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STRUCTURE AND STEREOCHEMISTRY OF A TRITERPENOID EPOXIDE FROM *ADIANTUM CAPILLUS-VENERIS*

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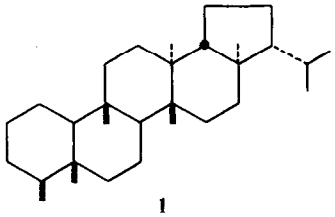
Abstract—A triterpenoid epoxide obtained from *Adiantum capillus-veneris* has been identified as 3α,4α-epoxyfilicane on the basis of several chemical and physical observations.

A TRITERPENOID epoxide isolated from the fern *Adiantum capillus-veneris* L. had provisionally been called "adiantoxide".[1,2] The initial work involving degradation of ring A, which has been reported in detail,[2] has shown that the epoxide function is attached to positions 3 and 4 of a pentacyclic skeleton having a structure very similar to that of friedelane. It was later found that the skeleton of the epoxide was of a new type, evidently biogenetically derived from hopane through several 1,2-shifts of Me groups and H atoms.[3] The common name "filicane" was proposed for the parent hydrocarbon (**1**), which, according to the rules of Allard and Ourisson,[4] should be given the systematic name "D:A-friedo-B′:A′-neogammacerane". We think, therefore, that the name adiantoxide should be dropped, as it would create confusion with adianane derivatives.[5]



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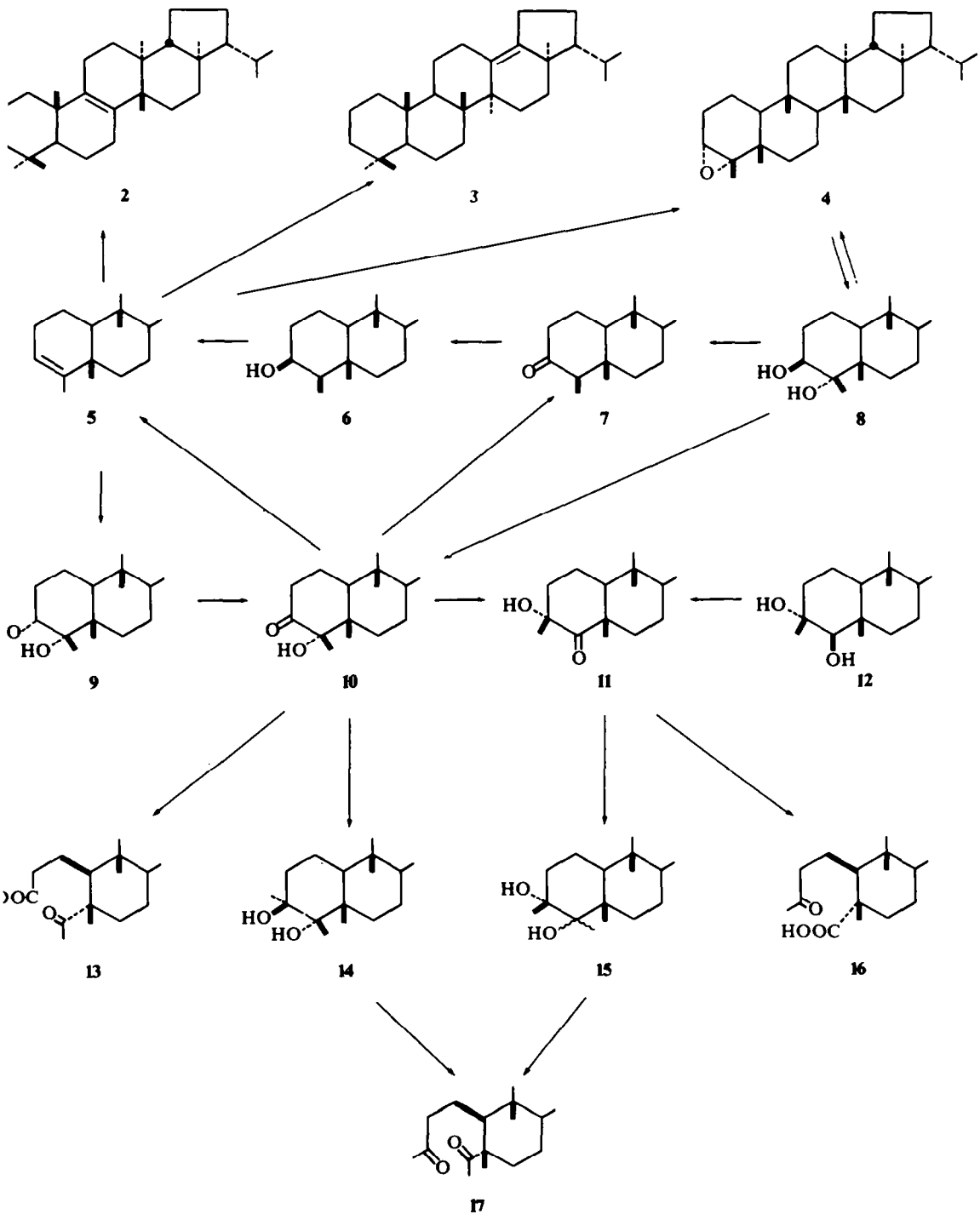
This paper presents data, not included before,[2] which has led to the assignment of structure and configuration **4** for the new epoxide. The reactions are summarized in Chart I. As reported,[2] the epoxide can be converted into the glycol **8** through reaction with trichloroacetic acid followed by hydrolysis, or through chromatography on moist alumina. Treatment of **8** with sulphuric acid, or better with BF_3-etherate, gives 3-filicanone (**7**). Oxidation of **8** with Jones reagent produces the ketol **10** and the keto acid **13**. LAH reduction of **7** to the β-ol **6**, followed by treatment with phosphorus oxychloride, or Huang-Minlon reduction of **10** gives 3-filicene (**5**), which has been isolated from several ferns.[6] The acid catalyzed isomerization of **5** produces

