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Tritepenoid Chemistry. VII.[1] Classification of Triterpenoid 1,3-Glycol Acetonides by NMR Spectra[2]

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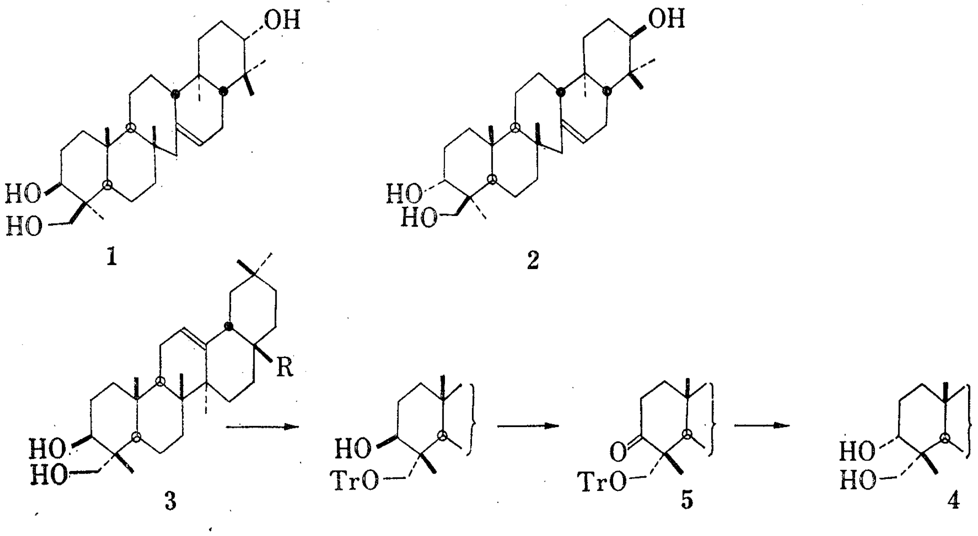
Triterpenoid glycols carrying hydroxy-groups at C_3 and at one of 4,4-dimethyl groups were converted to the corresponding acetonides (**A–D**), whose characterization by nuclear magnetic resonance spectroscopy were discussed in connection with their stereochemical properties, and a reliable method to determine their stereochemistry was presented. The stabilities of these acetonides to hydrolytic cleavage were also discussed. The conformation of the monoacetonide (**16**) derived from platicodigenin was suggested to be as **16b**.

The 1,3-glycol system carrying hydroxy-groups at C_3 and one of 4,4-dimethyl group is frequently occurring in natural triterpenoids. For determination of their configurations, nuclear magnetic resonance (NMR) spectroscopy of their acetate is well used method which gives reliable informations in most cases. However the method is not always promising, particularly for heavily substituted compounds reliability is considerably reduced, since firstly we sometimes meet troubles to select the desired signals from others appeared in the same region due to the presence of extra acetoxy-groups, and since secondarily conformation



3a : R=COOMe
3b : R=CH_2OH
3c : R=CH_2OAc

Chart 1

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[1] Part VI: Y. Tsuda, T. Sano, A. Morimoto, M. Hatanaka, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), 22, 2383 (1974).

[2] A part of this work was presented at the 14th Symposium on the Chemistry of Natural Products, Fukuoka, Oct. 1970.

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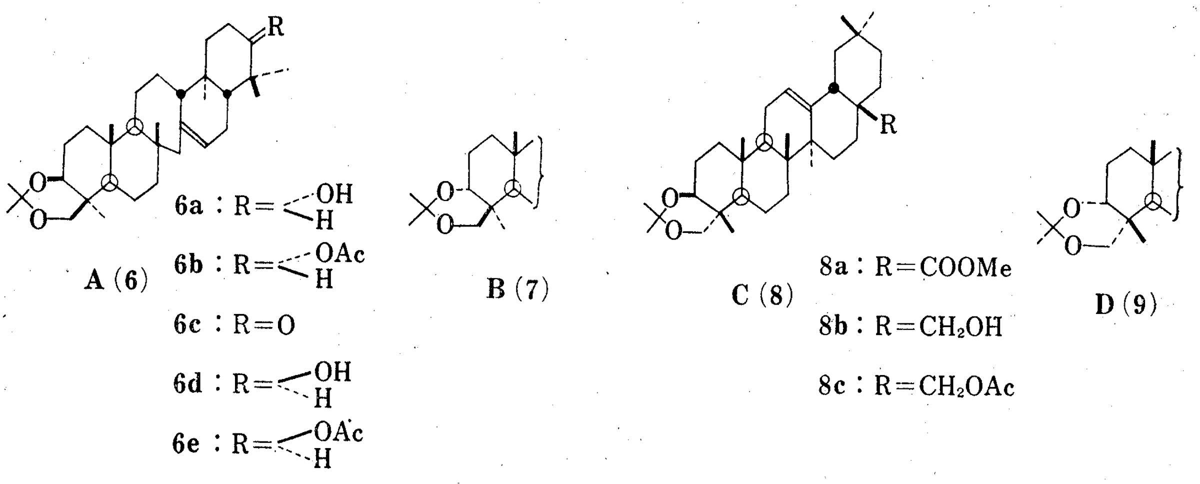


