-1}$ (concentration independent, intramolecularly hydrogen bonded OH). NMR in $CDCl_3$: $\delta$ 0.76 (3H), 0.87 (6H), 0.95 (3H), 0.97 (3H), 1.20 (3H) (all singlets, tertiary methyls), 1.67 (6H, singlet, Br-CH=$(CH_3)_2$), 3.13 (1H, quartet-like, -C<u>H</u>-OH (3-eq.)), 3.48 (1H, sextet, -C<u>H</u>=OH (12-eq.)), and 3.94 ppm (1H, triplet-like, -C<u>H</u>-O-), no signal more than 4.0 ppm excepting that of OH which was replaced by $D_2O$.

**Reduction of XVIII to III**——A mixture of XVIII (80 mg) and zinc dust (900 mg) in ether (7 ml) and AcOH (1.5 ml) was refluxed for 6 hr. After working up as above. the product was recrystallized from AcOEt to give III (50 mg) which was identified with the authentic sample by mixed melting point, the thin layer chromatography (loc. cited), and IR spectra.

**Acknowledgement** The authors are grateful to the Central Analytical Laboratory for the elemental analysis, IR and NMR spectra, ORD and DC curves measurement. Thanks are due to Tokyo Kyoiku University Forest for *Betula* leaves, the source of betulafolienetriol, and to Research Laboratory, Takeda Chemical Industry Co. Ltd. for mass spectrum and the extraction of Ginseng. Thanks are also due to Yakurikenkyu-kai and the Ministry of Education for grants.