[Chem. Pharm. Bull. 20(6)1204—1211(1972)]

UDC 547.597.02.04 : 581.192

Chemical Studies on the Oriental Plant Drugs. XXVII.[1] The Acid Catalyzed Reactions and the Absolute Configuration at $C_{(20)}$ of Dammarane Type Triterpenes[2]

Osamu Tanaka,[3a] Masahiro Nagai,[3b] Tomihiko Ohsawa,[3c] Nobutoshi Tanaka,[3d] Ken-ichi Kawai and Shoji Shibata[3]

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received November 26, 1971)

On acid treatments, betulafolianetriol (VII) having the same configuration at $C_{(20)}$ as dammarenediol II (VI) gave an equilibrated mixture of VII and its $C_{(20)}$ epimer (VIII). The derivatives of betulafolienetriol (IV) and VII having a hydroxyl or methoxyl group at $C_{(12)}$ also showed the configurational equilibration at $C_{(20)}$ hydroxyl under the same condition, whereas those without hydroxyl or methoxyl at $C_{(12)}$ showed no or negligible epimerization at $C_{(20)}$.

The acid catalyzed pyran ring formation from the side chain of betulafolienetriol (IV) gave 3,20-*epi*-panaxadiol (XII) and 3-*epi*-panaxadiol (XI) by the retention and the inversion of its $C_{(20)}$-configuration, respectively.

It reveals that $C_{(20)}$-configuration of panaxadiol (I) and protopanaxadiol (III) (epimeric at $C_{(3)}$ and $C_{(20)}$ of IV) are same as that of dammarenediol I (V).

Since the chirality at $C_{(20)}$ of panaxadiol (I) has already been established as R, dammarenediol I type triterpenes have (*R*)-configuration at $C_{(20)}$, and dammarenediol II type compounds S. This conclusion has also been supported by the IR-absorptions of $C_{(20)}$ keto and $C_{(20)}$ hydroxyl of 12-keto-3-acetates (XVII and XVIII) of betulafolianetriol (VII) and dihydroprotopanaxadiol (X).

The mechanism of epimerization at $C_{(20)}$ on the acid treatments of dammaran-20-ol compounds having O-function at $C_{(12)}$ was discussed.

As previously reported,[4] the hydrolysis of ginsenosides-Rb_1, Rb_2, and Rc, the neutral saponins of Ginseng roots, with dil. mineral acid in boiling aqueous ethanol afforded panaxadiol (I), whereas the hydrolysis of these saponins with conc. HCl at room temperature yielded a chloride (II) from which protopanaxadiol (III) (12β-hydroxydammarenediol-I)[5] was yielded by the treatment with base. For the purpose of studying these structural conversion of the sapogenin during the acid hydrolysis more extensively, the acid catalyzed reactions of betulafolienetriol (IV)[6a-c] (=3-*epi*-12β-hydroxydammarenediol-II,[7] epimer of protopanaxadiol (III) at $C_{(3)}$ and $C_{(20)}$) and its derivatives have been investigated as the model compounds.[2]

1) Part XXVI: M. Nagai, O. Tanaka and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **19**, 2349 (1971).
2) Preliminary communication of a part of this study: O. Tanaka, M. Nagai, T. Ohsawa, N. Tanaka and S. Shibata, *Tetrahedron Letters*, **1967**, 391, in part, O. Tanaka, N. Tanaka, T. Ohsawa, Y. Iitaka and S. Shibata, *ibid.*, **1968**, 4235.
3) Location: *Hongo, Bunkyo-ku, Tokyo*; Present addresses: *a) Institute of Pharmaceutical Sciences, School of Medicine, Hiroshima University, Kasumi 1-2-3, Hiroshima-shi*; *b) Hoshi College of Pharmacy, Ebara 2-4-41, Shinagawa-ku, Tokyo*; *c) Institute for Physical and Chemical Research, Yamato-machi, Saitama*; *d) Kyorin Pharmaceutical Industry Co., Ltd., Ukima 1-3-32, Kita-ku, Tokyo.*
4) S. Shibata, O. Tanaka, T. Ando, M. Sado, S. Tsushima and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 595 (1966).
5) O. Tanaka. M. Nagai and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **14**, 1150 (1966). Preliminary report: O. Tanaka, M. Nagai and S. Shibata, *Tetrahedron Letters*, **1964**, 2291.
6) *a)* F.G. Fischer and N. Seiler, *Ann.*, **644**, 146, 162 (1961); *b)* F.G. Fischer and N. Seiler, *ibid.*, **626**, 185 (1959); *c)* S. Shibata, M. Nagai and O. Tanaka, *Shoyakugaku Zasshi*. **18**, 27 (1962).
7) Dammarenediol-I (V) is the C-20 epimer of dammarenediol-II (VI).