Chart 2

TABLE I. NMR Spectra of Acetonides (60 MHz)

Type	Comp.	O–CMe$_2$–O	–C$_4$–CH$_2$–O–	C$_3$–H	C–Me	>CH–OR (R=H or OAc)	COOMe or C$_{28}$–H
A	(**6a**)	1.38 1.45	3.16d. 3.95d. J=12[a]	3.38[b] (m)	0.70(1), 0.87(2), 0.98(1), 1.09(1), 1.17(1)	3.38[b] (m)	—
	(**6b**)	1.35 1.40	3.20d. 3.98d. J=12	3.45(m)	0.68(1), 0.83(2), 0.91(1), 1.05(1), 1.13(1)	4.50(m)	—
	(**6c**)	1.36 1.41	3.16d. 3.96d. J=13	3.56(m)	0.85(1), 0.93(1), 1.06(1), 1.09(2), 1.15(1)	—	—
	(**6d**)	1.37 1.41	3.15d. 3.97d. J=12	3.45[b] (m)	0.70(1), 0.87(1), 0.89(1), 0.95(1), 1.08(1), 1.17(1)	3.45[b] (m)	—
B	(**7d**)	1.48(2)	3.72 ABq J=10, δ_{AB}=18[a]	4.40 (t, J=8.5)	0.71(1), 0.84(1), 0.90(1), 0.96(1), 1.04(1), 1.16(1)	3.50(bs)	—
	(**7e**)	1.43(2)	3.67 ABq J=11, δ_{AB}=21	4.43 (t, J=9)	0.70(1), 0.87(2), 0.96(1), 1.04(1), 1.14(1)	4.66(bs)	—
	(**7a**)	1.40(2)	3.67 ABq J=11, δ_{AB}=23	4.42 (t, J=8.5)	0.68(1), 0.80(2), 0.95(1), 1.05(1), 1.11(1)	3.19(m)	—
C	(**8a**)	1.42 1.43	3.5[b] (bs)	3.6[b]	0.72(1), 0.92(2), 0.95(1), 1.05(1), 1.15(1)	—	3.63
	(**8b**)	1.42 1.43	3.61[b] (bs)	3.6[b]	0.90(2), 0.93(1), 0.98(1), 1.05(1), 1.19(1)	—	3.38 ABq J=12, δ_{AB}=22
	(**8c**)	1.45 1.46	3.5[b] (bs)	3.6[b]	0.90(2), 0.95(1), 1.00(1), 1.07(1), 1.20(1)	—	3.84 ABq J=12, δ_{AB}=21
	(**15**)	1.42(2)	3.48(bs)	3.53 (d, J=4)	0.71(1), 0.91(1), 0.97(1), 1.15(1), 1.25(1), 1.28(1)	5.13[c] (bs-m) 5.66[d]	3.63
D	(**9a**)	1.38(2)	3.43 ABq J=13, δ_{AB}=27	3.6[b]	0.70(1), 0.73(1), 0.89(1), 0.93(2), 1.18(1)	—	3.63[b]
	(**9b**)	1.40(2)	3.47 ABq J=12, δ_{AB}=29	3.62(bs)	0.70(1), 0.88(2), 0.96(2), 1.23(1)	—	3.39 ABq J=11, δ_{AB}=22.5
	(**9c**)	1.39(2)	3.47 ABq J=12, δ_{AB}=28	3.60(bs)	0.70(1), 0.88(2), 0.97(2), 1.22(1)	—	3.88 ABq J=11, δ_{AB}=22

[a] J and δ_{AB} are given in Hz. [b] The signal was overlapped. [c] C$_2$–H [d] C$_{16}$–H

of the terminal ring which carries the above substituents is fairly labile and may be altered by a little change of substitution patterns, thus increasing the probability of misassignment.

