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BIOGENETIC-TYPE TRANSFORMATION OF 3-KETO-4,5-EPOXY-EUDESMANES: SYNTHESIS OF CYPERANES, EREMOPHILANES AND SPIROVETIVANES

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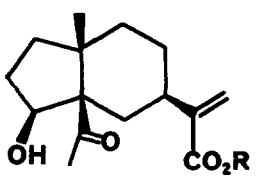
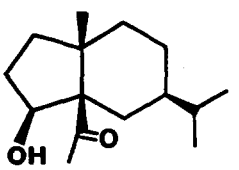
Abstract: Cyperanes, eremophilanes and spirovetivanes have been prepared by acid catalyzed rearrangement of 3-keto-4,5-epoxy-eudesmanes. These transformations are of biogenetic significance and reinforce the hypothesis that the oxigenate eudesmanes are precursors of several sesquiterpene skeletons.

Recently we have reported the isolation from aerial parts of *Dittrichia viscosa* of a new sesquiterpene, the cyperanic acid, which was identified as **1a** on the basis of chemical transformations and spectroscopical data.[1] This compound is representative of a small group of natural products which incorporate the cyperane framework and possess a carbonyl function at C-4 , e.g. **1a**, 2[2], 3[3] and 4[4,5].



1a R=H

1b R=Me



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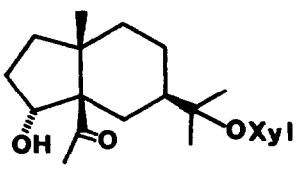

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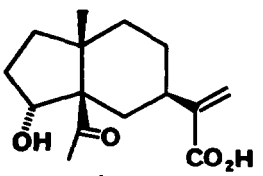

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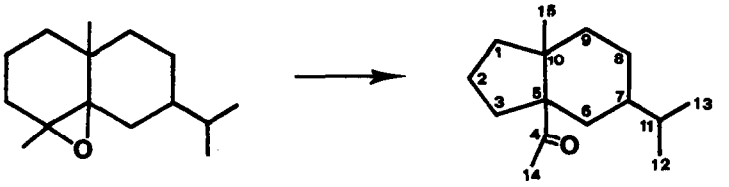
The structural features of these compounds support the biogenetic consideration that the cyperane skeleton is derived from an epoxy-eudesmane precursor (e.g. i⟶ii).[6]



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A number of reports of acid-catalyzed rearrangements of epoxy-eudesmanes to compounds with a different sesquiterpene skeleton has been noted.[6] Some of these transformations engendered confusion and controversy concerning the structures and stereochemistry of the products obtained.[7]

The subject of the present investigation is to report a biogenetic-type synthesis of some sesquiterpene compounds, involving 3-keto-4,5-epoxy-eudesmanes as intermediates.

It was thought that this study would accomplish the following goals: (a) provide evidence for the structure and stereochemistry of cyperanic acid **1a**, (b) provide a simple method for the synthesis of eremophilanes and spirovetivanes from readily available natural products.

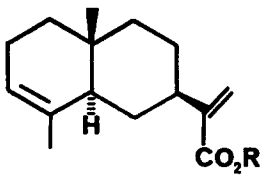
The co-occurrence of costic acid **5a** in *D. viscosa*[8] led us to consider this compound as a logical starting material for these researches. As our first objective, we undertook the preparation of the isomeric epoxy ketones **9a** and **9b** in which the presence of the carbonyl group at C-3 allows for the facile Lewis acid mediated epoxide ring opening, with skeletal rearrangement.[9]

We were extremely gratified to find that interaction of the endocyclic double bond of ester **5b**[8] with selenium dioxide[10] gave rise to the rearranged allylic alcohol **6a** as a major product (47%), which was formed in a dissociation-recombination pathway of a seleninic acid intermediate.[11] From the ^{1}H NMR spectrum of **6a**, an α-orientation of the 3-hydroxy group could be deduced; in addition, the ^{13}C NMR data (see Table) revealed a clear upfield shift of carbon 1, relative to Δ^{4}-eudesmane **6e**,[12] due to steric shielding.[13] The oxidative process of **5b** also generated the allylic alcohol **7** and the ether **6c** only in small amounts (10 and 8% yield, respectively). Epoxidation of **6a** with *p*-nitroperbenzoic acid yielded the α-epoxy-alcohol **8a**. As only one epoxide was obtained, the epoxy group more likely possessed an α-orientation.