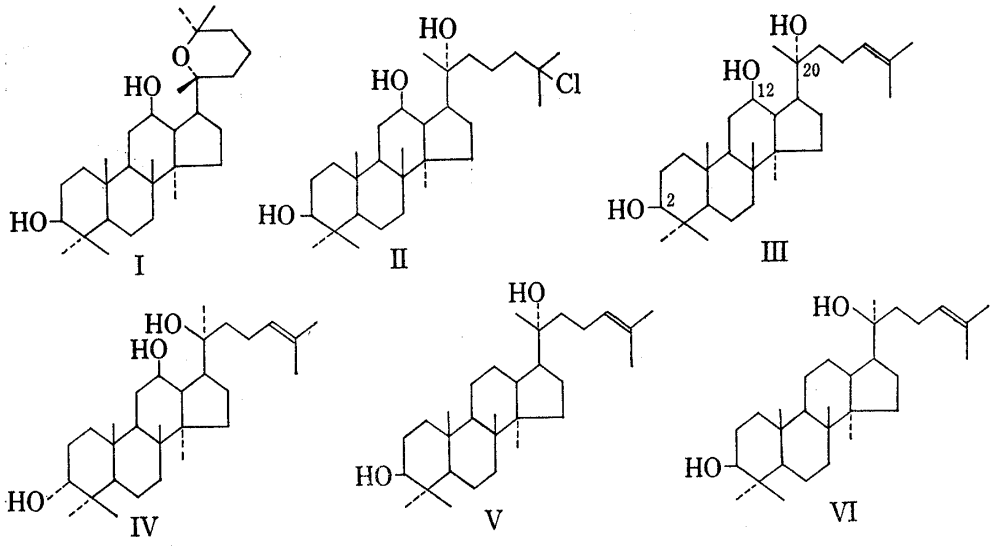


Chart 1

In the present paper, the experimental details dealt with the chirality at C-20 of dammarane type triterpenes are described.

Under the same condition of the hydrolysis as being employed for Ginseng saponin, betulafolianetriol (VII) (=dihydrobetulafolienetriol) was refluxed with dil. mineral acid in aqueous ethanol to afford an equilibrated mixture of VII and its $C_{(20)}$ epimer (VIII), mp 252—253°, with an excess of the latter compound. The structure of VIII was established by the conversion into a diketonic compound (IX), mp 124—126°, which was proved to be identical with the 3,12-diketone derived from dihydroprotopanaxadiol (X).[5]

Acid treatment of betulafolienetriol (IV) under the similar condition as above mentioned afforded two crystalline compounds, XI, mp 261—263°, and XII, mp 230—233°. The former compound (XI), which shows higher *Rf* value on the thin-layer chromatogram than the latter (XII), was proved to be 3-*epi*-panaxadiol, since mild oxidation of XI with chromic acid in pyridine gave a ketone (XIII), mp 236—238°, IR $\nu_{max}^{CS_2}$ 3396 (12β-OH, intramolecularly hydrogen bonded, concentration independent) and 1715 cm^{-1}, which was identical with the 3-ketone[1] obtained from panaxadiol (I).

The structure of the latter compound (XII) was established to be the $C_{(20)}$ epimer of XI on the basis of the following evidences. As shown in panaxadiol (I),[8a] the presence of 2,2,6-trimethyltetrahydropyran ring in XII was demonstrated by the mass spectrum——base peak at *m/e* 127 (ion (P) in Chart 2), as well as by the nuclear magnetic resonance (NMR) spectrum——singlets at δ 1.28 (6H) and δ 1.23 ppm (3H) attributable to three tertiary methyls attached to the carbon atom bearing an oxygen function. The infrared (IR) spectrum of XII in CCl_4 showed a free OH band at 3637 cm^{-1} and a hydrogen bonded OH band at 3355 cm^{-1}, the latter of which corresponds to the absorption of 12β-hydroxyl of panaxadiol (I).[8b] On oxidation with Jones' reagent, XII gave a diketone (XIV), mp 180—182°, IR $\nu_{max}^{CS_2}$ 1718 cm^{-1} and no OH band, whose optical rotatory dispersion (ORD) curve resembles that of the diketone (XV), mp 246—248°, prepared from panaxadiol (I) (Fig. 1). The suspicion of contamination of $C_{(20)}$ epimer in betulafolienetriol (IV) used in the present experiment was rigorously eliminated since 20-*epi*-betulafolienetriol (XVI) can be readily distinguished from IV by the thin-layer chromatography (TLC). This result disclosed that the acid

8) *a*) S. Shibata, M. Fujita, H. Itokawa, O. Tanaka and T. Ishii, *Chem. Pharm. Bull.* (Tokyo), **11**, 759 (1963). Preliminary report: S. Shibata, M. Fujita, H. Itokawa, O. Tanaka and T. Ishii, *Tetrahedron Letters*, **1962**, 419; *b*) S. Shibata, O. Tanaka, M. Nagai and T. Ishii, *Chem. Pharm. Bull.* (Tokyo), **11**, 762 (1963). Preliminary report: S. Shibata, O. Tanaka, M. Nagai and T. Ishii, *Tetrahedron Letters*, **1962**, 1239.