Introduction of O,O-isopropylidene group between the above glycol removes these difficulties; the acetonide fixes ring A more rigid and protons concerning on *m*-dioxane ring appear usually in the separated region from geminal protons to acetoxy-group when the product is acetylated, so the procedure makes more easy to solve stereochemical problems and informations obtained will be more reliable. These acetonides are classified into following four types (**A**—**D**) depending on the stereochemistry of the starting glycols (see Chart 3). Serratriol (**1**) and lycoclavanol (**2**) provide the acetonides of type **A** and of type **B** respectively, only when the forced condition (heating with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in dimethylformamide (DMF)[1] were applied. Methyl hedragenate (**3a**) and methyl 3-epihederagenate (**4a**) formed acetonides of type **C** and of type **D** respectively by conventional method (acetone and *p*-toluenesulfonic acid). Methyl 3-epihederagenate (**4a**), in turn was prepared from the keto-tritylate (**5**) by hydrogenation under high pressure over Raney Ni, followed by chromatographic separation from accompanying equatorial isomer (**3a**).

For these acetonides the signals attributed to two isopropylidene methyls and to protons concerning on *m*-dioxane ring were assigned and listed in Table I.

Discussion

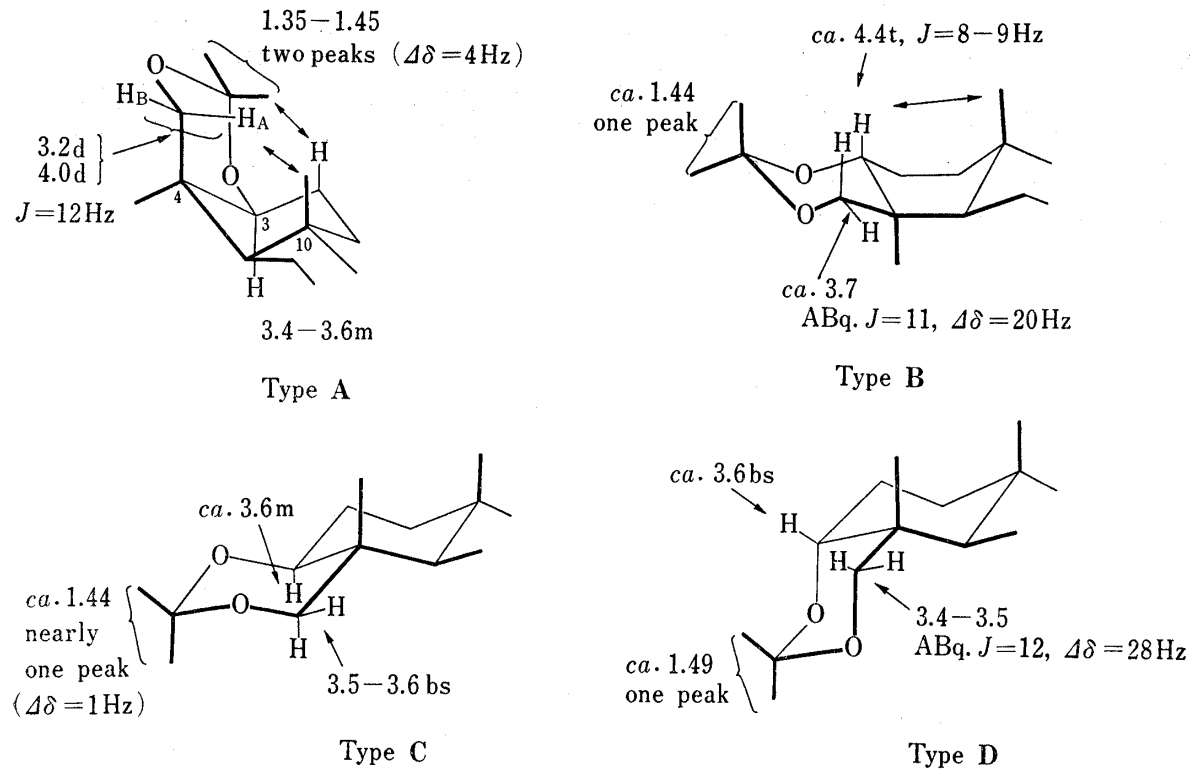
The type **A** acetonide will have *cis*-decalin conformation, in which there are serious interaction between one of the isopropylidene methyls and 2β-H, and an 1,3-diaxial interaction between 24β-H and 10-Me. Therefore, this type of acetonide showed following characteristic features. i) The methyl peaks of isopropylidene group appear as separated signals. The difference of chemical shifts is not large but appreciable (*ca.*4 Hz) when compared to those of the other three. ii) Two hydrogens at C_{24} (H_A, H_B) show the considerable difference (Δ=0.8 ppm) in chemical shifts and appear as two doublets (at δ=3.2 and 4.0, J=12—13 Hz). iii) C_3-H appeared as a multiplet of $W_{1/2}$=15 Hz indicating that it is in axial orientation.

