The Backbone Rearrangement of 3β,4β-Epoxyfriedelane and the Synthesis of Dendropanoxide[1]

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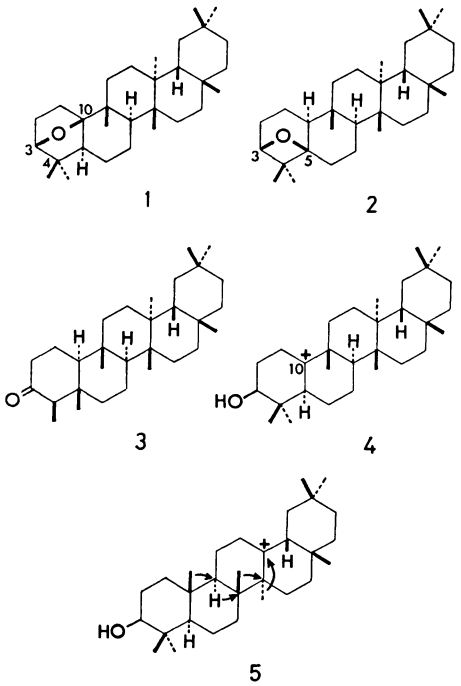
Dendropanoxide (**1**) was synthesized by the reaction of 3β,4β-epoxyfriedelane (**19**) with boron trifluoride etherate in ether at −10 °C. In the rearrangement reaction, 4α-fluorofriedelan-3β-ol (**20**), D : B-friedo-olean-5(10)-en-3β-ol (**21**), β-amyrin (**22**), and D : B-friedo-olean-5-en-3β-ol (**23**) were also produced.

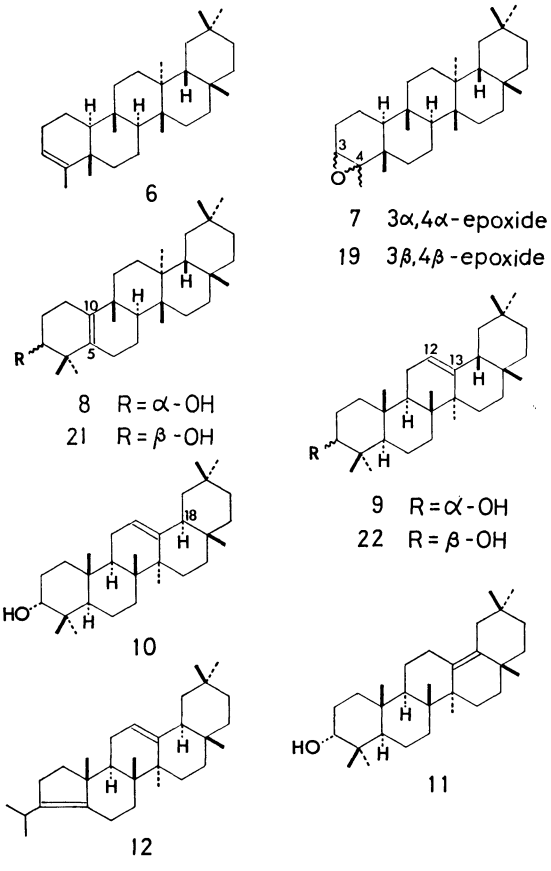
A triterpene oxide, named dendropanoxide,[2] isolated from *Dendropanax trifidus* Makino (=*Gilibertia trifida* Makino, Araliaceae) is also known as epoxyglutinane[3] and campanulin[4] and distributed in a number of plants of Araliaceae and Ericaceae families.[5] Although two alternative structures, D : B-friedo-olean-3,10-oxide (**1**)[3,4,6] and D : B-friedo-olean-3,5-oxide (**2**),[2,3,5] had been proposed, the D : B-friedo-olean-3β,10β-oxide structure (**1**) was recently assigned for this triterpene oxide by X-ray study.[7]

From an interest in biogenetic relationship between dendropanoxide (**2**) and friedelin (**3**),[8] conversion of **3** into **1** was attempted. Dendropanoxide (**1**) may arise by the following biogenetic pathways.[9] An alunusane (glutinane) type intermediate (**4**) may be derived by a sequence of 1,2-shifts of methyl groups and a hydrogen atom from a protonated β-amyrin type intermediate (**5**) which is originated from squalene. A cationic center at C-10 of the resulting intermediate (**4**) then may suffer an attack by an oxygen atom of the C-3 hydroxyl group from β-side, followed by deprotonation in the last step to give dendropanoxide (**1**).

