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Synthesis of the Skeleton of Dammarane-Type Triterpene

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3β-Acetoxyhexakisnordammaran-20-one (V) was prepared from hydroxyhopanone (II) through IV, VI, VII, VIII, IXc and XII. Since the total synthesis of II has already been performed, the present transformation provides the total synthesis of the basic skeleton of dammarane-type triterpene.

The chemical properties of dammarane-type triterpenes have been studied[2] in relation with the investigation of *Ginseng* sapogenins.[3] In connection with these studies, the present authors have attempted the synthesis of the basic skeleton of the triterpenes of this type. The total synthesis of α-onocerin(I), a constituent of *Ononis spinosa* and *Lycopodium clavatum*, was performed by Stork and his co-workers.[4] In 1967, Tsuda and Hattori succeeded to convert I into hydroxyhopanone(II), a triterpene first isolated from dammar resin,[5] through gammaceran-3-on-21-ol(III).[6a] Hopenone-I(IV), which was derived from II by acid treatment[7] has also been prepared from I through III by Jeger, *et al.*[6b] The present paper describes the preparation of 3β-acetoxyhexakisnordammaran-20-one (V)[8] starting from hydroxyhopanone (II).

Hydroxyhopanone (II) extracted from commercial dammar resin was treated with acid to give hopenone-I (IV),[7] which was reduced with $LiAlH_4$ affording hop-17(21)-en-3β-ol (VI),[9] mp 221—224°. The acetate (VII),[9] mp 253—259°, derived from VI was ozonolyzed in methylene chloride to yield 3β-acetoxy-17,21-dioxo-E-secohopane (VIII), mp 191—193°, $[\alpha]_D^{19}$ −3.7° ($CHCl_3$), which was already prepared from IV by the different route.[7] The diketone (VIII) was reduced with $NaBH_4$ in a mixture of ethanol and methylene chloride. The reduction products, which were shown to consist of four epimeric diols, IXa, b, c and d by thin-layer chromatography, were separated by column chromatography on silica gel to give crystalline IXc, amorphous IXd, and a mixture of IXa and IXb. The diol (IXc), mp 208—210°, $[\alpha]_D^{18}$ +47.9° ($CHCl_3$), IR $\nu_{max}^{CCl_4}$: 3637, 3447 (OH), 1738 and 1242 cm^{-1} (acetoxyl), NMR δ: 2.01 (3H singlet, $OCOC\underline{H}_3$) near 3.34 (2H broad multiplet, $-C\underline{H}-OH$) and 4.47 ppm (1H triplet-like, $-C\underline{H}-OAc$), was acetylated with acetic anhydride in pyridine at room temperature to yield a triacetate (X), mp 183.5—185°, $[\alpha]_D^{21.5}$ +10.5° ($CHCl_3$), IR $\nu_{max}^{CCl_4}$: 1737 and 1239 cm^{-1} (acetoxyl) and no hydroxyl band, NMR δ: 2.00 (3H singlet, $-OCOC\underline{H}_3$), 2.02 (6H singlet, $-OCOC\underline{H}_3$), and near 4.32—4.72 ppm (3H overlapped multiplet, $-C\underline{H}-OAc$). Whereas, acetylation of

1) Location: *a) 3-chome, Izumi-cho, Narashino-shi, Chiba; b) Hongo, Bunkyo-ku, Tokyo.*
2) M. Nagai, N. Tanaka, S. Ichikawa and O. Tanaka, *Tetrahedron Letters*, **1968**, 4239; O. Tanaka, N. Tanaka, T. Ohsawa, Y. Iitaka and S. Shibata, *ibid.*, **1968**, 4235, and references cited therein.
3) Y. Iida, O. Tanaka and S. Shibata, *Tetrahedron Letters*, **1968**, 5449 and the references cited therein.
4) G. Stork, J.E. Davies and A. Meisels, *J. Am. Chem. Soc.*, **85**, 3419 (1963).
5) J.S. Mills and A.E.A. Werner, *J. Chem. Soc.*, **1955**, 3132.
6) *a)* Y. Tsuda and M. Hattori, *Chem. Pharm. Bull* (Tokyo), **15**, 1073 (1967); *b)* K. Schaffner, L. Caglioti, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **41**, 152 (1958).
7) H. Fazakerley, T.G. Halsall and E.R.H. Jones, *J. Chem. Soc.*, **1959**, 1877.
8) J.S. Mills, *J. Chem. Soc.*, **1956**, 2196.
9) H.R. Arthur, W.H. Hui, C.N. Lam and S.K. Szeto, *Aust. J. Chem.*, **17**, 697 (1964).