In type **B** acetonide, ring A is forced to adopt a boat form where 3β-H has changed to axial orientation. In accord with this, the signal of C_3-hydrogen appeared as a clean triplet (J_1=J_2=8—9 Hz), in contrast to a broad singlet ($W_{1/2}$=5 Hz) of the original acetate.[1] This hydrogen was strongly deshielded (δ=4.4) when being compared to the corresponding hydrogen in the others (δ=3.4—3.6 ppm). This deshielding is probably due to the serious interaction to this hydrogen by 10-Me. The isopropylidene methyls appeared as one peak, and protons at C_{24} exhibited an AB quartet ($\Delta\delta$=18—23 Hz, J=10—11 Hz).

The acetonide of type **C** has *trans*-decalin and that of type **D** has *cis*-decalin conformation. Both of them have no such serious interaction as those in acetonides of type **A** and of type **B**. Two isopropylidne methyls appeared as one peak or showed slight separation. The C_3- and C_{23}-hydrogens appeared in normal region (δ 3.5—3.6). Distinction between these acetonides is as follows. The 3-H of type **C** has an axial orientation, the signal of which appeared as a multiplet, while that of type **D**, equatorial to ring **A**, appeared as a broad singlet. Moreover the signals due to the C_{23}-hydrogens in type **C** appeared as a broad singlet. On the other hand the C_{23}-hydrogens of the type **D** gave a clean AB quartet ($\Delta\delta$=28 Hz, J=12 Hz).

For the signals discussed here we propose the name "type classification signals". The above results are picturized in Chart 3.

Of four types of acetonide there are significant differences in their stabilities to hydrolysis. Acetonides of type **A** and type **B** were much more labile than those of type **C** and type **D**. This difference is obviously attributable to the non-bonded interactions in type A and in type **B**. Actually these were hydrolysed even under mild condition such as Jones' oxidation, whereas the others were unaffected under the same condition. Thus serratriol acetonide (**6a**) and lycoclavanol acetonide (**7d**) were smoothly oxidized by Jones' procedure to the same trioxo-



