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BORON TRIFLUORIDE ETHERATE-CATALYZED BACKBONE REARRANGEMENT OF 3α,4α- AND 3β,4β-EPOXY-D:A-FRIEDO-18β,19αH-LUPANES

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Treatment of 3α,4α- and 3β,4β-epoxy-D:A-friedo-18β,19αH-lupanes with boron trifluoride etherate gave migrated lupane derivatives, D:B-friedo-18β,19αH-lup-5- and -5(10)-en-3-ols, 18β,19αH-lup-12-en-3-ols, lup-18-en-3-ols, and lup-19-en-3-ols. D:B-Friedo-18β,19αH-lup-1(10)-en-3α-ol and 3β,10β-epoxy-D:B-friedo-18β,19αH-lupane were also obtained from α- and β-epoxides, respectively. The reaction product ratios in the same reaction in various solvents are listed in Tables.

The studies on acid-catalyzed backbone rearrangements of triterpenes are of interest because these rearrangements constitute a model reversal of their biosynthesis.[1] There appear a number of reports on migrated oleanane, ursane, and hopane derivatives.[2] However, there are only a few reports on a series of migrated lupane derivatives.[3] In previous papers, we reported backbone rearrangements of 3α,4α- and 3β,4β-epoxyshionanes[4,5] and 3β,4β-epoxyfriedelane[6] catalyzed by boron trifluoride etherate in various solvents. This paper deals with backbone rearrangements of 3α,4α- and 3β,4β-epoxy-D:A-friedo-18β,19αH-lupanes (1 and 2) induced by boron trifluoride etherate to give migrated lupane derivatives. Solvent effect on the rearrangement reaction is also examined.

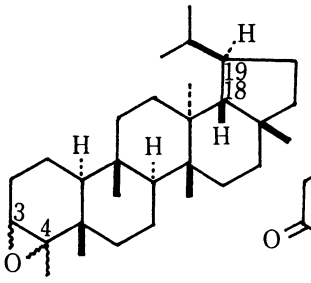
3α,4α-Epoxy- and 3β,4β-epoxy-D:A-friedo-18β,19αH-lupanes (1 and 2) were prepared from friedelin via D:A-friedo-18β-lup-19-en-3-one (3)[3c] and D:A-friedo-18β,19αH-lupan-3β-ol (4);[7] the structure of 1 was unambiguously established by X-ray crystallographic technique.[7]

Treatment of the 3α,4α- and 3β,4β-epoxides (1 and 2; 30-84 mg) in benzene, tetrahydrofuran, or ether (15-25 ml) with boron trifluoride etherate (0.3-0.5 ml) at room temperature or 0 °C gave a reaction mixture, which was separated by preparative TLC. The spectral data of five products (5-9) were identical with those of authentic samples,[7] respectively. A fluorohydrin (10) and a 3β,10β-oxide (11) were easily assigned from their spectral data. The structure of a 1(10)-en-3α-ol (12) was determined by its oxidation with the Jones reagent to yield 1(10)-en-3-one (13), the ^{1}H-NMR spectrum of which showed the presence of a -CO-CH$_2$-CH=C- grouping. An inseparable product mixture containing a 12-en-3α-ol (14), an 18-en-3α-ol (15), and a 19-en-3α-ol (16) was oxidized with the Jones reagent giving a mixture of the cor-

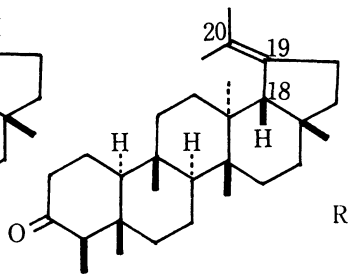
responding ketones (17-19), which was separated by HPLC. This was the same for characterization of a mixture of unsaturated 3β-ols (20-22); the mixture was oxidized and the oxidation product was subjected to separation by HPLC to yield 17, 18, and 19. Small-scale experiments using 1 or 2 (ca. 10 mg) and boron trifluoride etherate (0.1 ml) were carried out in solvents (5-10 ml) such as acetonitrile, dichloromethane, hexane, and dimethoxyethane. These results were summarized in Tables 1 and 2.

The cationic center at C-4 was initially formed by boron trifluoride etherate-attack to an oxygen atom of the epoxide. These migrated lupane derivatives (6-9, 11, 12, 14-16, and 20-22) are considered to be derived from the corresponding intermediate cations, formed by a sequence of 1,2-shifts of methyl group(s) and hydride(s) from the C-4 cation. In a solvent [ether, tetrahydrofuran, or dimethoxyethane (DME)] apt to coordinate with a cation, the rearrangement reaction was interrupted in early stages to give the 5-ene (6 or 7), the 5(10)-ene (8 or 9), and the 3β,10β-epoxide (11), while the rearrangement in solvents with low nucleophilicity proceeds up to C/D/E rings. The formation of the 3β,10β-epoxide (11) is characteristic of the reaction of 2 in ether. In the product mixture from 1, a fluorohydrin derivative and 5 were undetectable.