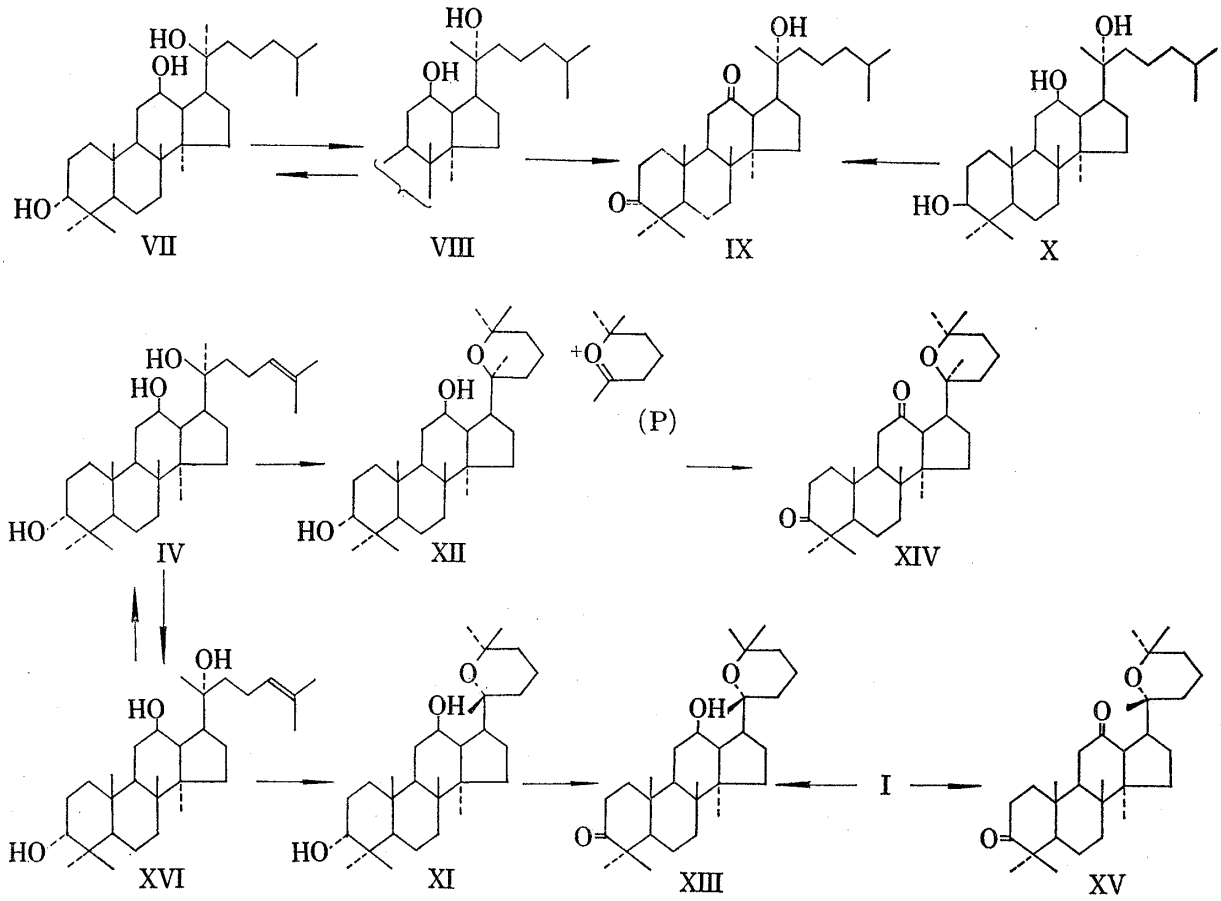


Chart 2

catalyzed epimerization of C-20 hydroxyl also occurs during the cyclization of the side chain.

In contrast to the above case, heating of IV with aqueous acetic acid, the similar condition to that used for the partial hydrolysis of ginsenosides-Rb_1, Rb_2, and Rc (formation of the prosapogenin),[9] yielded an equilibrated mixture of IV and its $C_{(20)}$ epimer (XVI), mp 230—232°, in an excess of the latter compound. In this case, the cyclization of the side chain (formation of tetrahydropyran ring) was almost negligible. The structure of XVI was established by the formation of VIII (*vide supra*) on catalytic hydrogenation.

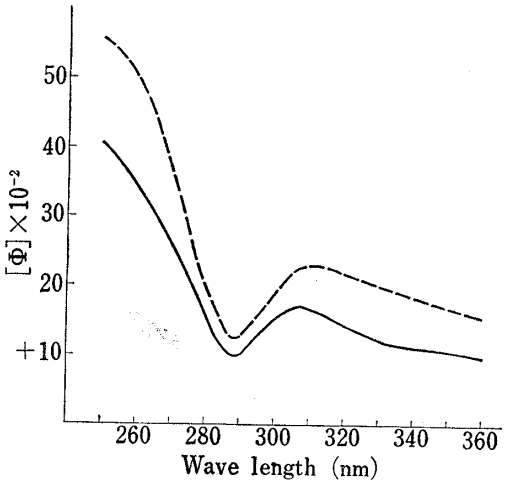


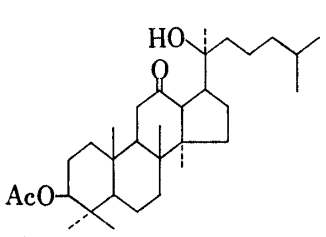
Fig. 1. ORD Curves (in MeOH)
XIV: —— XV: -----

It has been found that the above cyclization of the side chain accompanied by the epimerization of $C_{(20)}$ hydroxyl proceeds more slowly by the action of *p*-toluenesulfonic acid in $CHCl_3$ than the case of the mineral acid. Betulafolienetriol (IV) was treated with *p*-toluenesulfonic acid, and the reaction process was followed with the TLC in comparison with the epimerization of VII under the same condition. In the early stage of the former reaction

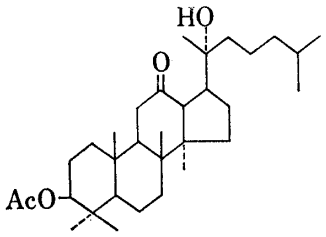
9) S. Shibata, T. Ando and O. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **14**, 1157 (1966).

