A Photochemical Reaction of Lupan-3-one

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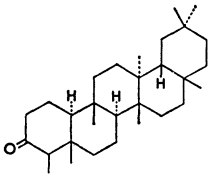
Lupan-3-one (**5**) was irradiated in *n*-hexane under an argon atmosphere using a high pressure mercury lamp. Besides three seco compounds, namely 10α-(2-formylethyl)-5β-isopropenyl-des-A-lupane (**6**), 10α-(2-carboxyethyl)-5β-isopropyl-des-A-lupane (**8**), and 10α-(2-carboxyethyl)-5β-isopropenyl-des-A-lupane (**9**), two seco-nor compounds, 10α-(carboxymethyl)-5β-isopropyl-des-A-lupane (**7**) and lactone of 10α-(carboxymethyl)-5α-hydroxy-5β-isopropyl-des-A-lupane (**10**), have been isolated and their structures have been determined. NMR signals of **10** were examined using Eu(fod)$_3$-d_{27} as a shift reagent.

In previous papers[1] we reported the photochemical reaction of friedelin (**1**), in which seco-nor products such as 5α-ethyl-10β-(formylmethyl)-des-A-friedelane (**2**) and 10β-(carboxymethyl)-5α-ethyl-des-A-friedelane (**3**) were obtained as abnormal products together with a normal product, 10β-(2-carboxyethyl)-5α-ethyl-des-A-friedelane (**4**). In connection with this observation, a formation of seco-nor derivatives was examined in a photo-reaction of lupan-3-one (**5**), bearing a 3-oxo-4,4-dimethyl moiety in the A ring. We wish to describe the isolation and structure determination of compounds (**6**—**10**) which were obtained by the photolysis of lupan-3-one (**5**) in *n*-hexane. Among these products, the seco-acid (**8**) had been obtained in about 50% yield by the photolysis of **5** in a mixture of water and acetic acid.[2]



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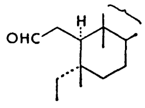

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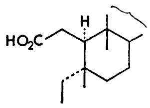

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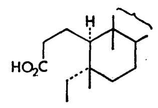

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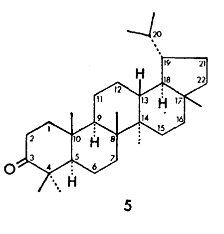

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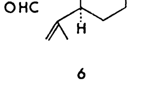

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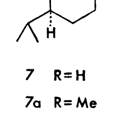

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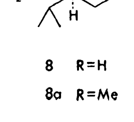
7a R=Me



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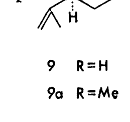

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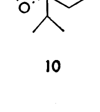

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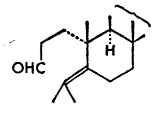
A solution of lupan-3-one (**5**) in *n*-hexane was irradiated at room temperature under an argon atmosphere for about 6.5 hr using a 100 W high pressure mercury lamp to give a complex reaction mixture, which was separated by silica gel column and thin layer chromatographies into hydrocarbon, aldehyde, ketone, lactone, and acid fractions.

From the aldehyde fraction, only one compound, $C_{30}H_{50}O$ (M^+ *m/e* 426) was isolated. This substance showed the presence of one olefinic methyl (δ 1.72), two olefinic protons (δ 4.65 and 4.85, each multiplet) and an aldehydic proton (δ 9.75, t, $J=2$ Hz) in NMR spectrum and exhibited characteristic IR absorption bands at 2720, 1735 (–CHO), 1640 and 895 cm^{-1} (–C=CH$_2$). Thus, the aldehyde was inferred to be 10α-(2-formylethyl)-5β-isopropenyl-des-A-lupane (**6**) and the structure was also supported by the fragmentation pattern of the mass spectrum.

The isolation of an unsaturated aldehyde with an isopropenyl group rather than an isopropylidene group in the photolysis of lupan-3-one (**5**) is unexpected. Since the well-documented photo-cleavage of cyclohexanones leads to a δ-unsaturated aldehyde by α-cleavage followed by transfer of a hydrogen atom from a δ-carbon (C-5 in the case of lupan-3-one (**5**)) *via* a six-membered ring transition state (reaction pathway "a"), the resulting unsaturated aldehyde from lupan-3-one (**5**) should be 10α-(2-formylethyl)-5-isopropylidene-des-A-lupane (**11**). The formation of the unsaturated aldehyde (**6**) with an isopropenyl moiety could be explained by α-cleavage of **5** followed by an abstraction of a hydrogen atom of $C_{(4)}$–CH_3 by the acyl radical through an eight-membered ring transition state (reaction pathway "b").[3] Although the occurrence of the reaction pathway "a" seems to be more likely than that of the path "b" in lupan-3-one (**5**), the aldehyde (**11**) was not obtained in the photolysate. However, the absence of the aldehyde (**11**) does not always mean that the path "a" did not occur at all,