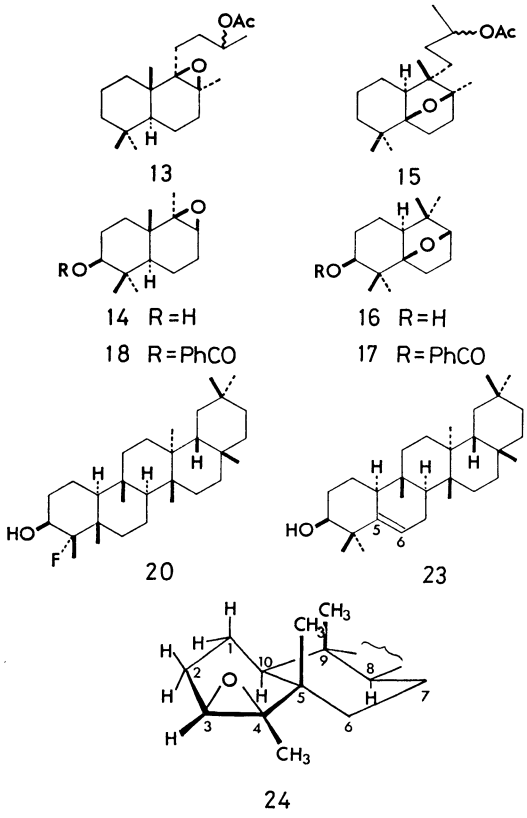


It has been reported that friedel-3-ene (**6**) affords only 3α,4α-epoxyfriedelane (**7**)[10] on epoxydation because of a preferential attack of oxidizing reagents from α-side, and that a treatment of the α-epoxide (**7**) with stannic chloride[10a] or boron trifluoride etherate[10b] gave D : B-friedo-olean-5(10)-en-3α-ol (**8**),[10] olean-12-en-3α-ol (**9**),[10b] 18α*H*-olean-12-en-3α-ol (**10**),[10b] olean-13(18)-en-3α-ol (**11**),[10b] and 18α*H*-A-neo-oleana-3(5),12-diene (**12**).[10b]

Recently Hadley and Halsall[11] reported a boron trifluoride-catalyzed rearrangement of epoxides (**13** and **14**) to give five-membered oxides (**15** and **16**, respectively) in both norlabdane and decalin series. In connection with a study on the rearrangement of tetramethyldecalin derivatives, we found also the formation of a five-membered oxide (**17**) by a similar treatment of an epoxide (**18**).[12] It is therefore suggested that a treatment of 3β,4β-epoxyfriedelane (**19**) with boron trifluoride etherate would produce, by epoxide opening followed by 1,2-methyl shift, the intermediate cation (**4**) (or its equivalent species) which would then afford dendropanoxide (**1**). In the case of shionane derivatives, a conversion of 3β,4β-epoxyshionane into dihydrobaccharis oxide was re-



cently achieved.[13] In the present paper, the formation of dendropanoxide (**1**) as well as 4α-fluorofriedelan-3β-ol (**20**), D : B-friedo-olean-5(10)-en-3β-ol (**21**), β-amyrin (**22**), and D : B-friedo-olean-5-en-3β-ol (**23**) by treatment of 3β,4β-epoxyfriedelane (**19**) with boron trifluoride etherate is described.



It was reported that 3β,4β-epoxyshionane was formed as a minor product together with 3α,4α-epoxyshionane on epoxidation of shion-3-ene.[14] Friedelin (**3**) was transformed *via* friedelan-3β-ol[8a,b] into friedel-3-ene (**6**)[8a,b] by the known procedures. Epoxidation of **6** with *m*-chloroperbenzoic acid gave two epoxides in a ratio of about 2 : 1. One epoxide, mp 234—236 °C, obtained as a major product, was shown to be identical with 3α,4α-epoxyfriedelane (**7**).[10] The other one, $C_{30}H_{50}O$, mp 237—250 °C,* therefore, is corresponding to 3β,4β-epoxyfriedelane (**19**), whose structure was supported by the spectral data (IR, PMR, and mass spectra) and the elemental analysis. Neither hydroxyl nor carbonyl group was observed in the IR spectrum. The PMR spectrum showed a multiplet ($W_{1/2}$ 3 Hz) signal at δ 2.90[14] due to the methine proton attached to a carbon atom (C-3) on the epoxide ring terminus; the corresponding signal of 3α,4α-epoxide (**7**) appeared at δ 2.86.