(within 4 hr), 3,20-*epi*-panaxadiol (XII) was formed mainly, and the formation of 3-*epi*-panaxadiol (XI) was observed almost simultaneously when the $C_{(20)}$ epimer (VIII) appeared in the mixture of the latter reaction. This observation proved that XII was produced from IV by the direct cyclization of the side chain prior to the epimerization of $C_{(20)}$ hydroxyl and that XI was yielded from IV through the epimerized compound XVI. Consequently XII has the same chirality of $C_{(20)}$ as that of IV (dammarenediol-II (VI) type), then the chirality of $C_{(20)}$ of XI and panaxadiol (I) is same as that of protopanaxadiol (III) (dammarenediol-I (V) type). Since the chirality of $C_{(20)}$ of I has already been established to be R,[1] it can be concluded that the chirality of $C_{(20)}$ of dammarenediol-I (V) and its homologs is R, then that of dammarenediol-II (VI), the $C_{(20)}$ epimer of V, and its homologs is S.[10] The tentative assignment of the chirality of $C_{(20)}$ of IV as R by Fischer and Seiler[6a] must be incorrect as already pointed out by Warnhoff, *et. al.*[11]

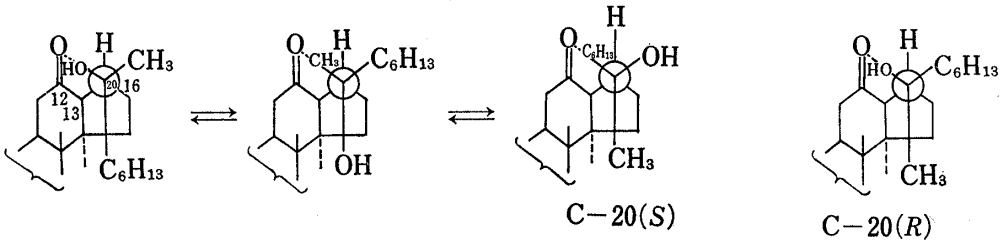
The evidence for the chirality at $C_{(20)}$ was also provided by the comparison of the IR spectra of the 12-keto derivative (XVII)[5] prepared from VII and its $C_{(20)}$ epimer (XVIII)[5] derived from X. In the spectrum of XVIII in CCl_4, a strong OH band at 3450 cm^{-1} (concentration independent) and a C=O band at 1696 cm^{-1} were observed while the absorption near 3620 and 1710 cm^{-1} were negligible indicating that the hydroxyl at $C_{(20)}$ is mostly hydrogen bonded with the 12-keto group in this compound. On the other hand, the spectrum of XVII exhibited prominent absorptions of free hydroxyl and carbonyl groups at 3620 and 1707 cm^{-1} and bonded hydroxyl and carbonyl groups at 3442 and 1697 cm^{-1} proving that the hydroxyl at $C_{(20)}$ is partly hydrogen bonded with the 12-keto group. This difference can be rationalized in terms of the conformational stability of the hydrogen bonded form of both compounds. As illustrated in Chart 3, the alkyl side chain (C_6H_{13}) is projected between $C_{(13)}$ (large) and $C_{(16)}$ methylene (medium) in the hydrogen bonded form of XVII, whereas, in case of XVIII, the alkyl side chain falls between the $C_{(17)}$ hydrogen (small) and $C_{(16)}$ methylene (medium) being less hindered than that of XVII ($C_{(20)}$S).



XVII



XVIII



C−20(*S*) C−20(*R*)

Chart 3

The facile epimerization of the tertiary hydroxyl group at $C_{(20)}$ of the dammarane type triterpenes was not observed in the compound without 12β-hydroxyl. 20(*S*)-Dammaran-20-

10) Almost simultaneously with our preliminary communications, Biellmann reported independently the same assignment as ours (J. F. Biellmann, *Bull. Soc. Chim. France*, **1967**, 3459 (J. F. Biellmann, *Tetrahedron Letters*, **1966**, 4803.).

11) E.W. Warnhoff and C.M.M. Halls, *Can. J. Chem.*, **43**, 3311 (1965); C.B. Barnes, N.N. Galbraith, E. Ritchie and W.C. Tayler, *Aust. J. Chem.*, **18**, 1411 (1965).

ol (XIX)[5] was treated with boiling dil. mineral acid in aqueous ethanol. The thin-layer chromatography of the reaction mixture revealed that the main product was the compound with the same *Rf* value and the same color reaction with H_2SO_4 as those of one of the dehydration products of XIX with $POCl_3$ in pyridine. Even under a milder condition, *i.e.*, *p*-toluenesulfonic acid in $CHCl_3$ at room temperature, the dehydration of C-20 hydroxyl was found to proceed faster than its epimerization, though the formation of a small amount of the $C_{(20)}$ epimer of XIX was observed in this case.