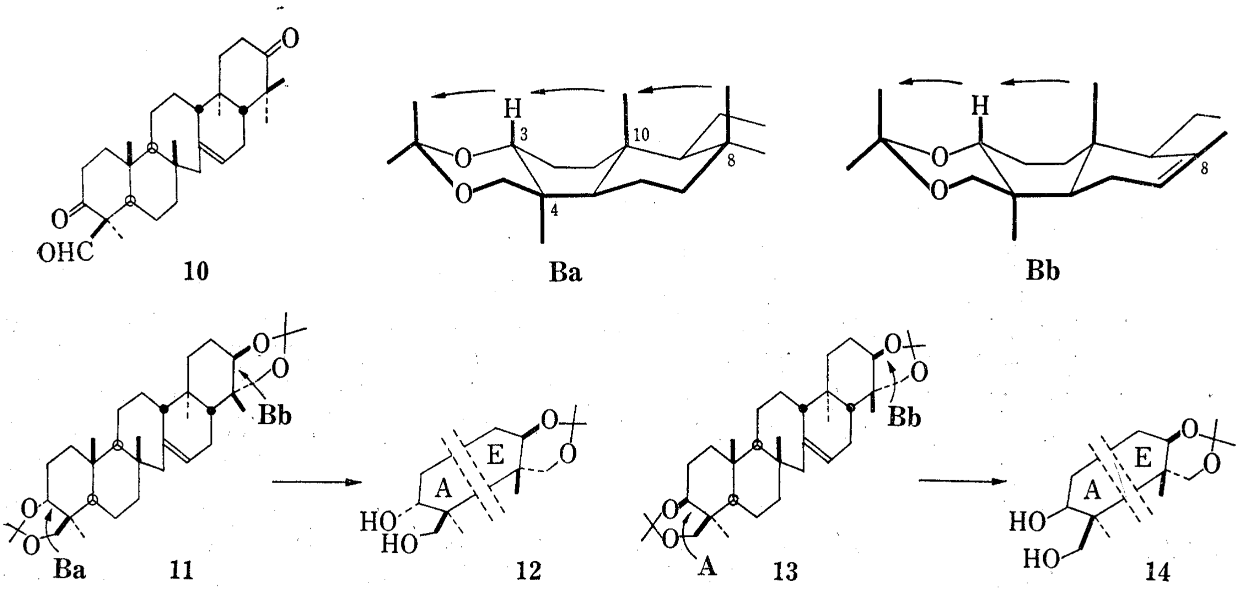
Type **A**

Type **B**

Type **C**

Type **D**

Chart 3



10

Ba

Bb

11

12

13

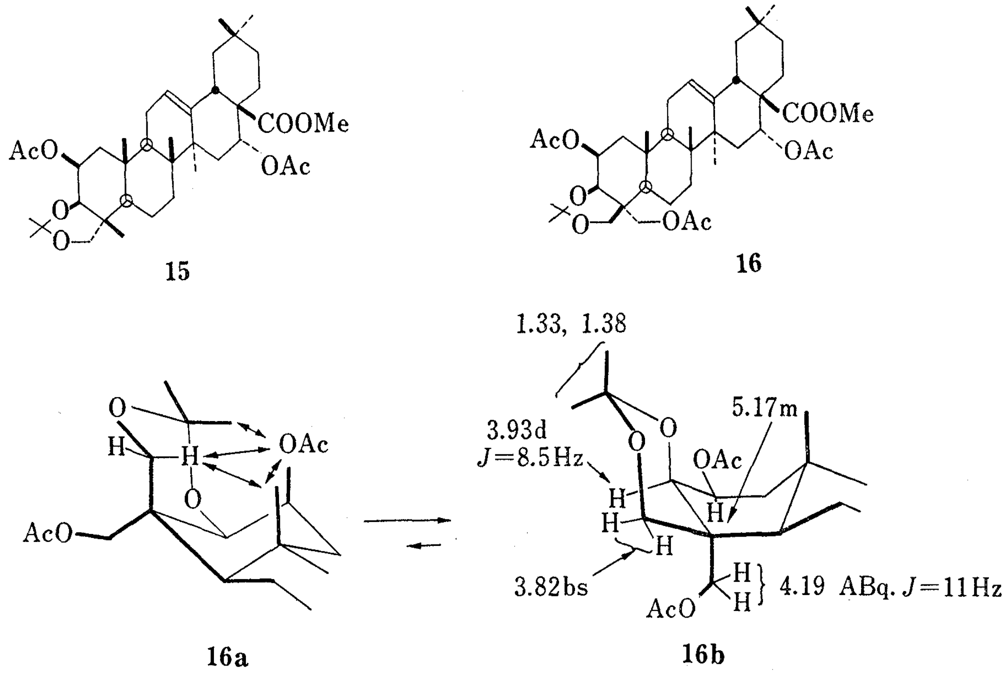
14

Chart 4

compound (**10**) respectively, providing a method of direct correlation of serratriol and lycoclavanol. [Direct Jones' oxidation of **1** and **2** gave a number of products as shown by thin-layer chromatography (TLC)].

In earlier paper[1] it was suggested that acetonide of type **B** are more vulnerable than that of type **A**, the bow-stern interaction in the boat conformation of ring A being the major factor of this destabilization. We must, however, emphasize the role of another factor, transmission of the steric compression due to C_8-Me. In fact, removal of C_8-Me from type **B** acetonide (**Ba**→**Bb**) markedly increased its stability. Thus acetonide of type **Bb** becomes more stable than that of type **Ba** and also than that of type **A** which carries C_8-Me group, since similar relation can be expected to hold for type **A** acetonide. For example, the diacetonide (**11**) can be selectively hydrolysed to the mono-acetonide (**12**), and (**13**) was hydrolysed to (**14**).[4] The stability of these acetonides are therefore the following order: **C**—**D**$\gg$**Bb**>**A**>**Ba**.