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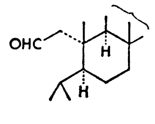

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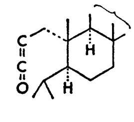

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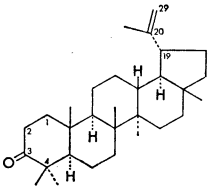
because the aldehyde (**11**) could further react photochemically or thermally.

The ketone fraction was shown to be lupan-3-one (**5**) and the recovery was about 12%.

The carboxylic acid fraction showed three spots on tlc. A compound with the highest R_f value had molecular formula $C_{29}H_{50}O$, which was confirmed by high resolution mass spectrometry, and showed IR absorption band at 1705 cm^{-1}. This acid was converted into the methyl ester (IR 1740 cm^{-1}; NMR δ 3.64 ($-CO_2C\underline{H}_3$) and 2.37 (2H, s, $-\overset{|}{\underset{|}{C}}-C\underline{H}_2-CO_2CH_3$); M^+ m/e 444). From these findings, the original acid could be formulated as 10α-(carboxymethyl)-5β-isopropyl-des-A-lupane (**7**). This acid with one carbon atom less than lupan-3-one (**5**) is corresponding to the photochemically unusual carboxylic acid (**3**) obtained by the photochemical reaction of friedelin (**1**) in *n*-hexane. Although in the case of lupan-3-one (**5**), the seco-nor aldehyde (**12**) was not isolated, the formation of the acid (**7**) was explicable by the oxidation of the seco-nor aldehyde (**12**), which could be produced by the autoxidation of the ketene (**13**) during a subsequent separation work-up after the irradiation, as stated elsewhere.[1]

The remaining two carboxylic acids were converted into their methyl esters and separated by tlc. A methyl ester with higher R_f value was identical with an authentic specimen (**8a**), which was prepared by photochemical reaction of lup-20(29)-en-3-one (**14**) in methanol followed by hydrogenation. Thus, the original acid was identified to be 10α-(2-carboxyethyl)-5β-isopropyl-des-A-lupane (**8**) and the spectral data were identical with those of tetrahydrocanaric acid.[2]



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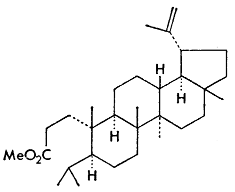

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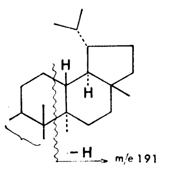
The other methyl ester with lower R_f value showed characteristic IR and NMR spectra due to an isopropenyl group. On hydrogenation, the methyl ester gave a saturated methyl ester, which was identical with 5β-isopropyl-10α-(2-methoxycarbonylethyl)-des-A-lupane (**8a**). The carboxylic acid, therefore, was formulated as 10α-(2-carboxyethyl)-5β-isopropenyl-des-A-lupane (**9**) and the formation could be explained by the oxidation of the unsaturated aldehyde (**6**) during work-up.

A lactone was isolated from the fraction between the ketone and the carboxylic acids by preparative tlc and recrystallized from chloroform–methanol. IR and NMR spectral data and the molecular formula, $C_{29}H_{48}O_2$, given by high resolution mass spectrometry, indicate the presence of a γ-lactone group with one carbon atom less than the original ketone (**5**). Fragment ions at m/e 191 ($C_{14}H_{23}$) and 205 ($C_{15}H_{25}$) correspond to species **15** and **16**, respectively, showing the presence of the intact rings D and E (and C).[4] The NMR spectrum showed the presence of an isolated methylene (δ 2.41, 2H, br.s) at the α-position to the carbonyl group and the absence of a hydrogen atom on the carbon atom adjacent to the ethereal oxygen atom.