The driving force to provoke backbone rearrangement in the rigid polycyclic



1 3α,4α-epoxide
2 3β,4β-epoxide



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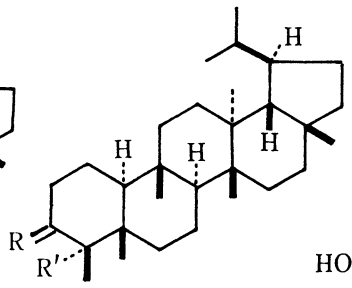
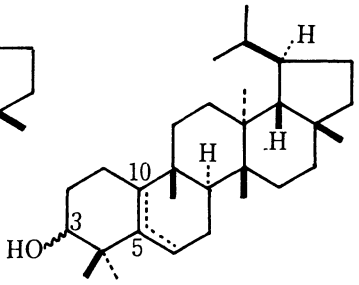
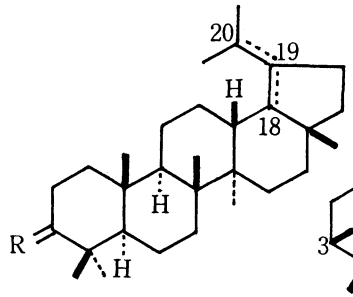


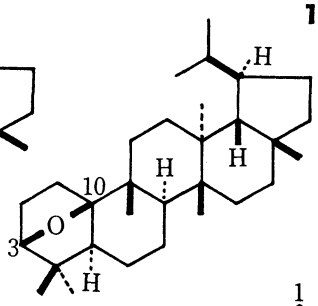
4 R=β-OH,α-H; R'=H
5 R=O; R'=H
10 R=β-OH,α-H; R'=F



6 Δ^5; 3α-OH
7 Δ^5; 3β-OH
8 $\Delta^{5(10)}$; 3α-OH
9 $\Delta^{5(10)}$; 3β-OH



15 Δ^{18}; R=α-OH,β-H
16 Δ^{19}; R=α-OH,β-H
18 Δ^{18}; R=O
19 Δ^{19}; R=O
21 Δ^{18}; R=β-OH,α-H
22 Δ^{19}; R=β-OH,α-H



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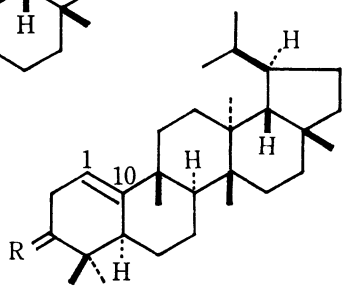
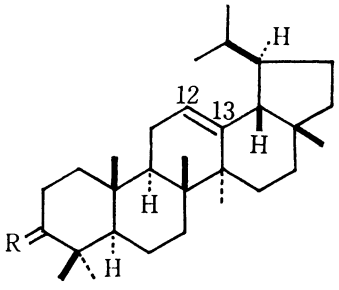


12 R=α-OH,β-H
13 R=O



14 R=α-OH,β-H
17 R=O
20 R=β-OH,α-H

ring is considered to be a release[8] of intercyclic tension due to 1,3-diaxial interaction among the alkyl substituents (especially between the side chain and the 13α-methyl group in shionane series[5]) and due to cis-fused D/E rings (in friedelane[6] and 18β-friedolupane series). D:C-Friedo-type products formed in the rearrangement of shionane series[5] were undetected in the product mixture from 1 and 2; this is considered to be due to a structure difference between the two frameworks of D:A-friedo-18β,19αH-lupane and shionane.

Table 1. Relative Amount Ratios of the Products in the Reaction of the 3α,4α-Epoxide (1) with Boron Trifluoride Etherate at Room Temperature[a]

Solvents	Time (min)	5-Ene (6)	5(10)-Ene (8)	1(10)-Ene (12)	12-Ene (14)	18-Ene (15)	19-Ene (16)
Hexane[d]	30	8	18	0	40	24	10
CH_3CN[d]	30	6	13	0	34	13	34
Benzene	60	trace[b]	63[b]	0	20[c]	11[c]	6[c]
CH_2Cl_2[d]	30	3	46	0	29	16	6
DME[d]	30	17	67	12	2	trace	2
Ether[d]	30	15	76	3	2	1	3
THF	45	15[b]	78[b]	7[b]	0	0	0

a) Room temperature refers to a temperature range between 20 and 28 °C. b) Determined by isolation of the product. c) Determined by conversion of the product into the corresponding ketone, which was isolated by means of preparative HPLC. d) Determined by small-scale experiments; the reaction products were subjected to the Jones oxidation. Relative yields of the 1(10)-, 12-, 18-, and 19-enes were estimated from the peak area of the corresponding ketones on HPLC under the same conditions as described before (refs. 5, 6b). A mixture containing D:B-friedo-18β,19αH-lup-5-en-3-one and 5(10)-en-3-one (ref. 7) was separated by HPLC and examined by GLC to determine relative yields of 5- and 5(10)-enes.