Pyridinium chlorochromate oxidation of **8a** led to the expected α-epoxy ketone **9a**.

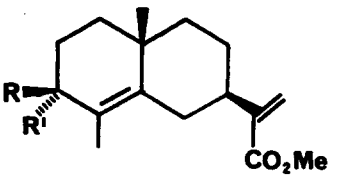
The preparation of the corresponding β-isomer **9b** was accomplished in four steps, starting

from allylic alcohol **6a**. Hydride reduction of ketone **6d**, obtained by oxidation of **6a**, gave the ß-alcohol **6b** as expected from the course of reduction of other eudesma-4-en-3-one derivatives.[14] The ^{13}C NMR values were in accord with the proposed stereochemistry at C-3. The ß-epoxy ketone **9b** was secured by epoxidation of **6b** (**8b**) followed by pyridinium chlorochromate oxidation. The relative stereochemistry of the α- and ß-epoxides **9a** and **9b**, anticipated from the expected course of epoxidation of allylic alcohols **6a** and **6b**, could be readily deduced on the basis of the ^{13}C NMR data. A comparison of the carbon shifts indicated that in **9b** C-9 is shielded and C-15 is deshielded. These shift alterations can be ascribed to the A/B cis-decalin relationship that places C-2 into such an orientation that it exerts a γ effect on C-9 and removes one from the C-15.



5a R = H

5b R = Me



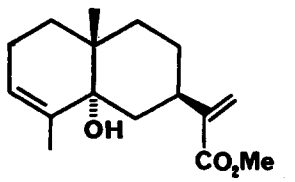
6a R = H , R' = OH

6b R = OH, R' = H

6c R = H , R' = OtBu

6d R, R' = O

6e R, R' = H



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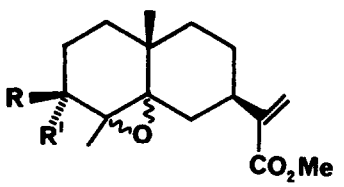
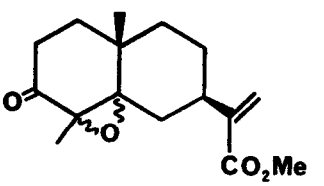


8a R = H , R' = OH, α-epoxide

8b R = OH, R' = H , ß-epoxide



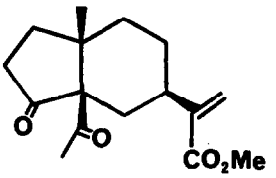
9a α-epoxide

9b ß-epoxide

With epoxy ketones **9a** and **9b** in hand, we turned our attention to their reactivity toward Lewis acids. Treatment of **9a** with 1 equiv of boron trifluoride etherate in benzene at 25 °C, for 5 min, resulted in the formation of two major products **10** and **11**, which were separated by chromatography. Tne less polar compound (18%), resulting from a 1,2-carbonyl

migration, was identical with the oxidation product of cyperanic acid methyl ester **1b** . This conversion confirmed the structure of **1a**, except for the stereochemistry at C-3, as it was proposed essentially on the basis of its spectral data. The structure of compound **11**, the major component of the mixture (60%), came from its analytical and spectroscopical data. The presence of the unsaturation between C-9 and C-10, in accord with the shielding observed at C-7, imposes a 1,2-methyl migration and the formation of a compound which incorporates the eremophilane framework. If the reaction of **9a** with boron trifluoride etherate is quenched later (20 min), the ketone **12** can be isolated instead of the eremophilane derivative **11**. The same compound **12** was also prepared by the action of boron trifluoride etherate on **11**. The formation of **11**, however, was not surprising since the 1,2-carbonyl migration in **9a**, over the α-face, is strongly hindered with respect to the methyl migration. The *cis*-hydrindanone **10** was presumably formed from a concerted mechanism which involves a fluorohydrin intermediate.[9c]

