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SYNTHESIS OF D:A-FRIEDO-18β,19αH-LUPAN-3-ONE AND D:B-FRIEDO-18β,19αH-LUP-5-EN-3β-OL AND A COMMENT ON THE STRUCTURE OF GUIMARENOL

Yasushi YOKOYAMA, Yoshihiko MORIYAMA,** Takahiko TSUYUKI, Takeyoshi TAKAHASHI,* Akiko ITAI,* and Yoichi IITAKA*
Department of Chemistry, Faculty of Science, The University of Tokyo,
*Faculty of Pharmaceutical Sciences, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113
**Institute of Chemistry, Kyoto Prefectural University of Medicine,
Taishogun, Kita-ku, Kyoto 603

D:B-Friedo-18β,19αH-lup-5-en-3β-ol was synthesized from friedelin via D:A-friedo-18β,19αH-lupan-3-one. The stereostructure of a 3α,4α-epoxide derived from the 3-one was determined by X-ray technique to show the 19αH configuration for both the epoxide and the 5-en-3β-ol. The disagreement of the spectral data of the synthetic 5-en-3β-ol with those of guimarenol is described.

Although a number of migrated oleanane, ursane, and hopane derivatives were isolated and their structures were elucidated,[1] only a few investigations on migrated lupane derivatives have been described, viz., the isolation of guimarenol (1) and lup-18-en-3β-ol from Ceropegia dichotoma[2] and the preparation of 3β,28-diacetoxy-18β,19αH-lupane derivatives from betulin.[3] The stereochemistry at C-13, C-14, C-17, C-18, and C-19 of guimarenol (1) remained undetermined.[2] A plausible stereostructure, D:B-friedo-18β,19αH-lup-5-en-3β-ol (2), can be suggested for guimarenol by means of biogenetic considerations[4] involving a sequence of migration of hydrides and methyl groups of an intermediate carbonium ion (A; path a) produced from squalene 2,3-oxide. We have recently reported the synthesis of two migrated lupane derivatives of a D:A-friedo type, D:A-friedo-18β-lup-19-en-3-one (3) and D:A-friedo-18β-lup-19-ene (4) from friedelin (5).[5] The present communication deals with a synthesis of D:A-friedo-18β,19αH-lupan-3-one (6) from 3 and a conversion of 6 into 2. Although this 3β-ol (2) could be proposed for the structure of guimarenol (1) on the basis of biogenetic considerations, the spectral data of the synthetic 3β-ol (2) were not identical with those of guimarenol (1).

D:A-Friedo-18β-lup-19-en-3-one (3)[5] was treated with sodium borohydride in methanol and then with acetic anhydride in pyridine to yield D:A-friedo-18β-lup-19-en-3β-yl acetate (7) quantitatively. The acetate (7) was dissolved in acetic acid and hydrogenated in the presence of platinum catalyst under atmospheric pressure at 40 °C to give a single hydrogenation product (8) in 84% yield. Treatment of the saturated acetate (8) with lithium aluminium hydride in refluxing tetrahydrofuran afforded an alcohol (9), which was then subjected to dehydration with phosphoryl chloride in pyridine under reflux condition. A dehydration product (10),

thus obtained in 84% yield, was treated with m-chloroperbenzoic acid in chloroform to afford a mixture of two epoxides in a ratio of 9:5 in 93% yield. ^{1}H-NMR measurement of each epoxide revealed that a major epoxide was 3α,4α-epoxide (11; δ 2.85, 1H, t, J = 2.5 Hz) and a minor one 3β,4β-epoxide (12; δ 2.90, 1H, t, J = 1 Hz).[6]