The significant difference of the reactivity between the compounds with or without 12β-hydroxyl group was also shown in the acid catalyzed cyclization of the side chain (formation of the tetrahydropyran ring). 20(*S*)-Dammar-24-en-20-ol (XX), mp 59—61°, prepared from IV through its 3,12-diketone (XXI), mp 152—153°, was refluxed with dil. mineral acid in aqueous ethanol to give no compound with tetrahydropyran ring, but a compound showing the same *Rf* value and the same color reaction with H_2SO_4 as those of one of the reaction products of XX with $POCl_3$ in pyridine.

Finally, the influence of the 12β-methoxyl group to the acid catalyzed reaction was examined in relation to the structural study of the Ginseng saponin. Betulafolianetriol (VII) was methylated by Hakomori's procedure[12] to give an amorphous dimethyl ether (XXII). Treatment of XXII with dil. mineral acid or *p*-toluenesulfonic acid under the same condition as above gave an equilibrated mixture of XXII and its $C_{(20)}$ epimer (XXIII) with an excess of the latter compound (XXIII). The structure of XXIII, which showed the higher *Rf* value on the thin-layer chromatogram was confirmed by the similarity of its NMR and IR spectra to those of XXII and the formation of the same equilibrated mixture (XXII and XXIII) by the acid treatment.

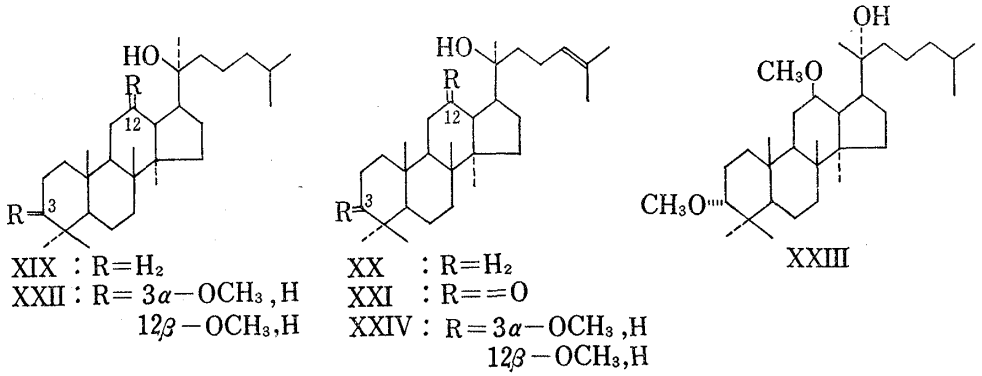


Chart 4

Betulafolienetriol (IV) was methylated by Hakomori's procedure affording an amorphous dimethyl ether (XXIV). On refluxing with dil. mineral acid in aqueous ethanol, XXIV gave mainly nonpolar substances (probably dehydration products), while the formation of the $C_{(20)}$ epimer of XXIV as well as the compound with the tetrahydropyran ring was negligible. The reaction of XXIV with *p*-toluenesulfonic acid in $CHCl_3$ proceeded more slowly than the case of IV, and the main products was the nonpolar substances though a small amount of the compound which seemed to be the $C_{(20)}$ epimer of XXIV was yielded. The formation of the compound with tetrahydropyran ring was observed in this case.

On the acid treatments as shown above, dammaran-20-ols and dammar-24-en-20-ols having a hydroxyl or methoxyl group at $C_{(12)}$ showed the configurational equilibration of their $C_{(20)}$ hydroxyl, whereas those without hydroxyl or methoxyl at $C_{(12)}$ showed no or negligible epimerization at $C_{(20)}$. The epimerization would be caused by a stabilization of the

12) S. Hakomori, *J. Biochem.*, **55**, 205 (1964).

$C_{(20)}$ carbonium ion produced by the acid treatments of 20-ol. A direct or indirect interaction between the electronegative oxygen functions at $C_{(12)}$ and the carbonium ions at $C_{(20)}$ forms a stabilized state, whereas carbonium ion without hydroxyl or methoxyl at $C_{(12)}$ is mostly stabilized by elimination of a proton from $C_{(21)}$ or $C_{(22)}$ forming olefins (dehydration products) in prior to the attack of OH^- to $C_{(20)}$ (as H_2O in the reaction medium).

The epimerization of the hydroxyl at $C_{(20)}$ and the tetrahydropyran ring formation from the side chain of derivatives of dammar-24-en-20-ol occurs competitively under those reaction conditions, and the pyran ring formation is accomplished in a manner that the oxygen atom of the hydroxyl group at $C_{(20)}$ with retention of its configuration attacks $C_{(25)}$ of a positively charged intermediate resulted by the addition of a proton to the double bond at $C_{(24)}$ to form an ether ring. Referring the thin-layer chromatograms detected during the reaction process, it was suggested that $C_{(20)}$ R hydroxyl reacts more readily than $C_{(20)}$ S hydroxyl in the tetrahydropyran ring formation.