IXc with the same reagent at 0° for a short time gave a mixture of two diacetate, XIa and XIb along with the triacetate (X): Diacetate (XIa)—mp 253—255°, $[\alpha]_D^{17.5}$ +55.9° ($CHCl_3$), IR $\nu_{max}^{CCl_4}$: 3640 (OH), 1737 and 1242 cm^{-1} (acetoxyl), NMR δ: 2.01 and 2.02 ppm (3H each, singlets, $-OCOCH_3$), diacetate (XIb)—mp 171.5—173.5°, $[\alpha]_D^{17.5}$ +19.3° ($CHCl_3$), IR $\nu_{max}^{CCl_4}$: 3630 (OH), 1737 and 1240 cm^{-1} (acetoxyl), NMR δ: 2.02 and 2.04 ppm (3H each, singlets, $-OCOCH_3$). Although the respective assignment of the position of the unacetylated hydroxyl group (either C-17 or —21) of both diacetates XIa and XIb has not been established, the coupling feature of the NMR signal due to a proton *geminal* to a free hydroxyl group—$W_{1/2}$ 15 Hz at δ 3.18 ppm in the spectrum of XIa and $W_{1/2}$ 17.5 Hz at δ 3.32 ppm in that of XIb[10]—indicated that the configuration of 17-hydroxyl group of the original diol (IXc) should be α (equatorial).

The amorphous diol (IXd), would be the C-21 epimer of IXc, because of the similarity of its nuclear magnetic vesorance (NMR) spectrum to that of IXc. Although the separation of the diols IXa and IXb has not been achieved as yet, the NMR spectrum of the mixture of IXa and IXb showed carbinyl proton signals at δ 3.25 ($W_{1/2}$ 20 Hz) and 3.55 ppm (triplet-like, $W_{1/2}$ 6 Hz), suggesting that both the compounds are epimers at C-21 having a β (axial)-hydroxyl group at C-17.

The Wagner–Meerwein type rearrangement of carbocyclic alcohols having α-*gem*-dimethyl group has been extensively studied, especially in the field of triterpene chemistry. Recently, Just, *et al.* reported this type of the rearrangement of the alcohol having *geminal* ethyl and methyl groups at its α-position.[11] However, little has been known of the rearrangement of the alcohol having a longer alkyl chain at the α-position.