Table 2. Relative Amount Ratios of the Products in the Reaction of the 3β,4β-Epoxide (2) with Boron Trifluoride Etherate at Room Temperature[a]

Solvents	Time (min)	D:A-Friedo-3-one (5)[f]	Fluorohydrin (10)[f]	5-Ene (7)	5(10)-Ene (9)	3β,10β-Oxide (11)[f]	12-Ene (20)	18-Ene (21)	19-Ene (22)
Hexane[d]	60	trace	trace	21	22	0	23	10	24
CH_3CN[d]	60	0	7	11	38	0	27	9	8
Benzene	60	2[b]	4[b]	13[b]	10[c]	0	18[c]	43[c]	10[c]
CH_2Cl_2[d]	60	0	3	25	33	0	16	14	9
DME[d]	60	0	0	26	67	2	2	1	2
Ether[e]	20	3[b]	25[b]	13[b]	33[b]	26[b]	0	0	0
THF	45	0	19[b]	12[b]	69[b]	0	0	0	0

Footnotes a - d are the same as those in Table 1. e) The reaction was carried out at 0 °C. f) Determined by GLC before the oxidation for small-scale experiments. GLC conditions: Shimadzu Gas Chromatograph GC-6A, FID; column, Dexsil 300GC; column temperature, 270 °C.

Characterization of products is as follows: 4α-fluoro-D:A-friedo-18β,19αH-lupan-3β-ol (10): mp 171 °C, IR 3470 cm^{-1}, ^{1}H-NMR[9] δ 0.84-0.93 (5 x CH_3), 1.07 and 1.25 (each 3H, s), 1.33 (3H, d, J=24 Hz; 4β-CH_3),[5] 3.68 (1H, m, $W_{1/2}$=13 Hz; 3α-H); MS m/e 446.3935 (M^+; $C_{30}H_{51}OF$); 3β,10β-epoxy-D:B-friedo-18β,19αH-lupane (11): mp 136-138 °C, ^{1}H-NMR δ 0.84-1.03 (6 x CH_3), 1.67 (6H, s), 3.72 (1H, d, J=5.5 Hz; 3α-H),[5,6a] MS m/e 426.3861 (M^+; $C_{30}H_{50}O$); D:B-friedo-18β,19αH-lup-1(10)-en-3α-ol (12): mp 103-109 °C, IR 3400 cm^{-1}, ^{1}H-NMR δ 0.63, 0.82, 1.01, 1.10 (each 3H, s), 0.89 (6H, d, J=6Hz), 0.96 (6H, s), 3.34 (1H, m, $W_{1/2}$=7 Hz; 3α-H), 5.22 (1H, m, $W_{1/2}$=8 Hz; 1-H), MS m/e 426.3847 (M^+; $C_{30}H_{50}O$); D:B-friedo-18β,19αH-lup-1(10)-en-3-one (13): mp 215-218 °C, IR 1710 cm^{-1}, ^{1}H-NMR δ 2.75 and 3.01 (each 1H, dt, $J_{2\alpha,2\beta}$= 21 Hz, $J_{1,2}$=3 Hz; $J_{2,5}$=3 Hz; 2α-H and 2β-H), MS m/e 424.3710 (M^+; $C_{30}H_{48}O$); 18β,19αH-lup-12-en-3-one (17): mp 152.5-153 °C, IR 1710, 850 cm^{-1}, ^{1}H-NMR δ 0.77 and 0.87 (each 3H, d, J=6 Hz), 0.94 and 1.01 (each 3H, s), 1.07 and 1.13 (each 6H, s), 5.21 (1H, t, J=4 Hz; 12-H), MS m/e 424.3708 (M^+; $C_{30}H_{48}O$) and m/e 218.2064 ($C_{16}H_{26}$; due to retro-Diels-Alder fragmentation); lup-18-en-3-one (18): mp 167-168 °C, IR 1710 cm^{-1}, ^{1}H-NMR δ 0.82-1.05 (7 x CH_3), 1.07 (3H, s), MS m/e 424.3691 ($C_{30}H_{48}O$); the spectral data of 18 were identical with those of authentic specimen prepared from 3β-acetoxy-lupa-18,20(29)-diene[10] by hydrogenation and successive treatment with lithium aluminium hydride and the Jones reagent (and purification by HPLC). lup-19-en-3-one (19): mp 174-177 °C, IR 1712 cm^{-1}, ^{1}H-NMR δ 0.77, 0.91, 0.95, 1.06 (each 3H, s), 1.01 (6H, s), 1.53 and 1.55 [each 3H, s, $>C=C(CH_3)_2$], MS m/e 424.3711 ($C_{30}H_{48}O$).

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