Treatment of 3β,4β-epoxyfriedelane (**19**) with boron trifluoride etherate in ether at −10 °C gave a complex mixture, which showed four spots on silver nitrate-impregnated silica gel TLC besides a spot attributed to the starting epoxide (**19**). The reaction mixture was separated by silver nitrate-impregnated silica gel column chromatography and by subsequent separation procedures described below into five components (**a**—**e**).

The least polar component **a** (yield: *ca.* 22%) was an oxide, $C_{30}H_{50}O$, mp 206—208 °C, $[\alpha]_D$ +71°, and was found to be identical in all respects with dendropanoxide (**1**), obtained by isolation from *Dendropanax trifidus* Makino according to Kimura's procedure[2], and with authentic D : B-friedo-olean-3β,10β-oxide (**1**), isolated from *Rhododendron macrophyllum* by Block and Constantine.[5,6] The second component **b** (y: *ca.* 1.7%) was identified to be the starting β-epoxide (**19**).

The third component **c** (y: *ca.* 21%) was a fluoride, $C_{30}H_{51}OF$, mp 223.5—224.5 °C. The presence of a secondary hydroxyl group was shown by the PMR spectrum (δ 3.72, 1H, dt, J=6 and 3 Hz) and by the IR spectrum (3450, 1100, and 1030 cm^{-1}). The fluoro alcohol was treated with potassium hydroxide in ethanol under reflux temperature to generate the starting β-epoxide (**19**). These observations led to the conclusion that the fluoro alcohol should be formulated as 4α-fluorofriedelan-3β-ol (**20**). The formation of a fluorohydrin in the reaction of an epoxide with boron trifluoride etherate is often encountered[15].

The fourth component **d** (y: *ca.* 23%) was found to be a mixture of three compounds. The mixture was subjected to fractional recrystallization from acetone to afford an alcohol, $C_{30}H_{50}O$, mp 236.5—237.5 °C. The physical and spectral data were completely identical with those of authentic D : B-friedo-olean-5(10)-en-3β-ol (**21**),[2-6] prepared by isomerization of dendropanoxide (**1**) with hydrochloric acid in ethanol,[2-6] and of the specimen derived from friedelin (**3**) by the known procedure.[16] On evaporation of the solvent, the mother liquor of the fractional recrystallization gave a residue. Although a separation of the residue by TLC under various conditions was attempted, it was not satisfactorily achieved. Then the residue was examined by high performance liquid chromatography (HPLC) and three peaks were detected at 18.0, 19.7, and 20.5 min, the shortest one of which was shown to be attributed to D : B-friedo-olean-5(10)-en-3β-ol (**21**). In the PMR spectrum of the residue obtained from the mother liquor, two signals due to olefinic protons at δ 5.20 and 4.87 besides tertiary methyl signals at δ 0.76—1.20 were observed. The mass spectrum showed two prominent peaks at *m/e* 218 and 205 with relative intensities 100 and 46%, respectively, together with the molecular ion peak at *m/e* 426. It is well known that a characteristic peak at *m/e* 218 due to a retro-Diels-Alder fragmentation is observed in pentacyclic Δ^{12}-triterpenes such as β- or α-amyrin.[17] From this fact as well as the PMR spectrum, in which an olefin proton of β-amyrin resonates at δ 5.20, it was concluded that one component in the residue must be β-amyrin itself. The validity of the conclusion was verified by direct comparison of the retention time (20.5 min) with that of authentic β-amyrin (**22**) in the HPLC examination. The structure of the third compound present in the residue of the mother liquor is left undetermined because of lack of the material and of difficulty of the separation.

* Due to thermal fragility, no sharp melting point was observed (*Cf.* Experimental).

The most polar component **e** (y: *ca.* 14%), eluted from the column, $C_{30}H_{50}O$, mp 208.5—209.5 °C, $[\alpha]_D$ +63.8°, proved to be identical with the authentic D : B-friedo-olean-5-en-3β-ol (**23**)[3,5,6] prepared by the reaction of 4α-bromofriedelin with silver acetate[16] and also by the isomerization of dendropanoxide (**1**) with boron trifluoride.[5,6]

The A-ring of the β-epoxide (**19**) is suggested to be in a conformation depicted as in **24**. The formation of dendropanoxide (**1**) from **19** can be explained by a mechanism involving a non-concerted process. The conversion of friedelin (**3**) into dendropanoxide (**1**) *via* the β-epoxide (**19**) was thus achieved.