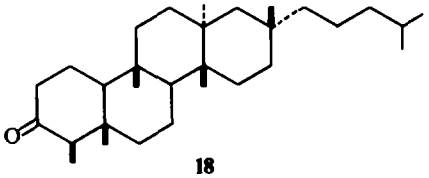
CHART 1



a mixture of 8-fernene (**2**)[7] and hopene-II (**3**)[8]. The reaction of **5** with osmium tetroxide yields the *cis* glycol **9**, which is oxidized by Jones reagent to the ketol **10**. In an attempt to isomerize the glycol **8** to **9** with sodium amoxide a different glycol is obtained which has the structure **12**. The new glycol is oxidized by Jones reagent to the ketol **11** and the acid **16**; **11** is also obtained from **10** with aluminum t-butoxide and with BF_3-etherate.

The structures and configurations of the compounds mentioned are based on the following considerations.

(1) The ketone **7** and the methyl ester of the keto acid **13** present CD curves which are practically superimposable on those of shionanone (**18**)[9] and methyl friedonate (**19**),[10] thus confirming that the structures and configurations of rings A and B are the same in the filicane, shionane and friedelane systems.



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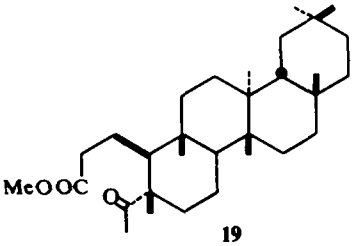