In order to determine the configuration of the isopropyl group on C-19 of 8 generated by the hydrogenation of 7, a single crystal of the 3α,4α-epoxide (11) was subjected to X-ray diffraction analysis. Crystals of 11 belong to a monoclinic space group $P2_1$ with the cell parameters of a = 13.996(6), b = 11.461(5), c = 8.199 (4) Å, β = 106.34(6)° and the two molecules are contained in a cell. A total of 2494 independent, non-zero reflections are measured on a Philips PW 1100 automatic diffractometer using graphite-monochromated Cu Kα radiation. The structure was solved by the direct method using program MULTAN[7] and was refined by the block-diagonal least-squares calculation assuming the anisotropic thermal vibrations. The final R-factor was 9.9% excluding hydrogen atoms. Figure 1 is a computer-generated perspective drawing of the molecular structure of the epoxide (11), and showed a 19αH-configuration as well as 18βH-configuration. Thus it was found that the acetate (8) could be formulated as D:A-friedo-18β,19αH-lupan-3β-yl acetate with the 19β-isopropyl group and that the hydrogenation of 7 had occurred from α-side preferentially to afford the 19αH-isomer (8).

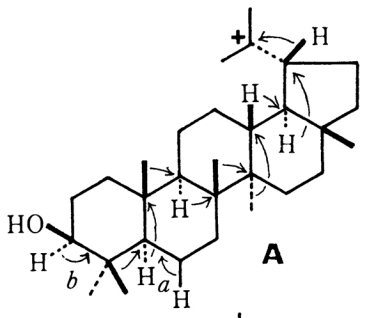
The alcohol (9) was subjected to oxidation with the Jones reagent to give D:A-friedo-18β,19αH-lupan-3-one (6) quantitatively. The ketone (6) is a biogenetically interesting compound, because it represents the ultimate rearrangement product from the original posturated ion (A) by path b in the migrated lupane series, corresponding to a friedelin-type compound in the migrated oleanane series.

The ketone (6) was treated with benzoyl chloride at reflux temperature to give a Δ^3-enol benzoate (13), which, on bromination with bromine in pyridine, gave a 4-bromo ketone (14) in 62% yield. According to the known procedure,[8] the bromide (14) was treated with silver acetate to give a 1:2 mixture of two unsaturated ketones, (15) and (16), in 74% yield, which could not be separated by TLC nor HPLC. Reduction of the mixture with sodium borohydride in methanol at 0 °C gave a mixture of the corresponding 3β-alcohols and 3α-alcohols, which was subjected to preparative TLC and preparative HPLC to separate into D:B-friedo-18β,19αH-lup-5-en-3β-ol (2), -5-en-3α-ol (17), -5(10)-en-3β-ol (18), and -5(10)-en-3α-ol (19) in a ratio of 1:7:14:2. The structures of these unsaturated alcohols were determined by comparison of their ^{1}H-NMR spectra and TLC chromatograms with those of the corresponding D:B-friedooleanane[9] and D:B-friedobaccharane derivatives.[10]

The melting point and the ^{1}H-NMR spectrum of the synthetic 5-en-3β-ol (2) were found to be not identical with those of guimarenol (1)[2] (*vide infra*). Oxidation of 2 with the Sarett reagent gave the ketone (15). The melting point and the ^{1}H-NMR spectrum of 15 were not in agreement with those of guimarenone (20) described previously.[2] The structure of guimarenol (1) could not be represented by D:B-friedo-18β,19αH-lup-5-en-3β-ol (2); further structural studies on guimarenol would be required.

Characterization of products is as follows; D:B-friedo-18β,19αH-lup-5-en-3β-ol (2): mp 166-167 °C, IR (Nujol) 3400, 825 cm^{-1}; ^{1}H-NMR[11] δ 0.88, 1.03, 1.13,