Although the reaction yields a mixture of products, rearrangement of **9a** is still synthetically useful because it makes the eremophilane-type sesquiterpenoids accessible. This transformation represents the second example reported of a chemically induced rearrangement of this type.[15]



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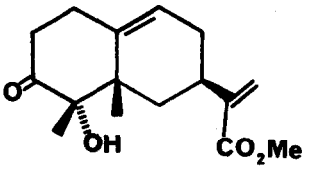

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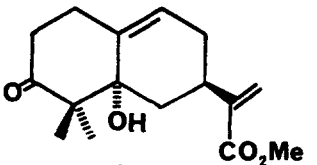

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We next investigated the chemistry of the β-epoxyde **9b**, confident that this isomer would easily assume the proper geometric alignement for a concerted carbonyl migration, leading to **10**. The interaction of **9b** with boron trifluoride etherate gave rise to unexpected results: the spirovetivane **13** (18%) was generated together with the anticipated ketone **10** (61%). The structure of **13** was fully supported by the ^{1}H and ^{13}C NMR spectra as well as the consideration that the 9,10 carbon bond in **9b** is properly oriented with respect to the epoxy ring to achieve a migration process. The striking feature in the ^{13}C NMR spectrum was the

Table. ^{13}C NMR data.[a]

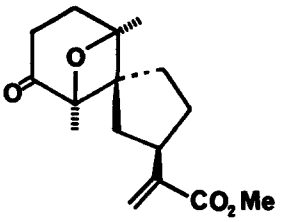
	5b	6a	6b	6c[b]	6d	6e	7	8a	8b	9a	9b	10	11	12	13
C-1	37.9	34.1	36.1	34.1	37.1	40.2	25.9	30.0[e]	30.0	31.7[h]	31.7[l]	35.6	37.6	36.7	34.2[p]
C-2	23.0	27.1[c]	28.8	22.5	33.5	19.0	22.6	26.7	26.2	33.2	33.1	32.9	38.5	38.5	36.4
C-3	121.1	69.5	71.3	81.3	198.5	33.1	124.6	68.2	68.9	207.4	206.0	208.1	210.6	216.1	219.4
C-4	134.7	139.3	138.6	143.0	128.8	134.3	137.9	72.6[f]	71.5[g]	71.6[i]	71.6[m]	216.6	82.3	45.7	86.6[q]
C-5	46.9	126.5	127.5	122.1	160.8	125.5	73.1	66.2[f]	66.5[g]	65.3[i]	64.3[m]	70.8	44.6	81.2	61.5
C-6	29.4	31.4	31.7	31.4	33.1	31.4	30.9	30.5[e]	32.2	31.5[h]	31.9[l]	37.8	30.2	30.4[n]	33.9[p]
C-7	40.7	40.4	40.6	40.2	39.9	40.6	35.0	38.1	38.5	38.0	38.8	36.1	33.4	33.6	40.9
C-8	27.5	27.7[c]	27.7	27.7	26.9	28.0	26.5	27.1	27.0	26.8	26.6	26.8	30.2	30.0[n]	31.3
C-9	40.3	42.1	41.4	41.9	41.5	42.1	33.9	37.2	35.5	37.9	34.6	30.3	125.1	124.2	27.7
C-10	37.3	34.8	35.0	34.8	35.5	34.4	35.9	33.2	33.6	33.8	33.9	42.0	137.8	138.4	86.4[q]
C-11	146.1	145.4	145.3	145.4	144.2	145.7	145.9	144.8	144.0	144.3	143.6	144.4	144.7	144.8	142.7
C-12	167.6	167.6	167.6	167.6	166.9	167.6	167.8	167.2	167.2	167.1	166.9	167.0	167.6	167.6	167.4
C-13	122.4	122.6	122.5	122.5	123.0	122.1	123.1	123.3	122.9	123.5	123.2	123.2	122.8	122.8	123.1
C-14	21.1	17.0	15.0	17.7	10.6	19.2	18.5[d]	17.9	18.7	11.2	11.8	29.6	15.9	24.1[o]	15.0
C-15	15.6	23.0	24.6	22.9	22.2	24.6	19.5[d]	20.9	22.9	20.5	22.7	21.6	24.1	24.8[o]	17.4
OMe	51.5	51.7	51.6	51.6	51.6	51.5	51.6	51.6	51.7	51.7	51.7	51.7	51.8	51.8	51.8