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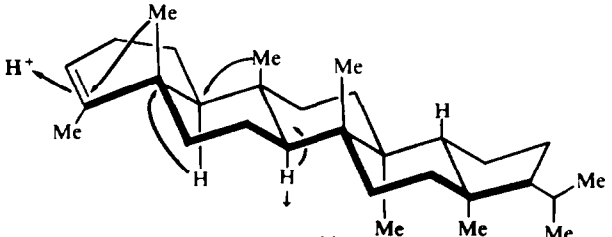
(2) The isomerization of the olefin **5** with acids to hopene-II (**3**) very closely resembles the well known 3-friedelene → 13(18)-oleanene conversion.[11] These "backbone rearrangements" are known to follow very strict steric rules, and configurational assignments based on them can be assumed to be entirely reliable. In our case the formation of **2** and **3** can only take place through a series of probably concerted 1,2-shifts, as outlined in **20** and **21**, and points to structure **4** for the *Adiantum* epoxide, the only open question being the configuration of the epoxide ring. This last point was cleared up by the evidence outlined below.

(3) When 3-filicene (**5**) was oxidized with *p*-nitroperoxybenzoic acid, the main product was identical with the natural epoxide. Since epoxidations are usually quite sensitive to steric shielding by neighbouring groups,[12] preferential formation of the α-epoxide would be expected because of the presence of the 5β-Me group.

(4) The *cis* glycol obtained from **5** with osmium tetroxide should also have the α configuration ([9]). Apart from the hindrance by the 5β-Me group this assumption



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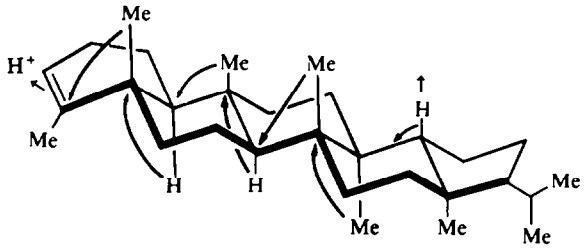

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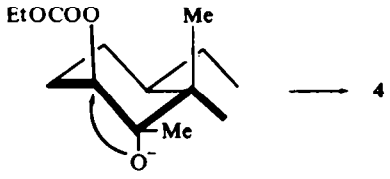
is justified by the observation that simple rigid cyclohexene derivatives with a substituent in position 1, such as 4-t-butyl-1-phenylcyclohexene, give with osmium tetroxide mainly the *cis* diol with an axial OH group in position 1.[13] On the other hand the formation of the same ketol **10** from **8** and **9** points to the diaxial *trans* configuration for the former glycol, which was confirmed by the evidence given below.

(5) The relation between the glycol **8** and the epoxide **4** is of fundamental importance for the assignment of the configuration to the latter compound. Ring openings of aliphatic epoxides usually take a *trans*-diaxial course.[14] Hydrolytic cleavage could lead to the diaxial glycol starting either from the α-epoxide (nucleophilic attack on C-3) or from the β-epoxide (attack on C-4); therefore, the isolation of **8** would not provide any information on the configuration of the epoxide. However, in the case of the reaction with an acid X–H, the 3β-X,4α-OH derivative would be expected to be formed from a diaxial opening of the α-epoxide, the 3β-OH,4α-X derivative from one involving the β-epoxide. It had been shown before[2] that the *Adiantum* epoxide reacts with trichloroacetic acid and with hydrogen chloride to give, respectively, a mono(trichloroacetic) ester and a chlorohydrin, both having a tertiary OH group. If it can be shown that these compounds are diaxial this would provide a very strong proof for the α configuration of the epoxide. The trichloroacetic ester can be converted under very mild conditions (alkaline hydrolysis, or reduction with LAH) into the glycol **8** which is certainly diaxial. Its IR spectrum in dilute CCl_4 solution shows a single free OH stretching band at 3630 cm^{-1} and no trace of the intramolecularly bonded OH, which would be expected in a diequatorial or *cis* glycol;[15] for instance, the *cis* glycol **9** shows bands at 3631 and 3583 cm^{-1}, the *trans* diequatorial glycol **12** at 3597 cm^{-1}, with inflections at 3636 and 3613 cm^{-1}. Also the ketol **10**, obtained from **8**, clearly has an axial OH group as shown by a stretching band at 3613 cm^{-1} (free OH);[16] the ketol **11**, in which the group is equatorial, exhibits only a broad band at 3502 cm^{-1} due to a strongly bonded OH group. Further chemical proof of the stereochemistry of **10** is provided by its easy reduction to **7** with zinc and acetic acid,[17] by its easy oxidative cleavage with chromic acid[18] and by its complete conversion into the hydrocarbon **5** under Wolff-Kishner conditions.[19]