1.24 (each 3H, s; t-CH_3), 0.90 (6H, d, J = 6 Hz; $(CH_3)_2CH$-), 0.97 (6H, s; 2 x t-CH_3), 3.45 (1H, m, $W_{1/2}$ = 7 Hz; 3α-H), 5.65 (1H, m, $W_{1/2}$ = 7 Hz; 6-H), MS m/e (%) 426 (M^+; 7), 274 (100), MW[12] 426.3852. [cf. guimarenol (1)[2]; mp 276-278 °C, ^{1}H-NMR δ 0.77, 0.89, 1.00, 1.03, 1.06, 1.13 (Me signals), 3.55 (1H, m, $W_{1/2}$ = 6 Hz; -CH-OH), 5.60 (1H, m, -CH=C)]; D:A-friedo-18β,19αH-lupan-3-one (6):[13] mp 260-262 °C, IR 1715 cm^{-1}, ^{1}H-NMR [Eu(fod)$_3$-d_{27}/6 = 0.2 (M/M) in $CDCl_3$] δ 1.72 (3H, d, J = 7 Hz), MS m/e 426 (M^+; 100); D:A-friedo-18β-lup-19-en-3β-yl acetate (7):[13] mp 240-242.5 °C, IR 1738 cm^{-1}, ^{1}H-NMR δ 1.63, 1.67 (each 3H, br. s), 2.04 (3H, s), 4.92



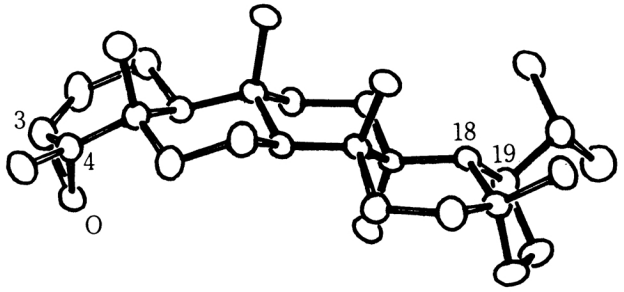
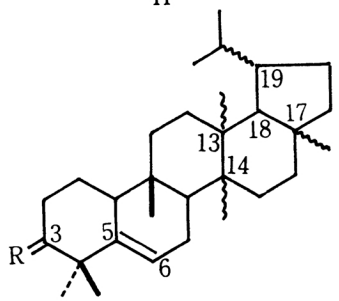
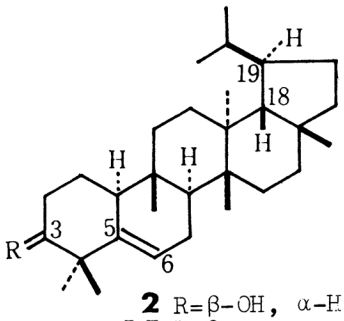


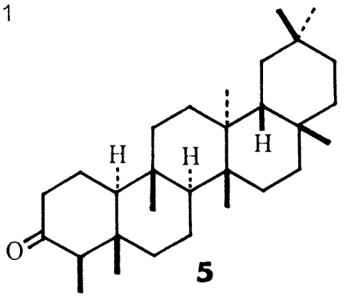
Fig. 1



1 R=β-OH, α-H
20 R=O



2 R=β-OH, α-H
15 R=O
17 R=α-OH, β-H



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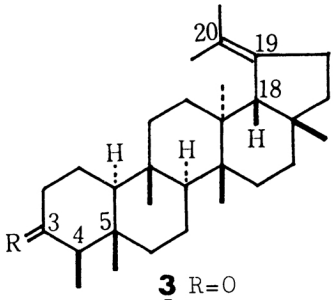
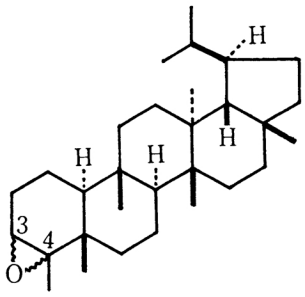
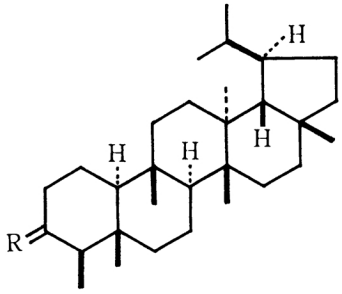