Experimental

General Procedure. Melting points were determined on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncorrected. Infrared (IR) spectra were determined on a Hitachi EPI-G2 infrared spectrometer. Mass spectra were measured using a Hitachi RMU-6 mass spectrometer operating at 70 eV with a direct inlet system. High resolution mass spectra were measured using a Hitachi RMH-2 mass spectrometer operating at 70 eV. Proton magnetic resonance (PMR) spectra were measured in a deuteriochloroform solution using a JEOL JNM PS-100 (100 MHz) or a Hitachi R-20B (60 MHz) spectrometer. Chemical shifts are expressed in δ value downfield from TMS as an internal standard and coupling constants in Hz. Optical rotation was measured with a JASCO DIP-SL polarimeter. High performance liquid chromatography (HPLC) analyses were determined on a Waters liquid chromatograph model ALC-GPS 202—401. Analytical and preparative thin layer chromatographies (TLC) were carried out on Kieselgel G nach Stahl (E. Merck) and Kieselgel 60 PF_{254} (E. Merck), respectively. Column chromatography was carried out on Wakogel C-200 (Wako Pure Chem. Ind.).

Preparation of 3β,4β-Epoxyfriedelane (19). To a solution of friedel-3-ene (**6**; 1.97 g) in benzene, *m*-chloroperbenzoic acid (1.74 g) in benzene was added with stirring at room temperature, and the solution was allowed to stand overnight. The reaction was stopped by addition of 10% sodium sulfite solution and the organic layer was washed with saturated sodium hydrogencarbonate solution and then with brine. After drying over sodium sulfate, evaporation of the solvent gave a residue, which was chromatographed on silica gel to afford 3α,4α-epoxide (**7**; 1.06 g), mp 234—236 °C, [IR (KBr) 865 cm^{-1}; PMR δ 0.82, 0.95, 1.07, 1.18, 1.19 (each 3H, s, *t*-CH_3), 1.00 (9H, 3×*t*-CH_3), and 2.86 (1H, t, J=2.5 Hz, $C_{(3)}$-H); mass spectrum *m/e* 426] and 3β,4β-epoxide (**19**; 0.49 g) as colorless needles (crystallized from acetone). The epoxide (**19**) showed no sharp melting point; on heating in a capillary, it began to melt at 237—240 °C and melted completely at 250 °C. In a sealed tube, it sublimed at 245—250 °C. IR (KBr) 1000, 890, 790, and 760 cm^{-1}; PMR δ 0.80, 0.96, 1.07 (each 3H, s, *t*-CH_3), 1.01 (9H, s, 3×*t*-CH_3), 1.18 (6H, s, 2×*t*-CH_3), and 2.90 (1H, m, $W_{1/2}$ 3 Hz, $C_{(3)}$-H); mass spectrum *m/e* 426 (M^+, 42%), 411 (33), 408 (8), 393 (8), 218 (100), and 205 (83); Found: C, 84.54; H, 11.88%. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81%.

Reaction of 3β,4β-Epoxyfriedelane (19) with Boron Trifluoride Etherate. To a solution of 3β,4β-epoxide (**19**; 300 mg) in anhydrous ether (200 ml) kept at −10 °C, boron trifluoride etherate (4 ml) was added with stirring, and the progress of the reaction was monitored by TLC. After 30 min, the starting material was almost consumed and the reaction was stopped by addition of a saturated potassium hydroxide methanolic solution (200 ml). The usual treatment gave a residue, which was subjected to column chromatography on silica gel (70 g) impregnated with silver nitrate (12 g) and the following solvents were used (each fraction 100 ml): frs 1 and 2, petroleum ether; frs 3—5, petroleum ether–benzene (5 : 1); frs 6—8, (4 : 1); frs 9—15, (3 : 1); frs 16—21, (2 : 1); frs 22—41, (1 : 1); frs 42—47, (1 : 2); frs 48—57, benzene; frs 58—63, benzene–ether (3 : 1).