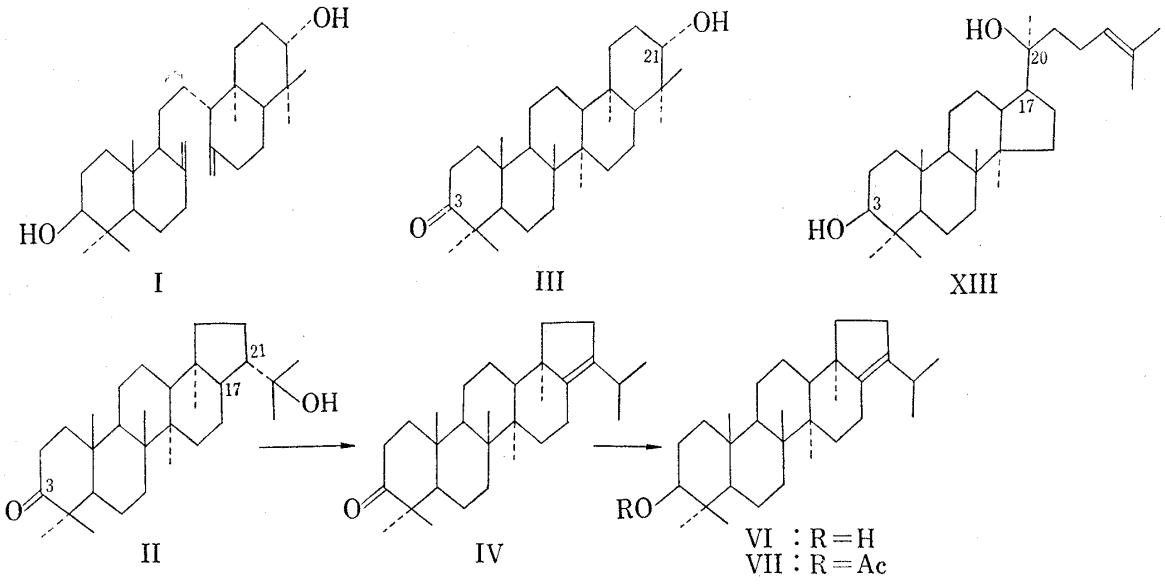
The ditosylate (XII) prepared from the diol (IXc) was treated with a mixture of dioxane and water in the presence of $CaCO_3$ under reflux for 5.5 hours,[6a,12] and the products which were shown to be a complex mixture by thin-layer chromatography, were separated into a non-polar and a polar fractions by column chromatography on neutral alumina.[13] By thin-layer chromatography on silica gel impregnated with $AgNO_3$, the non-polar fraction (IR: no OH band) was revealed to be a mixture of several substances. Owing to the difficulty of the separation of each component, this non-polar fraction was ozonolyzed without further purification, and the resulted products were separated by preparative thin-layer chromatography to give a compound, colorless needles, mp 200—203° from methanol which was identical with 3β-acetoxyhexakisnordammaran-20-one (V)[8] derived from dammarenediol-II (XIII) in every respects (mixed mp, thin-layer and gas liquid chromatography, and infrared (IR) spectrum).

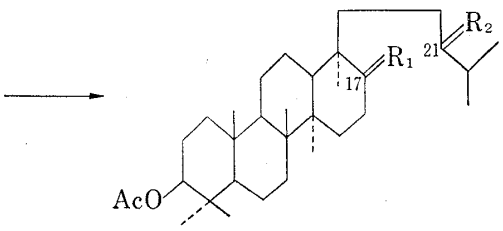
Taking the stereochemistry of Wagner–Meerwein type rearrangement into account,[12,14] the intermediate which afforded V, would be formulated as XIV having unnatural 17β-H configuration, though it has not been isolated in a pure state as yet. Ozonolysis of XIV would yield firstly a 17β-H ketone (XV) which would readily be isomerized to give the more stable 17α-H ketone (V) during the decomposition of the ozonide.

On preparative thin-layer chromatography followed by fractional recrystallization, the polar fraction of the solvolysis products, which was a mixture of the compounds with lower *Rf* values in thin-layer chromatography than non-polar fraction gave colorless prisms, mp 159—160° (XVI), IR $\nu_{max}^{CCl_4}$: 3635 (OH), 1738, 1242 cm^{-1} (acetoxyl) as one of its main components. This compound (XVI) showed NMR signals attributable to seven tertiary methyl groups at δ 0.79 (3H singlet), 0.83 (6H singlet), 0.89 (3H singlet), 1.06 (3H singlet), and

10) The signal due to a proton on a carbon atom bearing an acetoxyl function (at C-17 or -21) was partly overlapped with that of the C-3 proton in the spectra of both the diacetate XIa and XIb.
11) G. Just, N.D. Hall and K. St. C. Richardson, *Can. J. Chem.*, **45**, 2521 (1967).
12) J.F. Biellmann and G. Ourisson, *Bull. Soc. Chim. France*, **1962**, 331.
13) The solvolysis of XII under other various conditions as well as the treatment of the diol (IXc) with phosphorus pentachloride also did not afford products of simple constituents giving a number of compounds.
14) J. Levisalles and J.-P. Pete, *Bull. Soc. Chim. France*, **1968**, 2903, 2912.

