Synthesis of *D*:*A*-Friedo-18β-lupane Derivatives[1]

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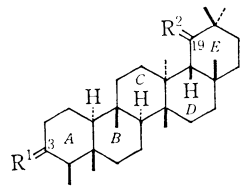
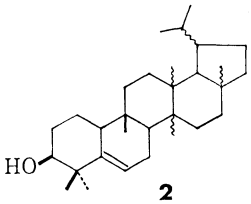
D: *A*-Friedo-18β-lup-19-ene and *D*: *A*-friedo-18β-lup-19-en-3-one with a new migrated lupane framework were synthesized and the former compound was converted into known methyl trinorshionanoate.

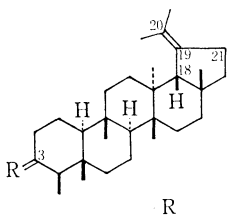
There have been reported a number of migrated triterpene compounds with *D*-, *D*: *C*-, *D*: *B*-, and *D*: *A*-friedo-type frameworks. Among them, a series of migrated oleanane derivatives, taraxerol, multiflorenol, walsurenol, alnusenone (=glutinone), and friedelin (**1**) are well known.[2] In a series of migrated lupane derivatives, however, only guimarenol (**2**) has been isolated from *Ceropegia dichotoma* as a migrated lupane derivative, which has been shown to possess a *D*: *B*-friedolupane framework.[3] Neither isolation nor synthesis of a triterpene with a *D*: *C*- or *D*: *A*-friedolupane framework has yet been reported. We wish to describe a synthesis of *D*: *A*-friedo-18β-lup-19-ene (**3**) and *D*: *A*-friedo-18β-lup-19-en-3-one (**4**) from friedelin (**1**) and also conversion of **3** into known methyl trinorshionanoate (**5**)[4] *via* a trinor ketone (**6**).

Friedelan-19α-ol (**7**),[5] prepared from friedelin (**1**) *via* friedel-18-ene (**8**), was treated with phosphorus pentachloride in toluene at 0 °C to give an olefin mixture. The mixture was separated by column chromatography on silica gel impregnated with silver nitrate into an olefin (**3**; yield 61%) and friedel-18-ene (**8**; yield 4%). The olefin (**3**) has a molecular formula $C_{30}H_{50}$ determined by elemental analysis and mass spectrum, and

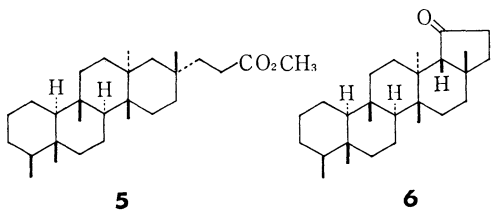




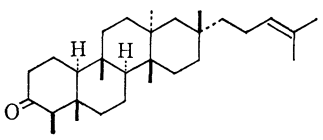
	R^1	R^2
1	O	H_2
7	H_2	β-H, α-OH
11	O	O
13	β-H, α-OH	α-H, β-OH
14	-O(CH$_2$)$_2$O-	O
15	-O(CH$_2$)$_2$O-	β-H, α-OH
16	O	β-H, α-OH



	R
3	H_2
4	O



5 **6**



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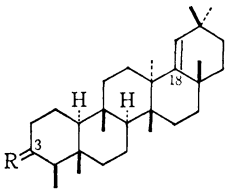
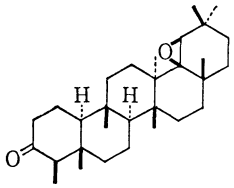


	R
8	H_2
10	O



12

shows a signal at δ 1.64 characteristic of an isopropylidene group together with signals at δ 0.78—0.90 due to six methyl groups in the ^{1}H NMR spectrum. These observations indicate the occurrence of *E*-ring contraction during the dehydration reaction and, therefore the structure of **3** could be inferred to be *D*: *A*-friedo-18β-lup-19-ene. The structure **3** was further confirmed by the following transformation.