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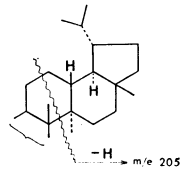

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NMR measurements using Eu(fod)$_3$-d_{27} as a shift reagent were applied in order to determine the structure of the lactone. The result was summarized in Fig. 1. A spectrum obtained in a mixture of Eu(fod)$_3$-d_{27} and the lactone in a molar ratio of 1.33: 1 in deuteriochloroform solution, was given in Fig. 2. In addition to the isopropyl group at C-19, the presence of a new isopropyl group was clearly shown. On irradiation of the signal around δ 5.3, two pairs of doublets due to two methyl protons (δ 3.54, J=7 Hz and δ 2.46, J=7 Hz) changed into two singlets. Judging from a large degree of the shift, one of the isopropyl groups must be located fairly near the carbonyl group. These observations suggest that the lactone could be represented by structure (**10**).

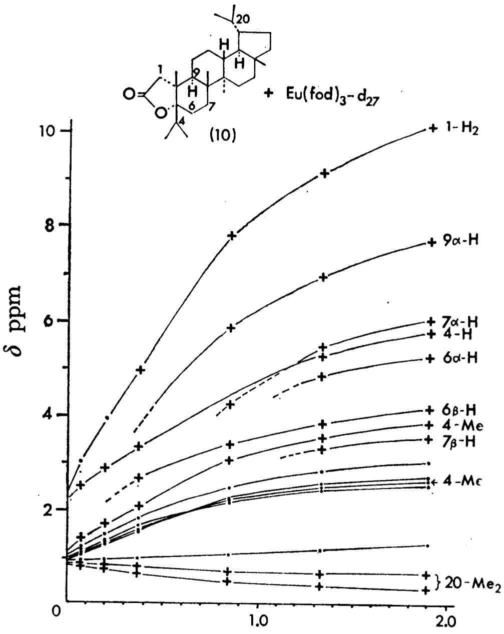


Fig. 1. Molar ratio of Eu(fod)$_3$-d_{27}/lactone (**10**) *vs.* chemical shift.

From the fact that two methylene protons adjacent to the carbonyl carbon were shifted with the largest slope and with nearly the same degree (see Figs. 1 and 2), it is considered that Eu(fod)$_3$-d_{27} is associated with the carbonyl group (and the ethereal oxygen) and located almost on a plane which bisects the methylene group at C-1. One proton (q, J=10.5 and 5.5 Hz) showing the second largest slope was assigned to 9α-(axial)-proton from the degree of shift (Figs. 1 and 2). These assignments, therefore, lead to the conclusion

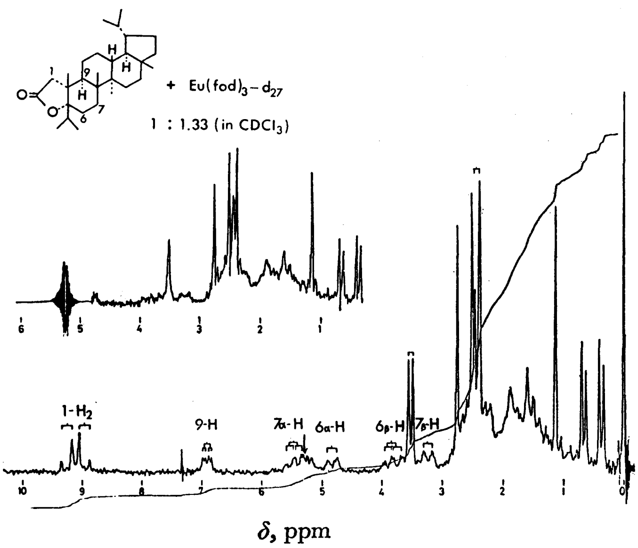
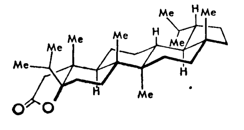


Fig. 2. NMR spectra.

that the ring juncture A/B is *cis* and then the C-5 isopropyl group is situated in β-side. The other stereochemistries are not compatible with the spectral data including pseudo-contact shift experiments. For example, a proton at C-9 of a *trans*-lactone (a C-5 epimer of **10**) would scarecely suffer the induced paramagnetic shift. Thus, the conformation of the lactone molecule is established as **17**. This conformation (**17**) could also explain a small shift of two methyl protons of 19α-isopropyl group. The remaining four protons (7α-, 6α-, 6β-, and 7β-) at ring B, which showed fairly large shifts, could be assigned as shown in Fig. 2 from the degree of the pseudo-contact shift and from the results of decoupling experiments (Figs. 1 and 2).