(6) Glycol **8** is easily reconverted in good yield into the epoxide **4** under the action of ethyl carbonate and sodium ethoxide. This reaction, which was first applied in the work on cascarillin,[20] very probably involves transesterification to give the less hindered secondary monoester, which is then cyclized through intramolecular displacement of the ester grouping by the tertiary alkoxy anion.[22] This facile reaction

would hardly be expected to take place with the diequatorial glycol to form the β-epoxide, and provides further proof for the configurations of **8** and **4**.



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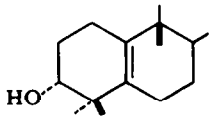
(7) In the NMR spectrum of epoxide **4** the H on C-3 shows up as an apparent triplet at 2·80 δ with a separation of 5 c/s between the two extreme peaks, evidently the X part of an ABX system. This is consistent with the assumed configuration, if one considers valid the Karplus equation as modified for steroid epoxides:

$$J_{H^*H'} \sim 5{\cdot}1 \cos^2 \Phi \qquad (1)$$

correlating the coupling constants between the oxirane proton (H*) and an adjacent cyclohexyl proton (H') with the corresponding dihedral angle.[21] Dreiding models show that in the ring A half-chair conformation of the α-epoxide the dihedral angles between the plane containing the C_2—C_3—H* bonds and those containing the C_2—C_3—2H(β) and C_2—C_3—2H(α) bonds are approximately 20° and 100°. Application of equation (1) gives $J_{H^*H\beta} \sim 4{\cdot}5$ c/s, $J_{H^*H\alpha} \sim 0$ c/s. On the other hand for the β-epoxide both dihedral angles are about 60°, which would correspond to $J \sim 1{\cdot}3$ c/s. As the splitting observed in the triplet should correspond to the sum of $J_{H^*H\beta} + J_{H^*H\alpha}$, the experimental value of 5 c/s is in much better agreement with the expectation for an α, rather than for a β-epoxide.

(8) Treatment of the epoxide **4** with BF_3-etherate gives a mixture of non-allylic unsaturated alcohols, and not even a trace of ketone.[2] Although the products were not further characterized, their formation must involve migration of the 5-Me group to the 4 position and further 1,2-shifts to give compounds like **23** and **24**.



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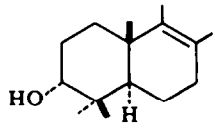

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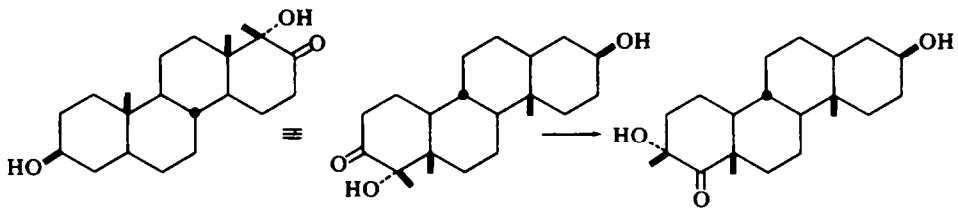
This is in agreement with a *trans* disposition of the epoxide bridge with respect to the 5-Me group, while the complete absence of ketone would be hard to account for in the case of the β-epoxide.