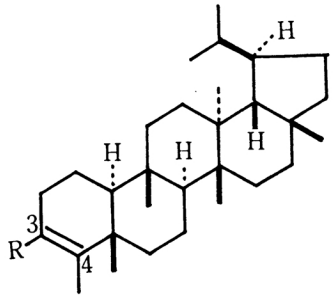
3 R=O
4 R=H_2
7 R=β-OAc, α-H



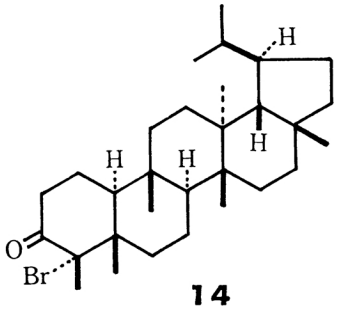
11 3α,4α-epoxide
12 3β,4β-epoxide



6 R=O
8 R=β-OAc, α-H
9 R=β-OH, α-H



10 R=H
13 R=$PhCO_2$



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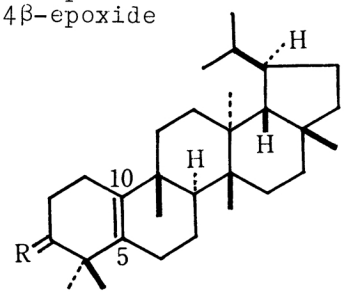

16 R=O
18 R=β-OH, α-H
19 R=α-OH, β-H

(1H, m, $W_{1/2}$ = 7 Hz), MS m/e 468 (M^+; 60), 317 (100); D:A-friedo-18β,19αH-lupan-3β-yl acetate (8):[13] mp 251-253 °C, IR 1735 cm^{-1}, ^{1}H-NMR δ 2.03 (3H, s), 4.94 (1H, m, $W_{1/2}$ = 6 Hz), MS m/e 470 (M^+; 58), 410 (100); D:A-friedo-18β,19αH-lupan-3β-ol (9); mp 225-227 °C, IR 3440 cm^{-1}, ^{1}H-NMR δ 3.75 (1H, m, $W_{1/2}$ = 7 Hz), MS m/e 428 (M^+; 100), MW[12] 428.3967; D:A-friedo-18β,19αH-lup-3-ene (10):[13] mp 169-170 °C, IR 795 cm^{-1}, ^{1}H-NMR δ 5.18 (1H, m, $W_{1/2}$ = 9 Hz), MS m/e 410 (M^+; 65), 318 (100); 3α,4α-epoxy-D:A-friedo-18β,19αH-lupane (11):[13] mp 200-202 °C, ^{1}H-NMR δ 0.80-0.93 (15H), 0.96, 1.07, 1.19 (each 3H, s), 2.85 (1H, t, J = 2.5 Hz), MS m/e 426 (M^+; 77), 411 (100); 3β,4β-epoxy-D:A-friedo-18β,19αH-lupane (12):[13] mp 215-216 °C, ^{1}H-NMR δ 0.78-0.93 (15H), 0.96, 1.05, 1.17 (each 3H, s), 2.90 (1H, t, J = 1 Hz), MS m/e 426 (M^+; 100); 3-benzoyloxy-D:A-friedo-18β,19αH-lup-3-ene (13):[13] mp 255-256 °C, IR 1732 cm^{-1}; ^{1}H-NMR δ 1.49 (3H, s), 7.4-7.7 (3H, m), 8.0-8.3 (2H, m), MS m/e 530 (M^+; 5), 105 (100); 4α-bromo-D:A-friedo-18β,19αH-lupan-3-one (14): mp 192.5-194.5 °C, IR 1715 cm^{-1}, ^{1}H-NMR δ 1.71 (3H, s), 3.38 (1H, ddd, J = 20, J = 13, J = 8 Hz; axial 2α-H), MS m/e 506 (M^+; 12), 504 (M^+; 12), 123 (100), MW[12] 506.2946 and 504.2992; D:B-friedo-18β,19αH-lup-5-en-3-one (15): mp 149-153 °C, IR (Nujol) 1718 cm^{-1}, ^{1}H-NMR δ 0.82, 0.90 (each 3H, s; t-CH_3), 0.83 (6H, d, J = 7 Hz; $(CH_3)_2CH$-), 1.21 (12H, s; 4 x t-CH_3), 5.63 (1H, m, $W_{1/2}$ = 11Hz; -CH=C), ms m/e 424 (M^+; 11), 274 (100), 123 (93), MW[12] 424.3731 [cf. guimarenone (20)[2]: mp 196-200 °C, ^{1}H-NMR δ 0.78, 0.86, 0.92, 1.01, 1.06, 1.22, 1.25 (Me signals), 5.75 (1H, m, -CH=C)]; D:B-friedo-18β,19αH-lup-5-en-3α-ol (17): mp 181-182 °C, IR 3320, 825 cm^{-1}, ^{1}H-NMR δ 3.20 (1H, dd, J = 4, J = 10 Hz), 5.61 (1H, m, $W_{1/2}$ = 9 Hz), MS m/e 426 (M^+; 10), 274 (100), MW[12] 426.3808; D:B-friedo-18β,19αH-lup-5(10)-en-3β-ol (18): mp 191-193 °C, IR 3350 cm^{-1}, ^{1}H-NMR δ 3.48 (1H, dd, J = 4, J = 10 Hz), MS m/e 426 (M^+; 13), 408 (100), 205 (72), MW[12] 426.3846; D:B-friedo-18β,19αH-lup-5(10)-en-3α-ol (19): mp 195.5-196 °C, IR 3620 cm^{-1}, ^{1}H-NMR δ 3.48 (1H, dd, J = 3, J = 4.5 Hz), MS m/e 426 (M^+; 10), 205 (100), MW[12] 426.3880.