[a] The δ values are in ppm from TMS.

[b] 3-O-tBu: $\underline{C}(CH_3)_3$: 79.4; $C(\underline{C}H)_3$: 26.7.

[c-q] Signal in any vertical column may be reversed.

presence of two heteroatom-bearing quaternary carbons (86.4 and 86.6 ppm) and a carbon whose chemical shift value (61.5 ppm) was diagnostic for a spiro carbon.[16]



13

The dehydratation of β-rotunol to a spirodienone is apparently the only reported example of the transformation of a eudesmane sesquiterpene to a spirovetivane.[17]

In summary, the reaction sequences involving acid-catalyzed rearrangement of the keto epoxides **9a** and **9b** provide a simple route to a variety of sesquiterpene skeletons and reinforce the biogenetic hypothesis that cyperanes, eremophilanes and spirovetivanes may be derived from eudesmane precursors.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 90 MHz on a Varian EM390 instrument in $CDCl_3$ solutions using TMS as reference. ^{13}C NMR spectra were recorded at 20.15 MHz on a Bruker WP80SY instrument, in the Fourier transform mode with proton decoupling throughout, in $CDCl_3$ solutions using TMS as reference. Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. Column chromatography was carried out on 0.063-0.200 mesh Merck silica gel. All extracts were dried over Na_2SO_4.

Treatment of ester **5b** with selenium dioxide. 2.4 ml (0.02 mol) of 80% t-butyl hydroperoxide were added under nitrogen to a stirring solution of 13 mg (0.12 mmol) of selenium dioxide in 16 ml of methylene chloride. A solution of 1.8 g (7.25 mmol) of costic acid methyl ester **5b** in 16ml of dry methylene chloride was added dropwise. After 12 h the reaction mixture was poured into water and washed with a sodium iodide solution to destroy the excess of t-butyl hydroperoxide. Then the organic phase was washed with a 10% sodium thiosulphate solution, dried and evaporated. Chromatography of the residue and elution with chloroform gave 190 mg

(8%) of ether **6c**: ^{1}H NMR δ 1.03 (s, 3H, 10-Me), 1.23 (s, 9H, t-Butyl), 1.79 (s, 3H, 4-Me), 3.76 (s, 3H, OMe), 4.16 (m, 1H, H-3), 5.50 (bs, 1H, H-13), 6.13 (bs, 1H, H-13). ^{13}C NMR: see table. Anal. Calcd. for $C_{20}H_{32}O_3$:C, 74.96; H, 10.06. Found: C, 75.12; H, 9.96.
Further elution with 95:5 chloroform-methanol gave 200 mg of alcohol **7** (10%): ^{1}H NMR δ 1.00 (s, 3H, 10-Me), 1.72 (s, 3H, 4-Me), 3.76 (s, 3H, OMe), 5.42 (m, 1H, H-3), 5.58 (bs, 1H, H-13), 6.13 (bs, 1H, H-13). ^{13}C NMR: see table. Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.81; H, 9.08, and 900 mg (47%) of alcohol **6a**: ^{1}H NMR δ 1.05 (s, 3H, 10-Me), 1.80 (s, 3H, 4-Me), 3.79 (s, 3H, OMe), 3.90 (m, 1H, H-3), 5.60 (bs, 1H, H-13), 6.18 (bs, 1H, H-13) ^{13}C NMR: see table. Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.78; H, 9.11.