Experimental[13]

Acid Treatment of Betulafolianetriol (VII)——a) A mixture of VII (2.96 g), EtOH (180 ml), H_2O (120 ml), and conc. H_2SO_4 (8.0 ml) was heated under reflux for 5 hr. The reaction mixture was poured into H_2O and extracted with ether. The ether-layer was washed with H_2O, dried, and evaporated to dryness and the residue was chromatographed on alumina (neutral, grade V). Elution with ether–benzene (1:4 and 2:3) afforded a crystalline material (1.08 g), which on recrystallization from EtOAc gave 20-*epi*-betulafolianetriol (VIII), mp 252—255°, $[\alpha]_D^{22°}$ ±0° ($CHCl_3$), *Anal.* Calcd. for $C_{30}H_{54}O_3$: C, 77.86; H, 11.76. Found: C, 78.04; H, 11.65. IR $\nu_{max}^{CHCl_3}$: 3602 and 3330 cm^{-1}.

On elution with ether–benzene (2:3) and EtOH–benzene (1:9), another crystalline material (0.86 g) was obtained, which after recrystallization from acetone was identified to be VII by mixed melting point and the comparison of the thin layer chromatogram and IR spectrum with those of the authentic sample of VII.

b) A mixture of VII (1 mg) and *p*-toluenesulfonic acid (2 mg) in $CHCl_3$ (0.5 ml) was kept at 34° for 46 hr. TLC (solvent: $CHCl_3$–EtOAc 1:1) of the crude reaction mixture revealed the presence of the equilibrated mixture of VII and VIII in an excess of the latter compound. The treatment of VIII under the same condition afforded the same result.

Oxidation of 20-*epi*-Betulafolianetriol (VIII)——VIII was oxidized with Jones' reagent in acetone under the usual condition and the product was recrystallized from aqueous MeOH to give the diketone (IX), mp 124—126°, which was proved to be identical with the diketone derived from dihydroprotopanaxadiol (X)[5] by mixed melting point and the comparison of IR spectra.

Acid Treatment of Betulafolienetriol (IV)——a) A mixture of IV (5.6 g), EtOH (210 ml), H_2O (100 ml), and conc. HCl (24 ml) was refluxed for 45 min. The reaction mixture was diluted with H_2O and extracted with ether repeatedly. The ether-layer was washed with H_2O, dried, and concentrated to dryness, and the residue was chromatographed on silica gel. Elution with $CHCl_3$: benzene (3:1 and 9:1) afforded a crystalline material, which on recrystallization from EtOAc to give 3-*epi*-panaxadiol (XI) (0.5 g) as colorless prisms, mp 261—263°, $[\alpha]_D^{25}$ −11.4° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.35; H, 11.21. IR ν_{max}^{KBr}: 3410, 3300 cm^{-1}.

The substance which was eluted with $CHCl_3$–benzene (9:1) after pure XI was rechromatographed on alumina (neutral, grade II), and the compound eluted with $CHCl_3$–benzene (1:9) was recrystallized from EtOAc to give a small amount of 3, 20-*epi*-panaxadiol (XII), as colorless needles, mp 230—233°, $[\alpha]_D^{25}$ −3.5° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 77.81; H, 11.29. IR $\nu_{max}^{CCl_4}$: 3637, 3355 cm^{-1}. NMR (in $CDCl_3$) δ: 0.82 (3H,), 0.88 (9H), 0.98 (3H), 1.23 (3H), and 1.28 (6H) (all singlets). Mass Spectrum: *m/e* 460 (M^+) and 127 (base peak).

b) A mixture of IV (3 mg), *p*-toluenesulfonic acid (4 mg) in $CHCl_3$ (0.7 ml) was allowed to stand at 25—28°.

c) A suspension of IV (1.5 g) in 75% aqueous AcOH (40 ml) was heated at 80° for 5 hr to give the equilibrated mixture of IV and its epimer (20-*epi*-betulafolienetriol XVI). The reaction mixture was chromatographed on silica gel to obtain XVI as colorless needles (from AcOEt), mp 230—232°, $[\alpha]_D^{17}$ +7° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.45; H, 11.25. IR $\nu_{max}^{CHCl_3}$: 3600 (free OH) and 3360 cm^{-1} (intramolecularly hydrogen bonded OH). NMR δ: 0.83, 0.88, 0.90, 0.93, 0.98 (all singlets and 3H each, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.11 (singlet 3H, $HO-\overset{|}{\underset{|}{C}}-CH_3$), 1.62, 1.66 (all singlets 3H each, $C=\overset{|}{\underset{|}{C}}-CH_3$), 3.38 (triplet-like,

13) All melting points were determined on a Kofler's block and uncorrected. Silica gel G (Merck) was used for the absorbant of the TLC. NMR spectra were obtained in $CDCl_3$ solution.

1H, HO–C–H$_{(eq)}$), 3.57 (broad 1H, HO–C$_{(12)}$-H$_{(ax)}$), and 5.10 ppm (broad, 1H, H–C$_{(24)}$=C–). The treatment of XVI with aqueous AcOH under the same condition as above also gave the same equilibrated mixture of IV and XVI. Catalytic reduction of XVI (30 mg) with Adams catalyst in AcOEt (12 ml) afforded 20-*epi*-betulafolianetriol (VIII) which was identified by mixed melting point and the comparison of IR spectrum and thin-layer chromatogram with those of the authentic sample of VIII.