(9) The configuration of ring A of glycol **8** is enantiomeric to that of ring A of the natural diterpenoid cascarillin.[22] The *Adiantum* epoxide also bears some resemblance with cascarillin A,[23] which also has an epoxy ring, but is enantiomeric in the A:B ring junction. An interesting resemblance is also to be found between rings C and D of

D-homosteroids obtained by the well known acyloin rearrangements of 17-hydroxy-20-keto steroids,[24] such as **25** and **26**. The conversion of **25** into **26** with aluminum t-butoxide or BF_3[25] is closely related with the similar conversion of **10** into **11**. Also



25 **26**

the transformation of the glycol **8** into its isomer **12** with sodium amoxide very probably proceeds through **10** which is isomerized to **11** and then reduced again in a Meerwein-Ponndorf type reaction. An alcohol-ketone equilibrium is usually assumed as the explanation for the epimerization of alcohols with alkoxides, the oxidation step being probably caused by air.[26] The β configuration for the 4-OH group in **12** is assumed on the basis of the fact that the reaction conditions should favour the formation of the more stable equatorial alcohol; it is confirmed by the IR data mentioned above. The relation between **12** and **8** is also shown by their conversion into the diketone **17**, through oxidation to the ketols **10** and **11**, followed by reaction with methyl magnesium iodide to give the diols **14** and **15**, and by cleavage with lead tetraacetate. The diol obtained from the ketol **10** has the diaxial configuration as shown by the presence of a single OH stretching band at 3633 cm^{-1};[16] the product obtained from the ketol **11** is probably a mixture of epimers at C-4 [bands at 3620, 3598 (inflection) and 3562 cm^{-1}] (**15**).

The epoxide **4** is one of the many examples of triterpenoids derived from a hopane precursor, which have been found in recent years in ferns.[6] The filicane skeleton is the last step in the biogenetic "backbone rearrangement" of hopane, which takes place in the opposite direction with respect to the acid catalyzed reaction; hopene-II, 7-fernene, 8-fernene, 9(11)-fernene and 5-adianene, which have also been found in ferns together with some of their oxygenated derivatives constitute intermediate steps in this rearrangement. One interesting biogenetic point is whether the epoxide oxygen of **4** derives from the initiation step in the cyclization of squalene, or is introduced at a later stage by oxidation of 3-filicene; the fact that all other pentacyclic triterpenoids so far found in ferns do not carry oxygenated functions in position 3, that 3-filicene is often present in ferns[6] and that 3-filicen-23-al has been isolated from *Adiantum pedatum*[27] speak in favour of the second hypothesis.

EXPERIMENTAL

M.ps were determined on a Kofler apparatus. IR spectra were taken on paraffin oil mulls, or on dilute solns in CCl_4, with a Perkin–Elmer mod 257 grating spectrophotometer; NMR spectra in $CDCl_3$ (TMS internal standard) on a Varian DA-60 IL spectrometer; specific rotations in $CHCl_3$ on a Perkin–Elmer mod 141 photoelectric polarimeter; CD measurements on a Roussel–Jouan dichrograph.

All comparison between compounds was made on the basis of IR spectra and mixed m.ps. Pet. ether refers to the fraction b.p. 30–50°. For the isolation of the epoxide **4** and for the preparation of compounds **8**, **10** and **13** reference is made to the previous paper.[2]

Filican-3-one (7)

(a) A soln of **8** (0·5 g) in $CHCl_3$ (50 ml) was treated with $BF_3 \cdot Et_2O$ (5 ml), left 3 hr at room temp, then washed with Na_2CO_3 aq, dried (K_2CO_3), evaporated and taken up in MeOH; the product was crystallized from $CHCl_3$–pet. ether: 0·30 g, needles, m.p. 249–251°, $[\alpha]_D^{18}$ −27° (*c* 1·2); lit.[5], m.p. 247·5–249°, $[\alpha]_D$ −27°.

(b) A soln of **10** (20 mg) in AcOH (10 ml) was refluxed 24 hr with Zn powder (2 g); the filtrate was diluted with H_2O, extracted with Et_2O, the Et_2O washed with Na_2CO_3 aq, dried ($MgSO_4$) and evaporated. The residue gave, after crystallization from $CHCl_3$–MeOH, a product identical with the one prepared by method (a).