Oxidation of the olefin (**3**) with ruthenium tetraoxide[6] in carbon tetrachloride at room temperature gave a ketone (**6**), $C_{27}H_{44}O$. The presence of α-monosubstituted five-membered ketone was demonstrated for **6** by IR ($\nu_{C=O}$ 1725 cm^{-1}) and NMR (δ 2.18, 2H, m and δ 2.20, 1H, s) spectra. CD measurement showed a positive Cotton effect. Godtfredsen *et al.*[7] reported that 3α,11α-diacetoxy-13β-fusidan-17-one showed a positive Cotton effect, while its 13α-isomer a strong negative maximum. Therefore the *D*/*E* ring juncture in **6** could be determined to be *cis*, leading to 18βH configuration.

The trinor ketone (**6**) in methanol was irradiated using a high pressure mercury lamp to afford methyl trinorshionanoate (**5**), which was identical with a specimen obtained from shionone (**9**).[5] The framework of **6** was thus confirmed and the structure of the olefin (**3**) was shown to be *D*: *A*-friedo-18β-lup-19-ene.

Since a C$_{(3)}$-functionalized *D*: *A*-friedolupane derivative is considered to be one of the important key compounds for preparation of migrated lupane derivatives with *D*: *B*- and *D*: *C*-friedo-type frameworks, *D*: *A*-friedo-18β-lup-19-en-3-one (**4**) was prepared as follows.

Friedel-18-en-3-one (**10**)[8] was converted into friedelane-3,19-dione (**11**)[9] *via* 18β,19β-epoxyfriedelan-3-one (**12**)[9] and friedelane-3α,19β-diol (**13**).[10] The diketone

(**11**) was stable to an alkaline treatment. This suggests an 18βH configuration (ring juncture *C/D/E*: *trans*-anti-*cis*) for **11**. The 18αH isomer (*trans*-syn-*trans*) is considered to be much less stable than the 18βH isomer.[5,11]

Treatment of the diketone (**11**) with ethylene glycol in the presence of *p*-toluenesulfonic acid in benzene gave a mono-ethylene acetal (**14**). The absorption band at 1685 cm^{-1} in the IR spectrum of **14** indicated that the carbonyl group at C-19 was left unchanged and that the ethylene acetalization occurred on the carbonyl group at C-3. Reduction of **14** with lithium aluminium hydride in tetrahydrofuran gave 19α-hydroxyfriedelan-3-one 3-ethylene acetal (**15**), which, on treatment with *p*-toluenesulfonic acid in acetone, afforded 19α-hydroxyfriedelan-3-one (**16**; ν_{OH} 3450 and 3620 and $\nu_{C=O}$ 1705 cm^{-1}) in about 76% yield from **11**. The NMR spectrum of **16** showed a multiplet at δ 2.1—2.5 due to three protons α and α′ to the carbonyl group and a doublet at δ 3.79 (J=5.5 Hz)[5] due to a proton on C-19β. The 19α-hydroxy configuration for **15** and **16** received support from the fact that the reduction of friedelan-19-one with lithium aluminium hydride gave friedelan-19α-ol (**7**) as a sole product.[5]

The dehydration reaction of the hydroxy ketone (**16**) with phosphorus pentachloride was examined under various conditions and it was found that the best results were obtained under the following reaction conditions. The hydroxy ketone (**16**; 0.012 mmol) in toluene (5 ml) was treated with phosphorus pentachloride (*ca.* 10 mg) at −10 °C for 20 h to give an olefin (**4**) as a single reaction product in 90% yield. Reaction under reflux conditions resulted in the formation of undesired friedel-18-en-3-one (**10**), and reaction with a larger amount of phosphorus pentachloride gave an unidentified olefin in considerable amounts (see Experimental).

The olefin (**4**), mp 276—278 °C, gave a molecular formula $C_{30}H_{48}O$ (by elemental analysis and mass spectrometry) and showed the presence of a carbonyl group ($\nu_{C=O}$ 1710 cm^{-1}) and an isopropylidene group (δ 1.65, br s, 6H) in the IR and NMR spectra, indicating that the olefin (**4**) corresponds to an *E*-ring contraction product. On Huang-Minlon reduction, the olefin (**4**) gave *D*: *A*-friedo-18β-lup-19-ene (**3**) identical with a specimen obtained from **7** (*vide supra*). Therefore, the structure of the olefin (**4**) was shown to be *D*: *A*-friedo-18β-lup-19-en-3-one.