Oxidation of 3-*epi*-Panaxadiol (XI) to the Monoketone (XIII)——To a solution of XI (0.2 g) in pyridine (6 ml) was added chromic anhydride (0.24 g) in pyridine (4 ml), and the mixture was kept at room temperature overnight. After working up in the usual way, the product was recrystallized from MeOH to give the monoketone (XIII), colorless needles, mp 236—238°, $[\alpha]_D^{25.5}$ 24.0° ($CHCl_3$), which was identified to be the 3-ketone[1] prepared from panaxadiol (I) by mixed melting point, and comparison of the thin layer chromatogram and IR spectrum with those of the authentic sample.

Oxidation of 3, 20-*epi*-Panaxadiol (XII) to the Diketone (XIV)——XII (0.2 g) was oxidized with Jones' reagent in acetone (30 ml) in the usual way and the product was recrystallized from MeOH to give the diketone (XIV) (45 mg), colorless needles, mp 180—182°, $[\alpha]_D^{21}$ +112° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.61; H, 10.53. IR $\nu_{max}^{CS_2}$: 1718 cm^{-1} and no OH band.

Oxidation of Panaxadiol (I) to be Diketone (XV)——Panaxadiol (I) (0.2 g) was oxidized with Jones' reagent in acetone (80 ml) in the usual way and the product was recrystallized from MeOH to yield the diketone (XV) (0.15 g), colorless needles, mp 246—248°, $[\alpha]_D^{24.5}$ +71.8° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.90; H, 10.60. IR $\nu_{max}^{CS_2}$ 1717 cm^{-1} and no OH band.

Acid Treatment of 20 (*S*)-Dammaran-20-ol (XIX)——A solution of XIX (10 mg) in 5% H_2SO_4 (in 57% aqueous EtOH) (10 ml) was heated under reflux for 5 hr. TLC (on silica gel impregnated with $AgNO_3$, solvent: pet. ether) revealed that the main product gave the same *Rf* value and the same color reaction with H_2SO_4 as those of one of the dehydration products of XIX (5 mg) with $POCl_3$ (0.2 ml) in pyridine (1.5 ml). Neither starting material nor C$_{(20)}$ epimer were detected. Treatment of XIX (5 mg) with boiling 2.5% HCl in aqueous EtOH (10 ml) for 45 min or with *p*-toluenesulfonic acid (17 mg) in $CHCl_3$ (2.5 ml) at 35° for 80 min also gave the same result as above.

Oxidation of Betulafolienetriol (IV) to the Diketone (XXI)——To a solution of IV (0.8 g) in acetone (30 ml) was added Jones' reagent at room temperature until the constant orange color was obtained. After working in the usual way, the products were purified by column chromatography on silica gel to give the diketone (XXI), colorless needles, mp 152—153.5° from MeOH, $[\alpha]_D^{10}$ −72.1° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.85; H, 10.77. IR ν_{max}^{KBr}: 3505 (OH) and 1710 cm^{-1} (C=O). NMR δ: 0.80 (3H), 1.03 (3H), 1.07 (3H), 1.09 (6H), (all singlets, –C–CH$_3$), 1.22 (singlet, 3H, HO–C–CH$_3$), 1.65, 1.59 (all singlets, 3H each, –C=C–CH$_3$), and 5.08 ppm (broad triplet, 1H, –C=CH–).

Dammar-24-en-20 (*S*)-ol (XX) from the Diketone (XXI)——A mixture of XXI (250 mg), 80% hydrazine (0.25 ml), diethyleneglycol (2.5 ml), KOH (150 mg) and EtOH (1.5 ml) was heated under reflux (oil bath temperature: 120—130°) for 1.5 hr. Then a downward cooler was connected to the reaction flask, and the mixture was heated at 200—220° for additional 5 hr. After cooling, the reaction mixture was diluted with water and extracted with ether. The ether-layer was washed with water, dried, and concentrated to dryness, and the residue was recrystallized from MeOH to give XX as colorless needles (120 mg), mp 59—61°, $[\alpha]_D^{12}$ +38.7° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.33; H, 12.52. IR ν_{max}^{KBr} 3425 cm^{-1} (OH) and no C=O band. NMR δ: 0.80 (3H), 0.84 (6H), 0.89 (3H), 0.96 (3H), (all singlets, –C–CH$_3$), 1.13 (singlet 3H, HO–C–CH$_3$), 1.60, 1.66 (all singlets, 3H each, –C=C–CH$_3$) and 5.09 ppm (broad, 1H, –C=CH–).

Acid Treatment of Dammar-24-en-20 (*S*)-ol (XX)——A solution of XX (20 mg) in 5.5% H_2SO_4 (in 57% aqueous EtOH) (20 ml) was heated under reflux for 5 hr. TLC of the reaction products indicated that the main product showed the same *Rf* value, and the same color reaction with H_2SO_4 as those of the dehydration product of XX (10 mg) with $POCl_3$ (0.4 ml) in pyridine (3 ml). Treatment of XX (2 mg) with 2.5% HCl in 63% aqueous EtOH (2 ml) under reflux for 40 min or with *p*-toluenesulfonic acid (0.1 mg) in $CHCl_3$ (1 ml) at room temperature for 10 days also afforded the same result as above.