Fractions 9—15, on evaporation of the solvents, afforded dendropanoxide (**1**; component **a**; 65 mg), mp 206—208 °C (recrystallized from acetone), mixed mp 206—208 °C; IR (KBr) 1100, 1010, 995, 980, and 955 cm^{-1}; PMR δ 0.91, 0.95, 0.97, 1.00, 1.02, 1.15, 1.17, 1.20 (each 3H, s, *t*-CH_3), and 3.75 (1H, d, J=4.8 Hz, $C_{(3)}$-H); $[\alpha]_D$ +71° (*c* 0.97, $CHCl_3$); mass spectrum *m/e* 426 (M^+, 15%), 411 (65), 344 (8), 343 (8), 205 (24), and 137 (100). Found: C, 84.64; H, 12.01%. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81%.

Fractions 25 and 27—30 yielded 3β,4β-epoxide (**19**; component **b**; 5 mg) and 4α-fluorofriedelan-3β-ol (**20**; component **c**), respectively, on evaporation of the solvents.

Fractions 31—39 were evaporated to give a mixture, which was separated by column chromatography on silver nitrate-impregnated silica gel (10 g) into the fluoro alcohol (**20**; component **c**) and a component **d**. The fluoro alcohol (**20**) obtained from fractions 27—30 and fractions 31—39 were combined and weighed 64 mg, mp 223.5—224.5 °C (recrystallized from chloroform–methanol); IR (KBr) 3450, 1100, and 1030 cm^{-1}; PMR δ 0.88, 0.96, 1.18 (each 3H, s, *t*-CH_3), 1.00, 1.02 (each 6H, s, 2×*t*-CH_3), and 3.72 (1H, dt, J=6 and 3 Hz, $C_{(3)}$-H); mass spectrum *m/e* 446 (M^+, 15%), 431 (18), 426 (20), 411 (14), 293 (36), 273 (36), and 205 (100); MW 446.3977 (by high resolution mass spectrometry). Calcd for $C_{30}H_{51}OF$: MW 446.3922.

A residue obtained from fractions 40—57 contained component **d** (by TLC examination). This residue and the component **d** from fractions 31—39 were combined (in total, weighed about 70 mg), and fractionally recrystallized from acetone to give D : B-friedo-olean-5(10)-en-3β-ol (**21**; component $\mathbf{d}_1$; 38 mg), mp 236.5—237.5 °C; IR (KBr) 3450, 1630, and 1040 cm^{-1}; PMR δ 0.95, 1.02 (each 9H, s, 3×*t*-CH_3), 1.05, 1.20 (each 3H, s, *t*-CH_3), 3.45 (1H, dd, J=9.5 and 4.5 Hz, $C_{(3)}$-H), and the absence of olefinic proton signal; mass spectrum *m/e* 426 (M^+, 17%), 411 (17), 408 (11), 393 (7), and 205 (100). Found: C, 84.72; H, 12.08%. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81%.

The mother liquors of fractional crystallization were combined and evaporated to give a residue, which was examined by PMR, mass spectrometry, and HPLC: PMR δ 5.20 and 4.87 (olefinic protons); mass spectrum *m/e* 218 (100%) and *m/e* 205 (46%); HPLC (μ-porasil, elution with 10% ether–hexane at flow rate 1.0 ml/min) 18.0, 19.7, and 20.5 min. The retention times of D : B-friedo-olean-5(10)-en-3β-ol (**21**) and β-amyrin (**22**) under the same conditions were 18.0 and 20.5 min, respectively. Therefore, the presence of β-amyrin (**22**; component $\mathbf{d}_2$) in the mother liquor received support. The structure of the third component ($\mathbf{d}_3$; with retention time 19.7 min) contained in the mother liquor remains undetermined.

On evaporation of the solvents, fractions 58—63 gave D : B-friedo-olean-5-en-3β-ol (**23**; 41 mg), mp 208.5—209.5 °C (crystallized from chloroform–methanol); IR (KBr) 3450, 1630, 1095, and 825 cm^{-1}; PMR δ 0.87, 0.97, 1.06, 1.11 1.18 (each 3H, s, *t*-CH_3), 1.02 (6H, s, 2×*t*-CH_3), 3.45 (1H, m, $W_1/_2$ 6 Hz, $C_{(3)}$-H), and 5.63 (1H, dd, J=4 and 1.8 Hz, $C_{(6)}$-H); $[\alpha]_D$ +63.8° (*c* 1.1, $CHCl_3$); mass spectrum

m/e 426 (M^+, 4%), 411 (2), 408 (2), 393 (2), 274 (100), 259 (66), and 205 (45). Found: C, 84.25; H, 11.99%. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81%.