Experimental

General Procedures. Melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and were uncorrected. IR spectra were measured in Nujol mull using a Hitachi EPI-G2 spectrometer. CD measurement was carried out on a JASCO Model J-20 spectrometer. Optical rotations were measured on a JASCO DIP-SL polarimeter. Mass spectra were taken on a Hitachi RMU-6-Tokugata mass spectrometer at 70 eV with a direct inlet system. The relative intensity was expressed in the parenthesis. ^1H NMR spectra were measured using a Hitachi R-20 spectrometer. Chemical shifts were expressed in δ downfield from TMS as an internal standard and coupling constants in Hz. GLC analyses were made using a Shimadzu Gas Chromatograph GC-6A equipped with a hydrogen flame ionization detector (column: Dexsil 300GC, temperature 290 °C). HPLC analyses were carried out on a Waters Liquid Chromatograph ALC/GPS 202/401 at room temperature with an RI detector (column: μ-Porasil 1/8 (inch)×1 (foot); solvent system: 5% ether–hexane; flow rate: 0.5 ml/min; pressure: *ca.* 250 psi). TLC was carried out on Kieselgel G (E. Merck) coated in 0.25 mm thickness. Wakogel C-200 (Wako) was used for column chromatography.

Dehydration of Friedelan-19α-ol (7). To a solution of friedelan-19α-ol[5] (**7**; 407 mg) in toluene (100 ml) kept at 0 °C, phosphorus pentachloride (*ca.* 660 mg) dissolved in toluene (25 ml) was added and the reaction mixture was stirred for 1.5 h at 0 °C. After addition of 15% sodium carbonate solution (70 ml), the reaction product was treated in usual way and subjected to separation by column chromatography on silica gel (40 g) impregnated with 20% silver nitrate. Elution with petroleum ether (320 ml) gave an isopropylidene derivative (**3**; 236 mg) and further elution with benzene (160 ml) and then with ether (80 ml) gave friedel-18-ene (**8**; 15 mg). The isopropylidene derivative (**3**) was recrystallized from acetone to afford *D*: *A*-friedo-18β-lup-19-ene (**3**; 218 mg), mp 181.5—182.5 °C; NMR ($CDCl_3$) δ 0.78—0.90 (6×CH_3), 1.64 (6H, s; $(CH_3)_2C{=}C\langle$), and the absence of signals due to olefinic proton; MS *m/e* (%) 410 (M^+; 14), 395 (12), 259 (39), and 121 (100); Found: C, 87.86; H, 12.43%. Calcd for $C_{30}H_{50}$: C, 87.73; H, 12.27%.

Oxidation of D: A-*Friedo-18β-lup-19-ene (3).* A ruthenium tetraoxide solution was prepared according to Nakata's procedure[6c] as follows. To ruthenium dioxide (83.6 mg) dissolved in carbon tetrachloride (10 ml), a solution of sodium periodate (361.4 mg) in water (10 ml) was added and the mixture was stirred for 19 h initially at 0 °C then at room temperature.