Methylation of Betulafolianetriol (VII) and the Acid Treatment of 3,12-Di-O-Methylbetulafolianetriol (XXII)——A mixture of NaH (50%, 2 g) and dimethylsufoxide (DMSO) (100 ml) was heated at 50—68° for 1 hr. To this reagent was added a solution of VII (1 g) in DMSO (70 ml) and the mixture was kept at 50—68° for 1 hr. After addition of CH_3I (10 ml) under cooling, the reaction mixture was allowed to stand at room temperature for 3 hr. After working up in the usual way, the crude product was chromatographed on silica gel to afford XXII, which was amorphous but homogeneous by thin-layer chromatography (on silica gel, solvent: EtOAc: $CHCl_3$=1:1). XXII: $[\alpha]_D^{30}$ −28.0° ($CHCl_3$), IR $\nu_{max}^{CCl_4}$: 3330 cm^{-1} (concentration independent). NMR δ: 0.83 (6H), 0.88 (3H), 0.90 (9H), 0.96 (3H) (all singlets, –C–CH$_3$), 1.07 (3H, singlet,

HO–C–CH_3), 2.76 (1H triplet-like, $\frac{1}{2}W=6$ cps, –O–$C_{(3)}$–H_{eq}), 3.25 (1H, broad, –O–$C_{(12)}$–H_{ax}), 3.28 (3H), and 3.33 ppm (3H) (all singlets, –C–OCH_3).

A solution of XXII (150 mg) in 2.5% H_2SO_4 (in 63% aqueous EtOH) (20 ml) was heated under reflux for 1.5 hr. TLC of the reaction mixture indicated the formation of the equilibrated mixture of XXII and its $C_{(20)}$ epimer (XXIII) (on silica gel, solvent: $CHCl_3$: EtOAc=6:1). Column chromatography on silica gel gave XXIII (42 mg) and XXII (25 mg). The epimer (XXIII), $[\alpha]_D^{23}$ −44° ($CHCl_3$), was amorphous but homogeneous by thin layer chromatography, IR $\nu_{max}^{CCl_4}$: 3330 cm^{-1} (concentration independent), NMR δ: 0.83 (3H), 0.89 (6H), 0.91 (3H), 0.96 (3H) (all singlets, –C–CH_3), 1.10 (3H, singlet, HO–C–CH_3), 1.62, 1.68 (all singlets, 3H each, –C=C–CH_3), 2.75 (1H, triplet-like, –O–$C_{(3)}$–H_{eq}), 3.22 (1H, broad, –O–$C_{(12)}$–H_{ax}), 3.28, 3.32 (both singlets, 3H each, –C–O–CH_3), and 5.11 ppm (1H, broad, –C=CH). Treatment of XXIII with acid under the same condition as above also afforded the same equilibrated mixture.

Methylation of Betulafolienetriol (IV) and the Acid Treatment of 3,12-Di-O-Methylbetulafolienetriol (XXIV)——IV (2 g) was methylated with NaH (4 g), DMSO (320 ml) and CH_3I (16 ml) under the same condition as that of the case of VII. Column chromatography of the crude product on silica gel gave XXIV, $[\alpha]_D^{19}$ −18.0° ($CHCl_3$), which was amorphous but homogeneous by TLC. XXIV: IR $\nu_{max}^{CCl_4}$: 3390 cm^{-1} (concentration independent), NMR δ: 0.83 (3H), 0.89 (6H), 0.91 (3H), 0.96 (3H) (all singlets, –C–CH_3), 1.10 (3H singlet, HO–C–CH_3), 1.62, 1.68 (3H each, all singlets, –C=C–CH_3), 2.75 (1H, triplet-like, –O–$C_{(13)}$–H_{eq}), 3.22 (1H, broad, –O–$C_{(12)}$–H_{ax}), 3.28, 3.32 (all singlets, 3H each, –C–OCH_3), and 5.11 ppm (1H broad, –C=CH–).

A solution of XXIV in 2.5% H_2SO_4 (in 50% aqueous EtOH) was refluxed for 2 hr. The reaction proceeded more slowly than the case of IV, and TLC of the crude reaction products indicated the presence of only the non-polar substance (probably dehydration product) and the starting material (XXIV).

XXIV (1 mg) was treated with *p*-toluenesulfonic acid (5 mg) in $CHCl_3$ (0.7 ml) at 30° for 250 hr. The reaction also proceeded more slowly than the case of IV and TLC of the crude products showed the presence of the starting material, non-polar substance (probably dehydration product), and a small amount of a compound which would be the C-20 epimer of XXIV but could not be isolated as yet.

Acknowledgement We are grateful to Tokyo Kyoiku University Forest, Nobeyama, for supplying the fresh leaves of the white birch, to the Central Analytical Laboratory for Elemental Analysis, of this Faculty IR and NMR spectra and ORD measurements, and to the Research Laboratory of Takeda Chemical Industry Co., Ltd. for the extraction of the plant materials and the measurements of mass spectra. We thank Ministry of Education and Yakurikenkyukai for grants.