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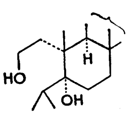

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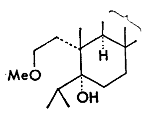

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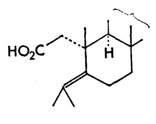

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The lactone (**10**) was reduced with lithium aluminium hydride in tetrahydrofuran to the corresponding diol (**18**), which in turn was coverted into the monomethyl ether (**19**) with methyl iodide and silver oxide in dimethylformamide.[5] The spectral data of these two derivatives could be explicable by their proposed structures. These observations furnish further evidence for the presence of the lactone structure in **10**.

It is most likely that the lactone (**10**) may be derived from 10α-carboxymethyl-5-isopropylidene-des-A-lupane (**20**), which was undetectable in the photo-reaction products of lupan-3-one (**5**) in *n*-hexane, although the formation of the unsaturated seco-nor acid (**20**) could hardly be explained. The elucidation of the mechanism is under way.

Experimental

IR spectra were measured using a Hitachi EPI-G2 spectrometer. NMR spectra were taken on a Hitachi R-20B (60 MHz) or a JEOL-PS-100 spectrometer (100 MHz) in deuteriochloroform solution containing tetramethylsilane as an internal standard. High resolution mass spectra were measured using a Hitachi RMH-2 or RMU-7M mass spectrometer operating at 70 eV. Measurements of low resolution mass spectra were carried out using a Hitachi RMU-6-Tokugata mass spectrometer with a direct inlet system operating at 70 eV unless otherwise stated. Gas chromatographic (glc) analyses were performed on a Shimadzu gas chromatograph model GC-4APF. For column chromatography Wakogel C-200 (Wako Pure Chemical Industries) and Activated Alumina (mesh 200—300, Showa Chemical Co.) were used. Thin layer chromatography (tlc) was carried out on Kieselgel G (E. Merck, Darmstadt) in 0.25 mm thickness. All melting points were determined on a hot block and reported uncorrected.

n-Hexane (extra pure grade, Wako Pure Chemical Industries) was found to contain 2-methylpentane, 3-methylpentane, and methylcyclopentane, but no unsaturated hydrocarbons as impurities by GC-MS examination (column: DC-550, 1m; oven temperature 10 °C). Any coloration with concentrated sulfuric acid was not observed.

The purity of the starting material, lupan-3-one (**5**) was checked by glc (column: OV-1 (2%); 270 °C and OV-17 (2%), 300 °C), tlc, and MS. And the absence of any compound with one carbon atom less than lupan-3-one (**5**) was confirmed.

Photochemical Reaction of Lupan-3-one (5). Lupan-3-one (**5**; 500 mg) was dissolved completely in dry *n*-hexane (750 ml) and the solution in a Pyrex vessel was then irradiated for about 6.5 hr at room temperature using a 100 W high pressure mercury lamp under an argon atmosphere.

Isolation and Characterization of the Reaction Products. After the solvent was distilled off under reduced pressure, the reaction products were roughly separated by silica gel (100 g) column chromatography into hydrocarbon, aldehyde, ketone, lactone, and carboxylic acid fractions. Each fraction was further separated and purified by repetition of column and/or preparative thin layer chromatography.

Elution with petroleum ether gave a mixture (about 20 mg) of hydrocarbons, which showed more than three spots on tlc (10% $AgNO_3$–SiO_2). Further examination of the mixture was not effected.

Successive elution with petroleum ether–benzene (1 : 1) afforded about 80 mg of a crude aldehyde (**6**). However, the aldehyde was so liable to decompose gradually in contact with air and rapidly on silica gel and alumina, that column chromatographic separations on silica gel and then on alumina could give only about 20 mg of the aldehyde (**6**).

Upon continued elution with benzene, a ketone (about 60 mg) was obtained, which was identified by direct comparison of the IR and MS data with those of the starting material, lupan-3-one (**5**).

Although further elution with benzene–ether (10 : 1) was continued, good separation was not obtained. A mixture (about 180 mg) of γ-lactone (**10**), carboxylic acids (**7**), (**8**), and (**9**) and other unknown minor compounds was eluted at the same time. The main four compounds were recorded in their order of elution. Since it was difficult to separate these compounds completely, further separation was accompanied with a considerable extent of loss. Repetition of column and thin layer chromatographic separations, though these methods were not so effective for the separation of the fraction obtained above, could afford about 20 mg of pure γ-lactone (**10**) and about 15 mg of pure seco-nor acid (**7**). A mixture of the remaining two carboxylic acids with the lowest and the second lowest R_f values was treated with diazomethane in ether to give a mixture of their methyl esters (**8a**) and (**9a**). The mixture was separated into **8a** and **9a**. Each weighed about 15—20 mg.