A solution of *D*: *A*-friedo-18β-lup-19-ene (**3**; 33.4 mg) in carbon tetrachloride (3 ml) was covered with water (2 ml) and stirred. The carbon tetrachloride solution (5 ml) of ruthenium tetraoxide was added dropwise and the stirring was continued for 21 h at room temperature. An excess of the oxidizing reagent was destroyed by addition of 2-propanol (2 ml). The reaction product was treated as usual and purified by column chromatography on silica gel (5 g). The unchanged hydrocarbon (6.2 mg) was eluted with petroleum ether (20 ml) and subsequent elution with petroleum ether–benzene (1: 1, 100 ml) gave a trinor ketone (**6**; 17.0 mg), mp 217—218 °C (crystallized from acetone); IR 1725 cm^{-1}; CD (*c* 0.0014, dioxane, at 26 °C) $[\theta]_{302}$ +7570, $[\theta]_{313}$ +7710, and $[\theta]_{325}$ +4190; NMR ($CDCl_3$) δ 0.77—1.00 (6×CH_3), 2.18 (2H, m; $-CH_2-CO-$), and 2.20 (1H, s; $-CH-CO-$); MS *m/e* (%) 384 (M^+; 32), 369 (37), 259 (39), 257 (41), 245 (29), 190 (41), 149 (82), and 109 (100); Found: C, 84.19; H, 11.73%. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53%.

Photoirradiation of Trinor Ketone (6). A solution of trinor ketone (**6**; 27.2 mg) in methanol (35 ml) in a quartz vessel was irradiated using a high pressure mercury lamp (100 W) for 2.5 h under a nitrogen atmosphere at room temperature. Column chromatographic separation on silica gel (6 g) gave methyl trinorshionanoate (**5**; 14.4 mg) together with unidentified hydrocarbons and the unchanged starting material (4 mg). The photo-produced methyl trinorshionanoate (**5**) was identical (mp, IR, NMR, MS, and TLC) with an authentic specimen prepared from shionone (**9**).[5]

Treatment of Friedelane-3,19-dione (11) with Alkali. Friedelane-3,19-dione[9] (**11**; 14.6 mg) in methanol (15 ml) was heated under reflux with sodium methoxide (*ca.* 55 mg) for 2 h. The residue, after removal of the solvent, was extracted with ether. The ethereal extract was worked up as usual and the examination on TLC showed only one spot identical with that of the starting diketone (**11**).

*Ethylene Acetalization of Friedelane-3,19-dione (**11**).* A mixture of friedelane-3,19-dione (**11**; 2.9 g), ethylene glycol (5 ml), *p*-toluenesulfonic acid (*ca.* 100 mg), and benzene (600 ml) was heated under reflux using Dean-Stark apparatus for 2.5 h. The reaction mixture was worked up as usual, and crystallization from dichloromethane–ether gave friedelane-3, 19-dione 3-ethylene acetal (**14**; 2.7 g), mp 271—272 °C) crystallized from chloroform–acetone); IR 1685 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (3H, d, J=7 Hz; *s*-CH_3), 0.89 (9H, s; 3× *t*-CH_3), 1.01, 1.18 (each 3H, s; *t*-CH_3), 1.11 (6H, s; 2×*t*-CH_3), 2.19 (1H, s; 18β-H), and 3.8—4.0 (4H, m; $-O-CH_2-CH_2-O-$); MS *m/e* (%) 484 (M^+; 5), 469 (4), 317 (7), 139 (35), and 99 (100); Found: C, 79.22; H, 10.62%. Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81%.

*Reduction of Friedelane-3,19-dione 3-Ethylene Acetal (**14**).* The ethylene acetal (**14**; 2.7 g) dissolved in tetrahydrofuran (500 ml) was treated with lithium aluminium hydride (300 mg) at reflux temperature for 6.5 h and the reaction mixture was worked up as usual to give 19α-hydroxyfriedelan-3-one 3-ethylene acetal (**15**; 2.6 g), mp 287—289 °C (crystallized from chloroform–acetone); IR 3500 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (3H, d, J=7 Hz; *s*-CH_3), 0.88, 1.08 (each 6H, s; 2× *t*-CH_3), 0.90, 1.01, 1.25 (each 3H, s; *t*-CH_3), and 3.7—4.0 (5H, m; 19β-H and $-O-CH_2-CH_2-O-$); MS *m/e* (%) 486 (M^+; 6), 471 (4), 468 (4), 317 (14), and 99 (100).