*Treatment of 4α-Fluorofriedelan-3β-ol (**20**) with Base.* 4α-Fluorofriedelan-3β-ol (**20**; 44 mg) in 5% potassium hydroxide ethanolic solution (20 ml) was heated under reflux for 21 h. The usual work-up and recrystallization from acetone gave 3β,4β-epoxyfriedelane (**19**; 17 mg).

*Isomerization of Dendropanoxide (**1**).* *(a) With Hydrochloric Acid in Ethanol*: Dendropanoxide (**1**; 103 mg) was dissolved in ethanol (20 ml) and conc hydrochloric acid (0.8 ml). The solution was heated under reflux for 30 min and then left at room temperature overnight. The reaction mixture, after the usual treatment, was purified by preparative TLC to afford D : B-friedo-olean-5(10)-en-3β-ol (**21**; 55 mg).

(b) With Boron Trifluoride Etherate: Boron trifluoride etherate (1.4 ml) was added to dendropanoxide (**1**; 631 mg) in ether (110 ml) at room temperature and the reaction mixture was allowed to stand at room temperature for 22 h. Work-up in a usual manner and a separation by column chromatography on 20% silver nitrate-impregnated silica gel using benzene as eluent gave D : B-friedo-olean-5(10)-en-3β-ol (**21**; 417 mg) and D : B-friedo-olean-5-en-3β-ol (**23**; 50 mg).

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References

1) A part of this work was reported in a preliminary form: T. Torii, K. Tachibana, S. Yamada, T. Tsuyuki, and T. Takahashi, *Tetrahedron Lett.*, **1975**, 2283.

2) K. Kimura, Y. Hashimoto, and I. Agata, *Chem. Pharm. Bull.*, **8**, 1145 (1960).

3) H. R. Arthur and W. H. Hui, *J. Chem. Soc.*, **1961**, 551.

4) S. Rangaswami and K. Sambamurthy, *Proc. Indian Acad. Sci.*, **54A**, 132 (1961).

5) G. H. Constantine, Jr. and J. H. Block, *Phytochemistry*, **9**, 1659 (1970). And references cited therein.

6) J. H. Block and G. H. Constantine, Jr., *Phytochemistry*, **11**, 3279 (1972).

7) J. D. White, J. Fayos, and J. Clardy, *J. Chem. Soc. Chem. Commun.*, **1973**, 357.

8) a) E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, **78**, 5041 (1956); b) G. Brownlie, F. S. Spring, R. Stevenson, and W. S. Strachan, *J. Chem. Soc.*, **1956**, 2419; c) T. Takahashi and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1956**, 353; d) H. Dulter, O. Jeger, L. Ruzicka, *Helv. Chim. Acta*, **38**, 1268 (1955).

9) *Cf.* A. Eshenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

10) a) J. W. ApSimon, R. R. King, and J. J. Rosenfeld, *Can. J. Chem.*, **47**, 1989 (1969); b) P. Sengupta, B. Roy, S. Chakraborty, J. Mukherjee, and K. G. Das, *Indian J. Chem.*, **11**, 1249 (1973).

11) M. S. Hadley and T. G. Halsall, *J. Chem. Soc. Perkin Trans. 1*, **1974**, 1334.

12) T. Tatee, T. Tsuyuki, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **48**, 2221 (1975).

13) K. Tachibana and T. Takahashi, *Tetrahedron Lett.*, **1975**, 1857.

14) a) S. Yamada, S. Yamada, Y. Moriyama, Y. Tanahashi, and T. Takahashi, *Tetrahedron Lett.*, **1972**, 5043; b) S. Yamada, S. Yamada, K. Tachibana, Y. Moriyama, Y. Tanahashi, T. Tsuyuki, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **49**, 1134 (1976). The PMR signals due to a proton on C-3 appeared at δ 2.89 for 3β,4β-epoxyshionane, while those for 3α,4α-epoxyshionane were observed at δ 2.83.

15) Ex. a) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 1230 (1960); b) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **20**, 2547 (1964); c) J. R. Bull, *Tetrahedron Lett.*, **1968**, 5959; d) P. A. Diassi and J. Fried, U. S. P. 3,364,204 (1964), *Chem. Abstr.*, **69**, 27638a (1968); e) J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **21**, 559 (1965); f) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *ibid.*, **21**, 2489 (1965).

16) J. M. Beaton, F. S. Spring, R. Stevenson, and J. L. Stewart, *Tetrahedron*, **2**, 246 (1958).

17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, Inc., San Francisco, London, Amsterdam (1964), p. 122.