1.18 ppm (6H singlet), lacking the signal of a proton on a carbon atom bearing a hydroxyl group. These spectral data indicated the presence of a function, $-C(CH_3)_2OH$, whose two methyl groups would correspond to the signal at δ 1.18 ppm (6H). The formation of this function in the side chain can be explained in term of the hydride shift from isobutyl carbonium





VIII : $R_1=O, R_2=O$

IXa or IXb : $R_1=\overset{OH}{H}<$, $R_2=sec-OH$

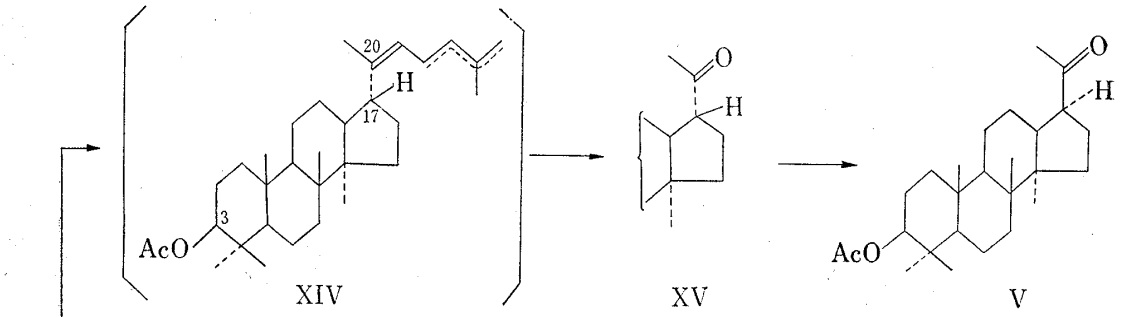
IXc or IXd : $R_1=\overset{OH}{H}<$, $R_2=sec-OH$

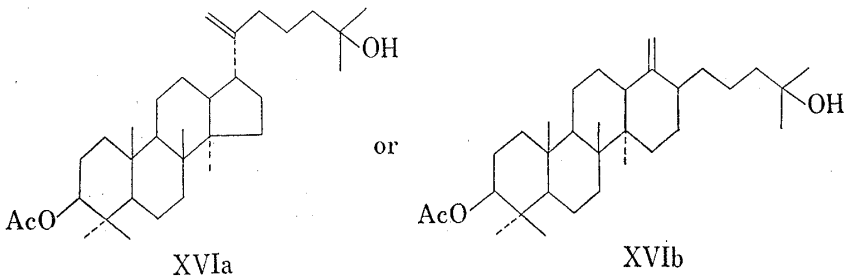
X : $R_1=\overset{OAc}{H}<$, $R_2=sec-OAc$

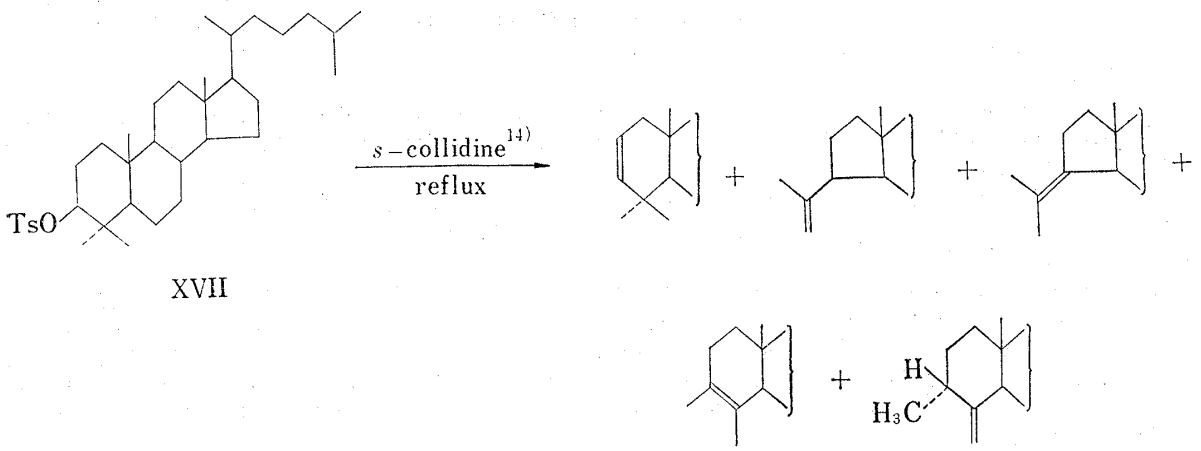
XIa or XIb : $R_1=\overset{OAc}{H}<$, $R_2=sec-OH$