Reaction of alcohol **6a** with *p*-nitroperbenzoic acid. 243 mg of 80% *p*-nitroperbenzoic acid under nitrogen to a stirring solution of 273 mg (1.03 mmol) of alcohol **6a** in 30 ml of dry chloroform. After 20 min the suspension was filtered and the filtrate was washed with water, dried and evaporated. Chromatography of the residue on neutral alumina (activity IV) and elution with chloroform gave 200 mg (69%) of α-epoxy-alcohol **8a**. ^{1}H NMR δ 1.09 (s, 3H, 4-Me), 1.43 (s, 3H, 10-Me), 3.76 (s, 3H, OMe), 5.56 (bs, 1H, H-13), 6.23 (bs, 1H, H-13). ^{13}C NMR: see table. Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.64; H, 8.56.

Oxidation of α-epoxy-alcohol **8a**. 180 mg of pyridinium chlorochromate were added under nitrogen to a stirring solution of 90 mg (0.32 mmol) of epoxy-alcohol **8a** in 25 ml of dry methylene chloride. After 12 h the suspension was filtered over celite and the filtrate evaporated. Chromatography of the residue on neutral alumina (activity IV) and elution with chloroform gave 70 mg (78%)of α-epoxy-ketone **9a**. ^{1}H NMR δ 1.09 (s, 3H, 10-Me), 1.40 (s, 3H, 4-Me), 3.80 (s, 3H, OMe), 5.58 (bs, 1H, H-13), 6.18 (bs, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 70.11; H, 7.91.

Oxidation of alcohol **6a**. 1.3 g of pyridinium chlorochromate were added under nitrogen to a stirring solution of 900 mg (3.4 mmol) of alcohol **6a** in 250 ml of dry methylene chloride. The mixture was stirred for 6 h. After workup (see above) chromatography of the residue on neutral alumina (activity IV) and elution with chloroform gave 490 mg (55%) of ketone **6d**. ^{1}H NMR δ 1.29 (s, 3H, 10-Me), 1.80 (s, 3H, 4-Me), 3.83 (s, 3H, OMe), 5.66 (bs, 1H, H-13), 6.26 (bs, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.18; H, 8.51.

Reduction of ketone **6d**. A solution of 203 mg of sodium borohydride in 10 ml of water was added to a stirring solution of 280 mg (1.07 mmol) of ketone **6d** in 30 ml of methanol. After 10 min few drops of acetone were added to destroy the excess of hydride. The solution was poured into water and brought to pH 2 with 3% sulphuric acid and extracted with chloroform. The combined organic layers were washed with water, dried and evaporated. Chromatography of the residue and elution with 95:5 benzene-ethyl acetate gave 270 mg (96%) of allylic alcohol **6b**. ^{1}H NMR δ 1.03 (s, 3H, 10-Me), 1.75 (s, 3H, 4-Me), 3.79 (s, 3H, OMe), 4.06 (m, 1H, H-3), 5.56 (bs, 1H, H-13), 6.19 (bs, 1H, H-13). ^{13}C NMR: see table. Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.65; H, 9.18.

Reaction of alcohol **6b** with *p*-nitroperbenzoic acid. 240 mg of 80% *p*-nitroperbenzoic acid were added under nitrogen to a stirring solution of 270 mg (1.02 mmol) of alcohol **6b** in 40 ml of dry chloroform. The mixture was stirred for 20 min after workup (see above), the residue was chromatographed on neutral alumina (activity IV). Elution with chloroform gave 258 mg (94%) of β-epoxy-alcohol **8b**. ^{1}H NMR δ 1.08 (s, 3H, 10-Me), 1.50 (s, 3H, 4-Me), 3.76 (s, 3H, OMe), 3.83 (m, 1H, H-3), 5.57 (bs, 1H, H-13), 6.15 (bs, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.59.