Addition of 2β-acetoxy group to type **C** acetonide (*trans*-decalin conformation) does not cause any appreciable change in its conformation, though the new group produces two additional 1,3-diaxial interactions. The NMR spectrum[5] (Table I) of polygalacic acid derivative (**15**)[6] is in good agreement with that of proposed for type **C**.



15 **16**

16a **16b**

Chart 5

On the other hand if 2β-acetoxy group is introduced to type A acetonide, serious interaction between one of acetonide methyls and 2β-OAc in addition to 1,3-diaxial interactions between 2β-OAc and C_{10}-Me and 24β-H will be created; the fact will cause the conformational change in ring A into boat form as to minimize the above interactions since the compound has labile *cis*-decalin structure. The example is seen in a monoacetonide (**16**)[7] derived from platicodigenin. The observed spectrum[5] agreed with neither of type **A** of the conformation **16a** nor an alternative structure of type **C**, but is well explained by **16b**. i) Two isopropylidene methyls appeared as two peaks with separation of 3 Hz; which suggests type **A**. On the contrary, H_A and H_B appeared as a broad singlet as in type **C**. But they were deshielded (δ 3.82) than those of type **C** (δ 3.5—3.6) and rather close to those of type **C** (δ 3.9—4.0). ii) Larger coupling constant (8.5 Hz) of 3α-H than that of the corresponding acetate (4 Hz) indicated the conformational change at ring A. Down-field shift (δ 3.93) of this proton from that of type **A** and of type **C** (δ 3.4—3.6) suggests the boat-form character of ring A as that in type **B**. iii) 2α-H appeared as a doublet of multiplets, the largest coupling constant (12 Hz) suggesting that one of the neighbouring proton is almost eclipsed to this proton.

Examples of practical application of the method described in this paper will be presented in forthcomming papers.

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4) Details of experiment will be presented in the subsequent paper in connection with the structural study of the original tetra-ols, diepilycocryptol and 21-epilycocryptol.

5) The NMR spectra of these compounds were provided by late Dr. T. Kubota, Shionogi Research Laboratory, to whom we cordially express our gratitude.

6) T. Kubota and H. Kitatani, *Chem. Comm.*, **1968**, 1005.

7) T. Kubota and H. Kitatani, *Chem. Comm.*, **1969**, 190.

Experimental

Unless otherwise stated mp's were determined on a Yanagimoto mp apparatus and uncorrected. NMR spectra were measured in $CDCl_3$ referred to internal TMS by using 60 MHz machine, and IR spectra were taken on Nujol mull.

The Compounds 6a—6d, 7a, 7d, and 7e——For preparation of these compounds see ref. 1).

Methyl Hederagenate Acetonide (**8a**)——Methyl hederagenate **3a** (5.0 g) and TsOH (250 mg) in 2,2-dimethoxypropane (50 ml) and DMF (50 ml) were gently heated under reflux for 1 hr. The mixture was poured into 5% K_2CO_3 solution (200 ml) and the resulting ppt. was collected (4.8 g), and washed twice with a small amount of cold MeOH. Crystallization from MeOH gave **8a**, mp 257—260°, identical with the compound (mp 250—252°)[8] obtained by a conventional method.

3β,23,28-Trihydroxyoleanene (**3b**)——This was obtained by lithium aluminum hydride (LAH) reduction of **3a**, and had mp 261—264° (from $CHCl_3$–MeOH). *Anal.* Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.40; H, 10.78.

3β,23,28-Trihydroxyoleanene Acetonide (**8b**)——The compound **3b** (5 g) and TsOH (500 mg) in acetone (150 ml) were heated under reflux for 4 hr. The mixture was neutralized with solid $NaHCO_3$ and the solvent was removed *in vacuo*. The residue was extracted with $CHCl_3$ which was washed with water, dried over $MgSO_4$, and evaporated to give an oil (5.2 g). Chromatography of the oil over neutral alumina and elution with benzene gave **8b** (4 g) (needles from $CHCl_3$–MeOH), mp 215—217°. IR: 3640 cm^{-1}. *Anal.* Calcd. for $C_{33}H_{54}O_3$: C, 79.46; H, 10.92. Found: C, 79.44; H, 10.76.

Acetylation of **8b** (3.63 g) with pyridine (15 ml) and Ac_2O (7 ml) and chromatography of the product in benzene through a short column of neutral alumina gave the corresponding acetate (**8c**) as an amorphous powder. IR: 1740 and 1225 cm^{-1}.