or $R_1=\overset{OH}{H}<$, $R_2=sec-OAc$

XII : $R_1=\overset{OTs}{H}<$, $R_2=sec-OTs$







XVII

ion, $-HC^{\delta+}-CH(CH_3)_2$ to *tert*-butyl carbonium ion, $-CH_2-C^{\delta+}(CH_3)_2$.[15] The mass spectrum of XVI exhibited the highest peak at *m/e* 468 with fairly strong intensity (53% relative to the base peak at *m/e* 204), which would be assigned to M^+-H_2O being consistent with the formulation as $C_{30}H_{50}\cdot OOCCH_3\cdot(tert)\cdot OH$. (mol. wt. 486). The IR absorption band at 1639 and 891 cm^{-1} (in CCl_4) as well as the NMR signals at δ 4.45 (1H, broad singlet) and 4.71 ppm (1H, broad singlet) revealed the presence of a vinyl group, $>C=CH_2$ in XVI. Referring the stereochemistry of the same type of the rearrangement of the compounds such as XVII[12,14,16], these evidences led to suggest that this compound (XVI) would possibly be represented by structure XVIa or XVIb, though the further investigation could not be achieved because of the difficulty in the isolation of this compound.

Experimental[17]

3β-Acetoxyhop-17(21)-ene(VII)[9]——Hopenone-I (IV) prepared from hydroxyhopanone (II) was reduced with $LiAlH_4$ in dry ether. The reaction product, hop-17(21)-en-3β-ol (VI) (72.2 g) was acetylated with acetic anhydride (870 ml) in pyridine (2.6 liter) at room temperature for 38 hr and the crude product was crystallized from a mixture of ethanol and $CHCl_3$ to give 3β-acetoxyhop-17(21)-ene (VII) as colorless needles, mp 247—250.5° (63.4 g). Further recrystallization from ethanol raised the melting point to 253—259°; IR $\nu_{max}^{CCl_4}$ 1739 and 1240 cm^{-1}.

3β-Acetoxy-17,21-dioxo-E-secohopane(VIII)——Ozone was passed through a solution of VII (10 g) in methylene chloride (1.5 liter) under dry ice–acetone cooling for 90 min. After evaporation of the solvent at low temperature *in vacuo*, the resulted residue was treated immediately with zinc dust (100 g) in acetic acid (1.4 liter) firstly under ice cooling and then at 80—90° for 1 hr. After allowed to stand at room temperature, the reaction mixture was filtered to remove zinc dust and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ to remove insoluble substance and the $CHCl_3$ solution was washed with water, dried, and then evaporated. The crude product was purified by column chromatography on silica gel using benzene and a mixture of benzene and $CHCl_3$ (1:1) as developing solvents to give 3β-acetoxy-17,21-dioxo-E-secohopane (VIII), colorless needles, mp 191—193° (from methanol) $[\alpha]_D^{19}$ −3.7° (c=1.37, $CHCl_3$), IR $\nu_{max}^{CCl_4}$ 1738, 1713, and 1241 cm^{-1}, NMR δ 2.02 (3H singlet) and 4.45 ppm (1H, broadened quartet).

$NaBH_4$ Reduction of VIII——The diketone (VIII) (15 g) in methylene chloride (500 ml) was added to $NaBH_4$ (17.1 g) in ethanol (1.5 liter) under ice–cooling and the mixture was stirred at room temperature for 3 hr. After treatment in the usual way, the reaction products were chromatographed on silica gel using $CHCl_3$, $CHCl_3$–MeOH (100:1), (50:1), and (25:1) as developing solvents, which eluted a mixture of the diols IXa and IXb (2.34 g), the crystalline diol IXc (2.84 g), and the amorphous diol IXd (0.94 g), in this order.

15) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co. Inc., New York 1959, pp. 591—594.
16) F. Kohen, B.K. Patnaik and R. Stevenson, *J. Org. Chem.*, **29**, 2710 (1964); F. Kohen and R. Stevenson, *ibid.*, **30**, 2268 (1965); J. Levisalles and J.-P. Pete, *Bull. Soc. Chim. France*, **1967**, 3747.
17) All melting points were determined on a Kopfler–type hot stage and uncorrected. The NMR spectra were obtained for $CDCl_3$ solution with TMS as internal standard at 100 Mc.