Filican-3β-ol (6)

The ketone **7** (0·28 g) was refluxed 5 hr with Et_2O (50 ml) containing LAH (0·1 g). Treatment with AcOEt, then with NaK tartrate, evaporation of the dried ($MgSO_4$) Et_2O layer and crystallization from $CHCl_3$–MeOH gave **6** (0·23 g), blades, m.p. 255–257°, $[\alpha]_D^{19}$ +19° (*c* 2·4). (Found: C, 84·19; H, 12·17. $C_{30}H_{52}O$ requires: C, 84·04; H, 12·23%).

3-*Filicene* (5)

(a) A soln of **6** (0·14 g) in pyridine (5 ml) and $POCl_3$ (0·5 ml) was left 24 hr at room temp, then heated 30 min on a steam bath, poured into H_2O, extracted with pet. ether and the extract was filtered through neutral Al_2O_3 (act. I). Evaporation of the eluate and crystallization from $CHCl_3$–MeOH gave blades, m.p. 222–224° (0·12 g), $[\alpha]_D^{18}$ +50·5° (*c* 1·3); lit.,[5] m.p. 228·5–229·5°, $[\alpha]_D$ +50°.

(b) A mixture of the ketol **10** (0·3 g), 85% $N_2H_4 \cdot H_2O$ (0·44 ml), KOH (0·4 g) and diethylene glycol (10 ml) was refluxed 2·5 hr; 85% $N_2H_4 \cdot H_2O$ (0·2 ml) was added and refluxing was continued for 7 hr. Dilution with H_2O, extraction with pet. ether and filtration of the dried ($CaSO_4$) extract through Al_2O_3 gave **5** (0·22 g, m.p. 223–225°), which was identical with the product obtained as under (*a*).

Conversion of **5** *into* 8-*fernene* (2) *and hopene-II* (3)

A suspension of **5** (0·20 g) in AcOH (160 ml) and conc HCl aq (75 ml) was refluxed 18 hr, then diluted with H_2O and extracted with hexane; the extract was washed with NaOH aq, dried ($MgSO_4$) and filtered through Al_2O_3. Evaporation of the eluate gave 0·19 g of a semi-solid product which was dissolved in $CHCl_3$ and diluted with MeOH. A solid (67 mg) precipitated, which was recrystallized from $CHCl_3$–MeOH, then from Me_2CO, to give blades (28 mg), m.p. 193–195°, $[\alpha]_D^{20}$ +3° (*c* 1·2), identical with an authentic sample of hopene-II; lit.,[8] m.p. 194–196°, $[\alpha]_D$ +2°. Further addition of MeOH to the filtrate of the first crystallization gave 40 mg of crystals, which were crystallized twice from Me_2CO to give needles, m.p. 183–185°, $[\alpha]_D^{20}$ +14° (*c* 0·8), identical with an authentic sample of 8-fernene; lit.,[7] m.p. 184–185°, $[\alpha]_D^{16}$ +15·2°. A better yield of 8-fernene (50%) was obtained when **5** (50 mg) was refluxed 12 hr with CF_3CO_2H (2 g) in benzene (20 ml).*

Conversion of **5** *into* **4**

A soln of **5** (210 mg) and *p*-nitroperoxybenzoic acid (150 mg) in $CHCl_3$ (30 ml) was stored at room temp for 16 hr, washed with Na_2CO_3 aq and evaporated. The residue was crystallized from pet. ether and then twice from Me_2CO, to give needles, m.p. 227–229°, identical with **4** of natural origin.[2]

Conversion of **8** *into* **4**

A soln of **8** (0·50 g) in Et_2CO_3 (5 ml) was treated with Na (85 mg), heated under N_2 2 hr at 130° and 30 min at 160°, cooled, diluted with H_2O and steam distilled to eliminate Et_2CO_3. The epoxide **4** (0·43 g) crystallized from the residue of the steam distillation in an almost pure state.

