Backbone Rearrangement of 3β,4β-Epoxyfriedelane. A Formation of Germanicol and Solvent Effects[1]

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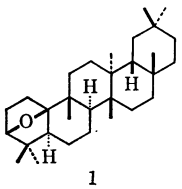
In the reaction of 3β,4β-epoxyfriedelane with boron trifluoride etherate in benzene, a backbone rearragement proceeds up to D/E rings, giving germanicol as the main product, together with D:B-friedo-olean-5(10)-en-3β-ol, D:B-friedo-olean-5-en-3β-ol, and β-amyrin. The reaction product ratio of this reaction in various solvents was examined by HPLC.

It has been reported that a treatment of 3α,4α-epoxyfriedelane with tin(IV) chloride[2a] or with boron trifluoride etherate[2b] gives D: B-friedo-olean-5(10)-en-3α-ol,[2] olean-12-en-3α-ol,[2b] 18αH-olean-12-en-3α-ol,[2b] olean-13(18)-en-3α-ol,[2b] and 18αH-A-neo-oleana-3(5), 12-diene.[2b] In connection with the synthesis of dendropanoxide (**1**), we previously investigated the boron trifluoride etherate-catalyzed backbone rearrangement of 3β,4β-epoxyfriedelane (**2**) in ether, and reported the formation of dendropanoxide (**1**), 4α-fluorofriedelan-3β-ol (**3**), D: B-friedo-olean-5(10)-en-3β-ol (**4**), D: B-friedo-olean-5-en-3β-ol (**5**), and β-amyrin (**6**), together with an unidentified alcohol in a minute quantity.[3] It has been also reported that the rearrangement reaction of 3β,4β-epoxyshionane with boron trifluoride etherate remarkably depends on the nature of solvents used.[4] The present paper describes the isolation and characterization of germanicol (**7**) in the reaction of 3β,4β-epoxyfriedelane (**2**) with boron trifluoride etherate in benzene and reports solvent effects on the reaction.

Treatment of 3β,4β-epoxyfriedelane (**2**) in benzene with boron trifluoride etherate at room temperature for 10 min gave a mixture of products, which proved by high performance liquid chromatography (HPLC) to consist of the unidentified alcohol[3] (45%), besides the known rearranged products:[3] D: B-friedo-olean-5(10)-en-3β-ol (**4**; 15%), D: B-friedo-olean-5-en-3β-ol (**5**; 15 %), and β-amyrin (**6**; 25%). This mixture was subjected to separation by column chromatography on silica gel and then by preparative HPLC to give the alcohol as crude crystals, which was recrystallized from chloroform–methanol. The alcohol was inferred to be germanicol (**7**)[5] by the following evidence. The alcohol showed mp 177—178.5 °C[5] and a molecular ion peak at *m/e* 426 together with prominent peaks at *m/e* 204, 189, and 177 typical of Δ^{18}-oleanenes.[6] The IR and NMR spectra indicated the presence of a secondary hydroxyl group, a trisubstituted double bond, and of eight tertiary methyl groups (*cf.* Experimental). In the NMR spectrum, the signal due to the olefinic proton resonating at δ 4.85 is characteristic of germanicol and its derivatives [*dl*-germanicol[5b] (δ 4.85, s), the acetate[7] (δ 4.88, d, J=2 Hz), and the butyrate[8] (δ 4.88, s)] and is different from those of taraxerol[9] (**8**; 5.54, 1H, dd, J=8 and 4 Hz, $C_{(15)}$–H), β-amyrin[3] (**6**; δ 5.20, 1H, t, J=4 Hz, $C_{(12)}$–H), 18αH-β-amyrin[10] (**9**; δ 5.15, 1H, m, $C_{(12)}$–H), D: B-friedo-olean-5-en-3β-ol[3] (**5**; δ 5.63, 1H, dd, J=4 and 1.8 Hz, $C_{(6)}$–H), walsurenol[11] (**10**; δ 5.62, 1H, m, $C_{(11)}$–H), or multiflorenol (**11**) derivatives[12] (δ 5.24—5.55, m, $C_{(7)}$–H). The structure (**7**) of this alcohol was confirmed by the following conversion. The alcohol (**7**) in anhydrous benzene was treated with potassium and methyl iodide.[13] Recrystallization of the product from acetone–benzene gave miliacin (**12**), which was found to be identical with an authentic specimen isolated from *Panicum miliaceum* L.[14]

Solvent effects on the formation of products in the reaction were then investigated. The small scale reaction using 3β,4β-epoxyfriedelane (1—3 mg) and boron trifluoride etherate in various solvents was carried out, and the products were examined by HPLC. The results are summarized in Table 1.