10α-(2-Formylethyl)-5β-isopropenyl-des-A-lupane (6): An amorphous solid, IR (KBr disk) 2720, 1735, 1640, and 895 cm^{-1}; NMR δ 1.72 ($CH_2{=}\underset{|}{C}{-}C\underline{H}_3$), 4.65, 4.85 (each m, $C\underline{H}_2{=}\underset{|}{C}{-}$), and 9.75 (t, J=2 Hz, $-C\underline{H}O$), 0.76, 0.82, 0.88, 0.95, 1.05, and 1.10 (other methyl protons); MS *m/e* (relative intensity %) 426 [3; $M^+(C_{30}H_{50}O)$], 411 [3; $(M-15)^+$], 383 [5; $(M-43)^+$], 369 [5; $(M-57)^+$], 345 [12; $(M-81)^+$], 327 [15; $(M-99)^+$], 231 (17), 205 (37), 191 (61), and 81 (100).

10α-(Carboxymethyl)-5β-isopropyl-des-A-lupane (7): An amorphous solid, IR (Nujol mull) 3400—2500 (br) and 1705 cm^{-1}; MW 430.3805, Calcd for $C_{29}H_{50}O_2$: 430.3808; MS *m/e* (%) 430 (13; M^+), 387 (16), 371 (6), 370 (4), 259 (8), 231 (10), 205 (16), 191 (31), and 95 (100).

5β-Isopropyl-10α-(methoxycarbonylmethyl)-des-A-lupane (7a): The above carboxylic acid (**7**; 15 mg) was treated with diazomethane and the methyl ester (**7a**; 12 mg) was obtained. An oil, IR (neat) 1740 cm^{-1}; NMR δ 2.37 (2H, s), 3.64 (3H, s), and other methyl protons; 0.75 (s), 0.83 (s), 0.91 (s), 1.05 (s), 0.75 (d, J=6.5 Hz), 0.82 (d, J=6.5 Hz), 0.84 (d, J=6.5 Hz), and 0.93 (d, J=6.5 Hz); MS *m/e* (%) 444 [23; $M^+(C_{30}H_{52}O_2)$], 401 (20), 371 (18), 370 (29), 205 (23), 191 (31), 178 (18), 177 (21), and 95 (100).

5β-Isopropyl-10α-(2-methoxycarbonylethyl)-des-A-lupane (8a): Mp 139—140 °C (recrystallized from chloroform–methanol); IR (KBr disk) 1745 cm^{-1}; MW 458.4130, Calcd for $C_{31}H_{54}O_2$: 458.4121; MS *m/e* (%) 458 (11; M^+), 443 (6), 415 (11), 371 (12), 253 (23), 231 (19), 209 (21), 205 (25), 191 (40), 137 (80), and 109 (100).

5β-Isopropenyl-10α-(2-methoxycarbonylethyl)-des-A-lupane (9a): An amorphous solid, IR (KBr disk) 1745, 1640, and 890 cm^{-1}; NMR δ 0.75 (3H, s), 0.76 (3H, d, J=7 Hz), 0.83 (3H, d, J=7 Hz), 0.84 (3H, s), 0.94 (3H, s), 1.08 (3H, s), 1.72 (3H, s), 2.25 (2H, m), 3.63 (3H, s), ~4.6 (1H, m), and ~4.8 (1H, m); MS *m/e* (%) 456 [5; $M^+(C_{31}H_{52}O_2)$], 441 (3), 425 (2), 413 (5), 375 (47), 369 (13), 231 (24), 205 (32), 191 (52), and 109 (100), (Ionization potential: 30 eV).

The methyl ester (**9a**; 10 mg) in methanol (30 ml) was hydrogenated in the presence of 10% palladium-carbon at room temperature overnight to afford **8a** quantitatively. This ester (**8a**) was identical (IR, NMR, and tlc) with a specimen mentioned above and also with an authentic specimen, prepared by photochemical reaction of lup-20(29)-en-3-one (**14**) in methanol followed by hydrogenation (*vide infra*).