*Deacetalization of Hydroxy Ethylene Acetal (**15**).* A solution of the hydroxy ethylene acetal (**15**; 160 mg) in acetone (160 ml) was heated with a catalytic amount of *p*-toluenesulfonic acid. The reaction product was purified by column chromatography on silica gel (20 g) to give 19α-hydroxyfriedelan-3-one (**16**; 139 mg), mp 261—265 °C; IR 3620, 3450, and 1705 cm^{-1}; $[\alpha]_D^{24}$ −9.9° (*c* 0.25, $CHCl_3$); NMR ($CDCl_3$) δ 0.74, 0.90, 1.02 (each 3H, s; *t*-CH_3), 0.88 (3H, d, J=7 Hz; *s*-CH_3), 1.09, 1.26 (each 6H, s; 2×*t*-CH_3), 2.1—2.5 (3H, m; $-CH_2-CO-CH-$), and 3.79 (1H, d, J=5.5 Hz; 19β-H); MS *m/e* (%) 442 (M^+; 3), 424 (13), 409 (13), 273 (43), 186 (31), and 123 (100); Found: C, 81.29; H, 11.32%. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38%.

*Dehydration of 19α-Hydroxyfriedelan-3-one (**16**).* Five portions of 19α-hydroxyfriedelan-3-one (**16**; each *ca.* 2 mg) dissolved in toluene (each 3 ml) were treated with phosphorus pentachloride (each *ca.* 10 mg) at reflux temperature, 60 °C, 40 °C, room temperature, and at −10 °C, respectively, and the reaction product was examined by GLC. A single product was obtained at reflux temperature and was shown to be friedel-18-en-3-one (**10**). A mixture of *D*: *A*-friedo-18β-lup-19-en-3-one (**4**) and an unidentified dehydration product was obtained in a ratio of 3: 4 and 1: 2 in the reactions at 60 °C and 40 °C, respectively. This mixture was inseparable by HPLC, silica gel chromatography, and by recrystallization. Reactions at room temperature and at −10 °C gave the same mixtures as above in a ratio of 3: 1 and 8: 1, respectively.

A solution of **16** (5.6 mg) in toluene (5 ml) was treated with phosphorus pentachloride (*ca.* 63 mg) at −10 °C for 20 h, and the reaction product was examined by GLC. Only the unidentified dehydration product was detected. A solution of **16** (5.4 mg) in toluene (5 ml) was treated with phosphorus pentachloride (*ca.* 10 mg) under the same conditions to yield a reaction product (4.6 mg), which was shown to be the desired isopropylidene derivative (**4**), mp 276—278 °C (crystallized from chloroform–acetone); IR 1710 cm^{-1}; $[\alpha]_D^{24}$ −24° (*c* 0.22, $CHCl_3$); NMR ($CDCl_3$) δ 0.73, 0.83 (each 3H, s; *t*-CH_3), 0.78 (3H, d, J=6 Hz; *s*-CH_3), 0.93 (9H, s; 3×*t*-CH_3), 1.65 (6H, br s; $(CH_3)_2C=C<$), and 2.0—2.5 (6H, m; $-CH_2-CO-CH-$ and $-CH_2-CH<$ $>C=C(CH_3)_2$); MS *m/e* (%) 424 (M^+; 13), 409 (4), 273 (33), and 121 (100); Found: C, 85.02; H, 11.48%. Calcd for $C_{30}H_{48}O$: C, 84.84; H, 11.39%.

Huang-Minlon Reduction of D: A-*Friedo-18β-lup-19-en-3-one(**4**).* A mixture of *D*: *A*-friedo-18β-lup-19-en-3-one (**4**; 23 mg), hydrazine hydrate (100 %, 0.3 ml), potassium hydroxide (200 mg), and diethylene glycol (2 ml) was heated under reflux for 1 h. An excess of hydrazine was distilled off and the distillation was continued until the vapor temperature reached to about 220 °C. Then the reaction mixture was heated under reflux for 4 h. Usual work up gave a residue, which was subjected to separation by column chromatography on silica gel (3 g) impregnated with 20% silver nitrate. Elution with hexane (20 ml) gave a hydrocarbon (11 mg), which was completely identical with *D*: *A*-friedo-18β-lup-19-ene (**3**) prepared from **7**.

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