3-Keto-23-trityl Compound (**5**)——Methyl hederagenate **3a** (4.5 g) and trityl chloride (4.5 g) in pyridine (45 ml) were heated on a water bath for 21 hr. After removal of pyridine *in vacuo*, the residue was extracted with ether which was washed with water and dried over $MgSO_4$. Evaporation of the solvent left an oil (7.0 g) which was then treated in acetone (500 ml) with Jones' reagent (5 ml) at 0° for 5 min. The mixture was diluted with water and extracted with methylene chloride. The organic extract was washed with water, dried over $MgSO_4$, and evaporated. The product on chromatography over alumina gave **5** (5.78 g) (plates from ether), mp 255—257°. IR: 1730 and 1700 cm^{-1}. NMR: δ 0.76 (3H), 0.81 (3H), 0.95 (6H), 0.98 (3H), 1.15 (3H), 2.60 (1H, d. $J=9$ Hz), 3.45 (1H, d. $J=9$ Hz), 3.63 (3H), 5.36 (1H, m), 7.33 (15H, m).

Methyl 3-Epihederagenate (**4a**)——The compound **5** (1.0 g) in dioxane (50 ml) was hydrogenated over Raney Ni (1 g) under 70 atm/cm^2 at 150° for 7 hr. After removal of the catalyst and the solvent the residue was chromatographed over alumina. i) Elution with benzene (500 ml) gave **4a** (150 mg) (prisms from *n*-hexane–ether), mp 222—224°. IR: 1735 cm^{-1}. NMR: δ 0.70 (3H), 0.74 (3H), 0.96 (9H), 1.16 (3H), 3.47 (2H, bs), 3.63 (3H), 5.30 (1H, m). ii) Elution with benzene–CH_2Cl_2 (10: 1) (100 ml) gave a mixture. iii) Elution with CH_2Cl_2 (200 ml) gave **3a** (450 mg), mp and mixed mp 261—264°. The diacetate of **4a** had mp 171—173° (needles from ether).

Methyl 3-Epihederagenate Acetonide (**9a**)——The compound **4a** (300 mg) and TsOH (50 mg) in dry acetone (50 ml) and 2,2-dimethoxypropane (5 ml) were heated under reflux for 3 hr. The mixture was poured into 5% Na_2CO_3 and extracted with ether which was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave **9a** (plates from *n*-hexane–ether), mp 166—171°, in quantitative yield. IR (KBr): 1730 cm^{-1}. The same compound was also obtained by a conventional method.

3α,23,28-Trihydroxyoleanene Acetonide (**9b**)——The compound **9a** (150 mg) and LAH (70 mg) in THF (30 ml) were heated under reflux for 3 hr. After decomposition of excess hydride with saturated sodium sulfate solution, the mixture was filtered and the ppt. was washed with ether. The combined ethereal filtrate was dried over $MgSO_4$ and evaporated to give **9b** as a colorless oil.

Acetylation of **9b** with pyridine (10 ml) and Ac_2O (5 ml) gave the corresponding acetate (**9c**) as a colorless oil.

3,21,24-Trioxoserrat-14-ene (**10**)——i) Serratriol acetonide **6a** (20 mg) in acetone (40 ml) was treated with Jones' reagent (five drops) at 0° for 5 min. The mixture was poured into ice-water and extracted with ether which was washed with water, dried over $MgSO_4$, and evaporated. Chromatography of the residue in benzene over alumina gave **10** (prisms from *n*-hexane), mp 195—198°. IR (KBr): 2725, 1729, 1713 cm^{-1}.

ii) Lycoclavanol acetonide **7d** (20 mg) was oxidized as above. Crystallization of the product from *n*-hexane gave prisms, mp 193—198°, which was identical with **10** by comparison of IR, TLC, and mp.

Hydride Reduction of 10——Trioxo-compound **10** (10 mg) in MeOH (5 ml) was reduced with $NaBH_4$ (10 mg) to give an alcohol (**1**), which was acetylated in Ac_2O (3 ml) and pyridine (6 ml) at room temp. for 12 hr. Crystallization of the product gave needles, mp 245—247°, which was identical with serratriol triacetate[1] as confirmed by comparisons of IR, TLC, and mp.

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[8] J. Simonsen and W.C.J. Ross, "The Terpenes," Vol. 5, Cambridge University Press, 1957, p. 174.