The attack of boron trifluoride etherate to the oxygen atom of the epoxide (**2**) gives rise to a cationic center at C-4 (or its equivalent species). A sequence of 1,2-shifts of methyl group(s) and hydride(s) would then be followed to give cations in various rearrangement stages, which after deprotonation afford the rearranged alcohols (**4**, **5**, **6**, and **7**). When the reaction was carried out in a solvent (such as DME, THF, or ether) apt to coordinate with a cation, the reaction was interrupted in early stages to give D: B-friedo-oleanene derivatives[3] (**1**, **4**, and **5**) together with the fluorohydrin[3] (**3**) and friedelin[3] (**13**). The rearrangement in solvents with low nucleophilicity (such as toluene, benzene, and



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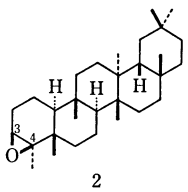

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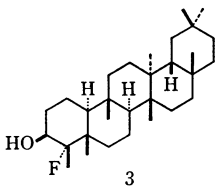

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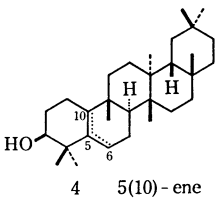
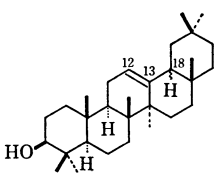
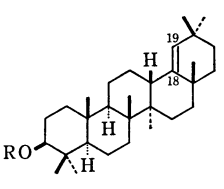


4 5(10)-ene
5 5-ene



6 18β-H
9 18α-H

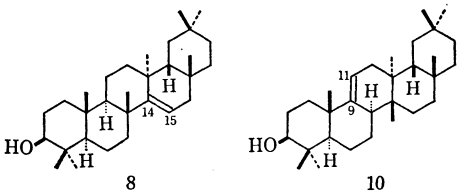


7 R=H
12 R=CH_3

Table 1. Relative amount ratios of the products in the reaction of **2** with boron trifluoride etherate[a]

Solvents	Temp (°C)	Time (min)	**2**	**12**	**3**	**1**	**5** (5-ene)	**4** 5(10)-ene	**6**[b] (12-ene)	**7**[b] (18-ene)
Toluene	r.t.[c]	10	0	5	0	0	10	15	25	45
Toluene	−5	10	0	5	0	0	10	10	30	45
Benzene	r.t.	10	0	5	0	0	15	15	25	40
CH_2Cl_2	r.t.	20	0	0	0	0	20	10	30	40
CH_2Cl_2	−5	20	0	0	0	0	30	5	25	40
Hexane	r.t.	20	0	5	0	0	15	10	30	40
Hexane	−5	20	0	5	0	25	20	15	15	20
Cyclohexane	r.t.	20	0	15	0	0	10	40	15	20
CH_3CN	r.t.	20	0	20	0	0	15	45	10	10
CH_3CN	−5	20	0	15	0	0	15	50	10	10
Ether	r.t.	20	0	5	60	15	5	15	trace	trace
Ether	−5	60	0	5	40	15	5	35	trace	trace
DME	r.t.	20	0	0	25	15	15	45	trace	trace
DME	−5	20	0	0	25	10	15	50	trace	trace
THF	r.t.	70	10	5	35	0	10	40	0	0
THF	−5	70	75	0	10	0	5	10	0	0

a) Relative yields were determined by HPLC. Measurements were carried out at room temperature using a Liquid Chromatograph Model ALC/GPC 202/401 (Waters Assoc.) with an RI detector; column: μ-PORASIL 1/8 (inch) × 1 (foot); solvent system: 10% ether–hexane; flow rate: 0.8 ml/min; pressure: *ca.* 450 psi. Even if HPLC analyses were carried out under these conditions, the retention times were variable. Mean values of their retention times were 5.1, 5.7, 6.9, 13.2, 14.5, 19.3, 21.2, and 21.8 min for **1**, **2**, **12**, **3**, **5**, **4**, **7**, and **6**, respectively. b) Errors are relatively large owing to the proximity of both retention times. c) Room temperature (r.t.) refers to a temperature range between 20 and 28 °C.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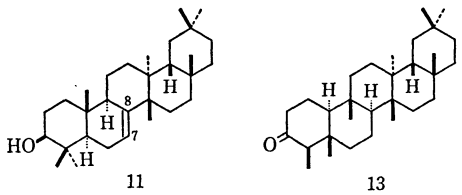
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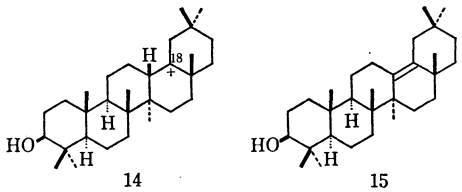
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dichloromethane *etc.*) proceeded up to D/E rings to give germanicol (**7**; main product) and β-amyrin (**6**), besides **4** and **5**, as the cationic center survives longer in these solvents. Germanicol (**7**) could be derived from a cation (**14**; or its equivalent species);[15] olean-13(18)-en-3β-ol (**15**) which might be also derived from **14** was not detectable in the reaction mixture. These results (Table 1) shown above are parallel to those observed for the solvent effects on the reaction of 3β,4β-epoxyshionane.[4]