Filicane-3α,4α-diol (9)

A soln of **5** (100 mg) and OsO_4 (80 mg) in pure cyclohexane (10 ml) was stored at room temp for 14 days, then treated with LAH (100 mg) and Et_2O (50 ml) and shaken for 8 hr. Excess hydride was decomposed with AcOEt, the soln was washed with satd NaK tartrate, evaporated and the residue crystallized from MeOH to give **9**, needles (60 mg), m.p. 248–250°, $[\alpha]_D^{21}$ +10° (*c* 0·7). (Found: C, 80·87; H, 11·55. $C_{30}H_{52}O_2$ requires: C, 81·02; H, 11·79%).

* The conversion of **5** into **3** with BF_3-etherate, which gives better yields, will be discussed in a forthcoming paper.

Conversion of **9** *into* **10**

A soln of **9** (10 mg) in Me_2CO (2 ml) was treated with Jones reagent[28] (50 μl), diluted at once with H_2O and extracted with $CHCl_3$; the extract was washed with Na_2CO_3 aq, evaporated and the residue taken up in Et_2O to give **10**, blades, m.p. 275–280°, identical with a sample obtained from the similar oxidation of **8**.[2]

3β-*Methyl*-23-*norfilicane*-3α,4β-*diol* (**12**)

A soln of **8** (0·50 g) in sodium amoxide (prepared from 1 g of Na and 25 ml of 1-pentanol) was refluxed 18 hr, then diluted with H_2O and acidified with 2N H_2SO_4 aq. Addition of Et_2O left undissolved crystalline material (0·30 g), which was crystallized from a mixture of MeOH (100 ml) and EtOH (100 ml), to give blades (0·18 g), m.p. 252–254°, $[\alpha]_D^{21}$ +19·5° (*c* 0·05); 0·10 g of the same product, m.p. 250–252°, was obtained on concentration of the mother liquor. (Found: C, 74·88; H, 11.74. $C_{30}H_{52}O_2 \cdot 2H_2O$ requires: C, 74·95; H, 11·74%). Crystallization H_2O was very difficult to eliminate completely. A sample that had been sublimed *in vacuo* gave the following results: (Found: C, 79·33; H, 11·72. $C_{30}H_{52}O_2 \cdot 1/2H_2O$ requires: C, 79·41; H, 11·77%).

The glycol **12** (23 mg) was stored 24 hr at room temp with benzoyl chloride (0·1 ml) and pyridine (1 ml), then worked up as usual to give a monobenzoate, m.p. 226–228° (from hexane). (Found: C, 80·83; H, 10·05. $C_{37}H_{56}O_3$ requires: C, 80·97; H, 10·29%).

3α-*Hydroxy*-3β-*methyl*-23-*norfilican*-4-*one* (**11**) *and keto acid* **16**

(a) The glycol **12** (125 mg) was dissolved in boiling Me_2CO (100 ml), the soln was cooled to room temp, treated with Jones reagent[28] (220 μl), stored for 5 min, diluted with H_2O and extracted with Et_2O. The organic layer was washed with H_2O, then extracted with 2N NaOH aq (3 × 50 ml). The dried ($MgSO_4$) Et_2O layer was evaporated and the residue crystallized from $CHCl_3$–MeOH to give **11** (50 mg), blades, m.p. 243–245°, $[\alpha]_D^{21}$ +47·5° (*c* 0·7). (Found: C, 80·09; H, 11·28. $C_{30}H_{50}O_2 \cdot \frac{1}{2}H_2O$ requires: C, 79·77; H, 11·38%). The alkaline extracts were acidified and extracted with Et_2O to give **16** (20 mg), which was crystallized from MeOH to give blades, m.p. 245–247°, $[\alpha]_D^{22}$ +7·5° (*c* 0·5). (Found: C, 78·63; H, 10·94. $C_{30}H_{50}O_3$ requires: C, 78·55; H, 10·99%). The methyl ester, prepared with diazomethane in Et_2O, had m.p. 150–152° (from pet. ether). (Found: C, 78·51; H, 11·18. $C_{31}H_{52}O_3$ requires: C, 78·76; H, 11·09%).