The diol IXc was recrystallized from EtOH as colorless needles (1.98 g), mp 208—210°, $[\alpha]_D^{18}$ +47.9° (c=1.92, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{56}O_4 \cdot C_2H_5OH$: C, 74.13; H, 11.35. Found: C, 74.42; H, 11.06. (molecular weight: Calcd., 504.7. Found by mass spectrometry, M^+ 504). IR $\nu_{max}^{CCl_4}$ 3637, 3447, 1738, and 1242 cm^{-1}.

The diol (IXd) was obtained in a semicrystalline state (0.74 g) on attempted crystallization from ethanol; IR $\nu_{max}^{CCl_4}$ 3622, 3402, 1738, and 1238 cm^{-1}. NMR (δ ppm) 2.03 (3H singlet), near 3.30 (2H broad multiplet), 4.47 (1H triplet-like).

A mixture of the diols IXa and IXb showed the IR bands at 3632, 3462, 1736, 1240 cm^{-1} in CCl_4 and NMR signals at δ 1.99 and 2.01 (singlets, $-OCOCH_3$), near 3.25 (1H broad multiplet W½ 20 Hz) and 3.55 ppm (1H triplet-like, W½ 6 Hz).

Complete Acetylation of the Diol (IXc)——A solution of IXc (100 mg) in acetic anhydride (0.5 ml) and pyridine (1 ml) was allowed to stand at room temperature overnight. After working up in the usual way, the triacetate (X) was obtained as colorless leaflets (83 mg) from EtOH, mp 183.5—185°, $[\alpha]_D^{21.5}$ +10.5° (c=1.52, $CHCl_3$), IR $\nu_{max}^{CCl_4}$ 1737, 1239 cm^{-1} and no OH band. NMR (δ ppm) 2.00 (3H singlet), 2.02 (6H singlet), near 4.72—4.32 (3H broad multiplet). *Anal.* Calcd. for $C_{36}H_{60}O_6$: C, 73.43; H, 10.27. Found: C, 73.46; H, 10.17.

Partial Acetylation of the Diol (IXc)——The diol (IXc) (500 mg) was acetylated with acetic anhydride (2.0 ml) and pyridine (4.0 ml) at 0° for 1 hr. The crude product was chromatographed on neutral alumina using n-hexane-$CHCl_3$ (5:1), (2:1), $CHCl_3$, $CHCl_3$–MeOH (30:1) as developing solvents to elute the triacetate (X) (88 mg), a mixture of the diacetate XIa and XIb (230 mg), and finally the starting material (IXc) (128 mg). The mixture of the diacetate XIa and XIb was further separated by preparative thin-layer chromatography on silica gel (solvent: $CHCl_3$) to give XIa (50 mg) and XIb (150 mg).

The diacetate (XIa) was recrystallized from EtOH as colorless needles, mp 253—255°, $[\alpha]_D^{17.5}$ +55.9° (c=0.72, $CHCl_3$). *Anal.* Calcd. for $C_{34}H_{58}O_5$: C, 74.68; H, 10.69. Found: C, 74.78; H, 10.61.

The diacetate (XIb) was recrystallized from MeOH as colorless needles, mp 171.5—173.5°, $[\alpha]_D^{17.5}$ +19.3° (c=1.04, $CHCl_3$). *Anal.* Calcd. for $C_{34}H_{58}O_5$: C, 74.68; H, 10.69. Found: C, 74.52; H, 10.59.