References and notes

1) E.g. T.K.Devon and A.I.Scott, "Handbook of Naturally Occurring Compounds", Academic Press, New York and London (1972), Vol. II (Terpenes); "Terpenoids and Steroids", ed by K.H.Overton, The Chemical Society, London, Vol. 1 (1971) - Vol. 8 (1978). 2) A.G.González, F.G.Jerez, and M.L.Escalona, An. Quim., 69, 921 (1973); Chem. Abstr., 80, 24792n. 3) E.Suokas and T.Hase, Acta Chem. Scand., B28, 793 (1974). 4) A.Eschenmoser, L.Ruzicka, O.Jeger, and D.Arigoni, Helv. Chim. Acta, 38, 1890 (1955); L.Ruzicka, Proc. Chem. Soc., 1959, 341. 5) Y.Yokoyama, T.Tsuyuki, Y. Moriyama, T.Murae, H.Toyoshima, and T.Takahashi, Bull. Chem. Soc. Jpn., 52, 1720 (1979). 6) Signals due to 3-H: 3α,4α-epoxyshionane, δ 2.83, t, J = 3 Hz; 3β,4β-epoxyshionane, δ 2.89, t, J = ca. 1 Hz; 3α,4α-epoxyfriedelane, δ 2.86, t, J = 2.5 Hz; 3β,4β-epoxyfriedelane, δ 2.90, m, $W_{1/2}$ = 3 Hz. 7) G.Germain, P.Main, and M.M. Woolfson, Acta Cryst., A27, 368 (1971). 8) J.M.Beaton, F.S.Spring, R.Stevenson, and J.L.Stewart, Tetrahedron, 2, 246 (1958). 9) M.Tori, T.Torii, K.Tachibana, S. Yamada, T.Tsuyuki, and T.Takahashi, Bull. Chem. Soc. Jpn., 50, 469 (1977), and references cited therein. 10) K.Tachibana, M.Tori, Y.Moriyama, T.Tsuyuki, and T. Takahashi, Bull. Chem. Soc. Jpn., 50, 1552 (1977), and references cited therein. 11) All ^{1}H-NMR spectra were determined in $CDCl_3$. 12) Determined by high resolution mass spectrometry. 13) Satisfactory result of elemental analysis was obtained for this compound.

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