(b) Ketol **10** (24 mg) in dry Et_2O (3 ml) was treated with $BF_3 \cdot Et_2O$ (100 μl). After 48 hr some crystals formed in the soln, which were found to be identical with **11**. More **11** was obtained after washing of the soln with Na_2CO_3 aq, evaporation and crystallization from Me_2CO.

(c) Ketol **10** (200 mg) and t-BuOK (300 mg) in toluene (10 ml) were refluxed under N_2 for 10 hr. Washing with 2N HCl, evaporation and crystallization from Me_2CO afforded **11** (70 mg), m.p. 245–247°.

3α-*Methylfilicane*-3β,4α-*diol* (**14**)

A Grignard reagent (from 100 mg Mg and 600 mg MeI in 25 ml Et_2O) was treated with **10** (60 mg) and refluxed 60 min. Addition of 2N H_2SO_4 aq, washing with Na_2CO_3 aq, evaporation of the solvent and crystallization from $CHCl_3$–MeOH gave **14** (45 mg), needles, m.p. 232–233°, $[\alpha]_D^{21}$ +18° (*c* 0·6). (Found: C, 81·05; H, 11·64. $C_{31}H_{54}O_2$ requires: C, 81·16; H, 11·87%).

3β-*Methylfilicane*-3α,4β-*diol and* -3α,4α-*diol* (**15**)

Ketol **11** reacted only very slowly with MeMgI in Et_2O. Therefore this compound (90 mg) was dissolved in THF (30 ml) and added to a Grignard soln (from 200 mg Mg, 1·2 g MeI and 25 ml Et_2O). The soln was refluxed for 2 hr, the Et_2O was then distilled off and refluxing was continued for 1 hr. After the usual work-up the product was crystallized from $CHCl_3$–MeOH to give a mixture, m.p. 225–242°, $[\alpha]_D^{25}$ +13° (*c* 0·6), no CO band in the IR. (Found: C, 81·25; H, 12·01. $C_{31}H_{54}O_2$ requires: C, 81·16; H, 11·87%).

Conversion of **14** *and* **15** *into the diketone* **17**

(a) The mixture of diols **15** (20 mg) in benzene (2·5 ml) was treated with a slight excess of $Pb(OAc)_4$. After 1 hr four drops of ethylene glycol were added and the benzene layer evaporated. Crystallization from MeOH–H_2O gave **17**, needles, m.p. 130–133°. (Found: C, 81·63; H, 11·37. $C_{31}H_{52}O_2$ requires: C, 81·52; H, 11·48%).

(b) When **14** was treated as under (a), a slightly less pure product was obtained, which after two crystallization from MeOH–H_2O had m.p. 127–130°. No depression in m.p. was observed for the mixture with the product obtained from **15**. The IR spectra were almost identical.

Circular dicroism. All measurements were taken on dioxan solns. 3-*Filicanone* (**7**): $\Delta\varepsilon_{301}$ −2·42, $\Delta\varepsilon_{292}$

$-2{\cdot}59$; *shionanone*[9] $\Delta\varepsilon_{300}$ $-2{\cdot}45$, $\Delta\varepsilon_{293}$ $-2{\cdot}61$. *Methyl ester of* **13**: $\Delta\varepsilon_{295}$ $-1{\cdot}07$; *methyl friedonate*:[10] $\Delta\varepsilon_{296}$ $-1{\cdot}08$.

OH *Stretching bands in dilute* CCl_4 *soln* (cm^{-1}). All measurements were taken on $2{\cdot}10^{-3}$M solns in CCl_4 in 2-cm quartz cells, calibrations being made on the 3139 cm^{-1} band of indene. The following bands were observed in the OH stretching region: **8**, 3630; **9**, 3631, 3583; **10**, 3613; **11**, 3502; **12**, 3597, 3613 (infl.), 3636 (infl.); **14**, 3633; **15**, 3559, 3621.

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