Lactone of 10α-(Carboxymethyl)-5α-hydroxy-5β-isopropyl-des-A-lupane (10): A white crystal, mp 245—246 °C with sublimation; IR (KBr disk) 1775, 1455, 1390, 1385, 1375, 1280, 1245, 995, 950, and 945 cm^{-1}; MW 428.3652, Calcd for $C_{29}H_{48}O_2$: 428.3652; MS *m/e* (%; fragment composition, determined by high resolution mass spectrometry) 428 (2; $C_{29}H_{48}O_2$), 413 (3; $C_{28}H_{45}O_2$), 400 (1; $C_{28}H_{48}O$), 385 (95; $C_{26}H_{41}O_2$), 357 (24; $C_{25}H_{41}O$), 205 (15; $C_{15}H_{25}$), 191 (33; $C_{14}H_{23}$), and 69 (100; C_5H_9); NMR δ 0.77 (3H, d, J=7 Hz), 0.79 (3H, s), 0.87 (3H, d, J=7 Hz), 0.95 (3H, s), 1.03 (6H, d, J=7 Hz), 1.12 (3H, s), 1.16 (3H, s), and 2.41 (2H, br.s). The data using Eu(fod)$_3$-d_{27} were shown in Figs. 1 and 2.

Reduction of Lactone of 10α-Carboxymethyl-5α-hydroxy-5β-isopropyl-des-A-lupane (10) with Lithium Aluminium Hydride. A mixture of the lactone (**10**; 45 mg) and lithium aluminium hydride (about 30 mg, in large excess) in tetrahydrofuran (10 ml) was heated under reflux for 8.5 hr. Usual work-up gave a crystalline product, which was purified by preparative tlc to afford 5α-hydroxy-10α-(2-hydroxyethyl)-5β-isopropyl-des-A-lupane (**18**; 20 mg). Mp 221—222 °C (recrystallized from chloroform–methanol); IR (KBr disk) 3500—3150 (br), 1070, and 990 cm^{-1}; NMR (sparingly insoluble in $CDCl_3$) δ 3.4—3.8 (2H, m); MS (no molecular ion was observed at any of the measured ionization potential at 70, 25, and 20 eV.) *m/e* (%) 389 [7; $(M-43)^+$], 371 [100; $(M-43-18)^+$], 333 [24; $(M-99)^+$], 205 (22), 191 (40), and 111 (100).

Methylation of 5α-Hydroxy-10α-(2-hydroxyethyl)-5β-isopropyl-des-A-lupane (18). A mixture of the diol (**18**; 40 mg), methyl iodide (1 ml), silver oxide (200 mg) and dimethylformamide (5 ml) was stirred at room temperature for 21 hr. After usual treatment, 5α-hydroxy-5β-isopropyl-10α-(2-methoxyethyl)-des-A-lupane (**19**; 25 mg) was obtained by preparative tlc. Mp 168—169.5 °C (recrystallized from chloroform–methanol); IR (KBr disk) 3600—3300 (br), 1110, 1040, and 995 cm^{-1}; NMR δ 3.34 (3H, s), 4.12 (1H, br.s, $O\underline{H}$); MS (the molecular ion (*m/e* 446) was not observed at any of the measured ionization potential at 70, 20, and 15 eV.) *m/e* (%) 403 [10; $(M-43)^+$], 385 [4; $(M-43-18)^+$], 371 [100; $(M-43-33)^+$], 347 (26; $(M-99)^+$], 315 (27), 205 (26), and 191 (48); Found: C, 80.44; H, 12.29%. Calcd for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18%.

Photochemical Reaction of Lup-20(29)-en-3-one (14) Followed by Hydrogenation. A solution of lup-20(29)-en-3-one (**14**; 400 mg) in methanol (700 ml) was irradiated using a 100 W high pressure mercury lamp under a nitrogen atmosphere for 16.5 hr at room temperature. After the solvent was removed, the reaction products were separated by silica gel column chromatography to afford 5β-isopropyl-10α-(2-methoxycarbonylethyl)-des-A-lup-20(29)-ene (**21**; about 100 mg) as a main product. IR (neat) 1750, 1645, and 890 cm^{-1}; NMR δ 3.65 (3H, s) and 4.50—4.75 (2H, m); MS *m/e* (%) 456 [43; M^+ $(C_{31}H_{52}O_2)$], 441 (22), 413 (16), 373 (9), 369 (30), 203 (77), and 189 (100).

Then, a mixture of the methyl ester (**21**; 40 mg) and 5% palladium-carbon (20 mg) in methanol was stirred under a hydrogen atmosphere at 50 °C for one day. After filtration, the reaction mixture was subjected to preparative tlc using a mixture of petroleum ether–benzene–chloroform (4: 1: 1) as an eluent. The main product (**8a**; 25 mg) was obtained as crystals.

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