Solvolysis of the Ditosylate (XII) of the Diol (IXc)——A solution of the diol (IXc) (2.1 g) and p-toluenesulfonyl chloride (11.3 g) in pyridine (40 ml) was allowed to stand at room temperature for 20 hr. Treatment of the reaction mixture as usual yielded the ditosylate (XII), IR $\nu_{max}^{CCl_4}$: 1736, 1240 cm^{-1}, no OH band: NMR (δ ppm): 2.02 (3H singlet, $-OCOCH_3$), 2.41 (6H singlet, methyls of tosyl groups), 4.10—4.55 (3H broad multiplet, $-C\underline{H}-OTs$ and-$C\underline{H}-OAc$), 7.23 and 7.71 (4H each, broad doublets, J=8 Hz, aromatic protons of tosyl groups), which was homogeneous by thin-layer chromatography and was subjected to solvolysis without recrystallization. The all of the resulted tosylate (XII) was refluxed in a mixture of dioxane (450 ml) and water (450 ml) under reflux in the presence of $CaCO_3$ (2.52 g) for 5.5 hr. After evaporation of the solvent to dryness *in vacuo*, the residue was shaken with a mixture of ether (300 ml), acetic acid (25 ml), and water (200 ml). The water layer was extracted with ether and the ether extract was combined with the original ether layer. The resulted ether solution was washed with firstly 1N $NaHCO_3$ (250 ml), and then water several times, dried, and evaporated to dryness to give a pale yellow residue, which showed several spots on thin-layer chromatography on silica gel (solvent: $CHCl_3$). This residue was subjected to column chromatography on neutral alumina using n-hexane, n-hexane–benzene (20:1), (5:1), and (1:1), benzene, benzene–$CHCl_3$ (15:1), (5:1), (1:1), and $CHCl_3$ as developing solvents to be separated to the non-polar and polar substances. The non-polar substances (460 mg), IR in CCl_4: no OH absorption, showed a single spot with a higher Rf value by the thin-layer chromatography on ordinary silica gel (solvent: $CHCl_3$), while gave several spots by thin-layer chromatography on silica gel impregnated with silver nitrate (solvent: benzene or benzene–$CHCl_3$ (5:1)). This non-polar fraction was subjected to ozone degradation without further separation as described below.

The preparative thin-layer chromatography of the polar substance (970 mg) on silica gel (solvent: $CHCl_3$) and the subsequent fractional recrystallization of the major fraction from MeOH and a mixture of EtOH and MeOH (1:2) afforded the compound (XVI) (5 mg) which was homogeneous even by the thin-layer chromatography on silica gel impregnated with silver nitrate (solvent: n-hexane: ether (3:1)). The compound (XVI), colorless prisms, mp 159—160° showed a OH band at 3635 cm^{-1}, acetoxyl bands at 1738 and 1242 cm^{-1}, and vinyl bands at 1639 and 891 cm^{-1} in its IR spectrum in CCl_4.

Another crystalline compound (2.4 mg), mp 133—134°, Mass Spectrum: M^+ 486 corresponding to the molecular formular $C_{32}H_{54}O_3$. Further examination of this compound could not be achieved owing to the shortage of the material.

Ozone Degradation of the Non-polar Fraction of the Solvolysis——A solution of the non-polar fraction mentioned above (50 mg) in methylene chloride (20 ml) was treated by stream of ozone under dry ice–acetone cooling for 30 min. The reaction mixture was concentrated *in vacuo* below 30° and the residue was decomposed with zinc dust (1.0 g) and acetic acid (3.0 ml) in the same way as the preparation of VIII from VII. The products, being a mixture of several compounds was separated by preparative thin-layer chromatography on silica gel (solvent: $CHCl_3$) gave a few mg of a crystalline compound, colorless needles, mp 200—203°, from methanol, which was proved to be identical with the authentic sample of 3β-acetoxy-

hexakisnordammaran-20-one (V)[8] prepared from dammarenediol-II (XIII) by mixed melting point, comparisons of thin-layer (solvent: $CHCl_3$) and gas liquid[18] chromatograms, and infrared spectra (CCl_4).

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Added in Proof (July 6, 1970) After this paper was submitted, the intermediate (XV) has been isolated in a small guantity from the ozone degradation products along with V. This compound (XV), colourless prisms (from MeOH), mp 194—198°, IR $\nu_{max}^{CCl_4}$: 1739, 1243 (acetoxyl) and 1713 cm^{-1} (C=O), Mass Spectrum M^+ 402, showed an ORD curve with negative Cotton effect ($[\alpha]_{589}$ −1.6°, $[\alpha]_{291}$ −464.9°, $[\alpha]_{269}$ 0°, $[\alpha]_{254}$ +122.3° in MeOH) anb was converted to V by heating with acetic acid at 90—93° for 3 hr.

18) Condition: 1.5% SE-30 on chromosorb W (AW), column temperature 269°, Carrier gas-N_2 (30 ml/min); relative retention time of V to cholestane was 1.62.