Driving force to provoke backbone rearrangement in the rigid polycyclic ring is considered to be a release[16] of intercyclic tension due to 1,3-diaxial interactions among the alkyl substituents (especially between the side chain and the 13α-methyl group in shionane series) and due to *cis*-fused D/E rings (in friedelane series). Thus, the acid-catalyzed backbone rearrangement of friedelane derivatives proceeds from ring A towards ring E, and constitutes a reversal of the biogenesis[17] of friedelin (**13**) from β-amyrin-type intermediate.[15] In the rearrangement of 3β,4β-epoxyshionane the formation of D: C-friedo-bacchar-7-en-3β-ol and D: C-friedo-bacchar-8-en-3β-ol was observed,[4] while the corresponding 7- and 8-enes were undetected in the product mixture from **2**. This is considered to be a structure difference between the two skeletons of friedelane and shionane. The acid-catalyzed backbone rearrangements hitherto reported for derivatives of friedelane,[2,3,18] alnusane (glutinane),[19] multiflorane,[20] and of taraxane[21] are limited to proceed up to C/D rings. Germanicol is the first example of product in which the backbone rearrangement of friedelane-oleanane-type effected up to E-ring.

Experimental

General procedures and preparation of 3β,4β-epoxyfriedelane (**2**) were the same as described in a previous paper.[3]

Isolation and Characterization of Germanicol (7). A solution of 3β,4β-epoxyfriedelane[3] (**2**; 175 mg) in anhydrous benzene (150 ml) was treated with boron trifluoride etherate (1 ml) at room temperature for 10 min and usual work-up gave a residue (*ca.* 170 mg). The residue was shown by HPLC examination to consist of germanicol[5] (**7**; 45%), D: B-friedo-

olean-5(10)-en-3β-ol[3,19] (**4**; 15%), D: B-friedo-olean-5-en-3β-ol[3,19] (**5**; 15%), and β-amyrin[3] (**6**; 25%). This residue was dissolved in benzene, passed through a column of silica gel (30 g), and eluted with the same solvent (each fraction 50 ml). Fractions 6—14, containing β-amyrin (**6**) and germanicol (**7**), were combined (*ca.* 133 mg) and subjected to preparative HPLC separation to afford about 30 mg of germanicol (**7**). The isolation yield of germanicol (**7**) was very poor, because the separation of **6** and **7** by HPLC was carried out with much difficulity owing to the proximity of their retention times (21.2 and 21.8 min for **7** and **6**, respectively). Recrystallization from chloroform–methanol gave pure germanicol (**7**; 10 mg), mp 177—178.5 °C, (lit, 176—177 °C,[5a] 173—175 °C,[5b] 179 °C,[5c] 176.5—177 °C,[5d] 180 °C,[5e] and synthetic *dl*-germanicol, 220—223 °C,[5f]); IR (KBr) 3450, 1630, and 840 cm^{-1}; NMR ($CDCl_3$) δ 0.74, 0.78, 0.89, 0.98, 1.02, 1.09 (each 3H, s, *t*-Me), 0.94 (6H, s, 2×*t*-Me), 3.20 (1H, dd, $J_{2\beta,3\alpha}=10$ and $J_{2\alpha,3\alpha}=5$ Hz, $C_{(3\alpha)}$-H), and 4.85 (1H, d, $J=1.5$ Hz, $C_{(19)}$-H); MS *m/e* (%) 426 (M^+; 50), 411 (31), 204 (100), 189 (83), and 177 (83).

Methylation of Germanicol (7). Potassium (100 mg) was added to a solution of germanicol (**7**; 5.7 mg) in anhydeous benzene (10 ml) and the mixture was refluxed for 2 h under a nitrogen atmosphere. A solution of methyl iodide (2 ml) in benzene (10 ml) was added and heating was continued for 4 h under reflux. After addition of methanol (2 ml) and benzene (10 ml), the organic solution was washed with water, 2M hydrochloric acid, and then with brine, dried over magnesium sulfate, and evaporated to afford a residue (7 mg). The residue was crystallized from acetone–benzene to give miliacin (**8**; 2.7 mg), mp 280—281.5 °C, (lit, 283 °C[14]); IR (KBr) 1635, 1180, 1110, 860, and 850 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (6H, s, 2×*t*-Me), 0.89, 1.02, 1.08 (each 3H, s, *t*-Me), 0.95 (9H, s, 3×*t*-Me), 3.35 (3H, s, -OMe), and 4.85 (1H, d, $J=1.5$ Hz, $C_{(19)}$-H); MS *m/e* (%) 440 (M^+; 44), 425 (23), 393 (5), 204 (100), 189 (75), and 177 (63). Identification of this compound with an authentic sample (mp 282.5—283 °C) of miliacin[14] was effected on mixed mp (280—283 °C), TLC, IR, NMR, and on mass spectra.

Reaction of 3β,4β-Epoxyfriedelane (2) with Boron Trifluoride Etherate in Various Solvents. Examination of the Products by HPLC. 3β,4β-Epoxyfriedelane (**2**; 1—3 mg) dissolved in a solvent (2—10 ml) was treated with boron trifluoride etherate (2 drops) at −5 °C or at room temperature. After usual treatment, the reaction mixture was extracted with ether to give a residue on evaporation of the solvent. The residue was subjected to examination by HPLC. The results are listed in Table 1. Authentic samples (**1**, **3**—**6**, and **12**) used for an identification of the products are the compounds obtained in the previous work.[3]

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