Oxidation of β-epoxy-alcohol **8b**. 160 mg of pyridinium chlorochromate were added under nitrogen to a stirring solution of 80 mg (0.30 mmol) of β-epoxy-alcohol **8b** in 20 ml of dry methylene chloride. The mixture was stirred for 12 h. After workup (see above) the residue was chromatographed on neutral alumina (activity IV). Elution with chloroform gave 68 mg (85%) of β-epoxy-ketone **9b**. ^{1}H NMR δ 1.02 (s, 3H, 10-Me), 1.49 (s, 3H, 4-Me), 3.73 (s, 3H, OMe), 5.56 (bs, 1H, H-13), 6.13 (bs, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.12; H, 7.91.

Treatment of α-epoxy-ketone **9a** with boron trifluoride etherate for 5 min. 0.04 ml of freshly distilled boron trifluoride etherate were added under nitrogen to a stirring solution of 100 mg (0.35 mmol) of ketoepoxide **9a** in 8 ml of dry benzene. The mixture was stirred for 5 min the was poured into water, neutralized with a solution of sodium carbonate and extracted with benzene. The combined organic layers were washed with water, dried and evaporated. Chromatography of the residue and elution with 97:3 chloroform-ethyl acetate gave 18 mg (18%) of **10**. ^{1}H NMR δ 1.20 (s, 3H, 10-Me), 2.10 (s, 3H, 4-Me), 3.73 (s, 3H, OMe), 5.50 (bs, 1H, H-13), 6.10 (s, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H,

7.97. Found: C, 69.14; H, 7.88.

Further elution with 95/5 benzene-ethyl acetate gave 60 mg (60%) of **11**. ^{1}H NMR δ 0.90 (s, 3H, 5-Me), 1.33 (s, 3H, 4-Me), 3.80 (s, 3H, OMe), 5.50 (bs, 1H, H-13), 5.90 (m, 1H, H-9), 6.19 (bs, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.13; H, 7.89.

Treatment of α-epoxy-ketone **9a** for 20 min. 0.04 ml of freshly distilled boron trifluoride etherate were added under nitrogen to a stirring solution of 100 mg (0.35 mmol) of ketoepoxide **9a** in 8 ml of dry benzene. After 20 min the reaction mixture was treated as described above. Chromatography of the residue and elution with 97:3 benzene-ethyl acetate gave 14 mg (14%) of **10** and 52 mg (52%) of **12**. ^{1}H NMR δ 0.90 (s, 3H, 4-Me), 1.46 (s, 3H, 4-Me), 3.75 (s, 3H, OMe), 5.45 (bs, 1H, H-13), 5.70 (m, 1H, H-9), 6.13 (bs, 1H, H-13). ^{13}C NMR: see Table. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.09; H, 7.91.

Treatment of **11** with boron trfluoride etherate. 0.02 ml of freshly distilled boron trifluoride etherate were added under nitrogen to a stirring solution of 40 mg (0.14 mml) of compound **11** in 5 ml of dry benzene. The mixture was stirred for 20 min. Then the reaction mixture was treated as described above. Chromatography of the residue and elution with 95:5 benzene-ethyl acetate gave 6 mg (14%) of **10** and 18 mg (45%) of **12**.

Treatment of ketoepoxide **9b** with boron trifluoride etherate. 0.04 ml of freshly distilled boron trifluoride etherate were added under nitrogen to a stirring solution of 85 mg (0.30 mmol) of ketoepoxide **9a** in 5 ml of dry benzene. After 5 min the reaction mixture was treated as described above. Chromatography of the residue and elution with chloroform gave 51 mg (61%) of **10** and 18 mg (18%) of **13**. ^{1}H NMR δ 1.43 (s, 6H, 4 and 10-Me), 3.73 (s, 3H, OMe), 5.50 (bs, 1H, H-13), 6.06 (bs, 1h, H-13). Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.10; H, 7.93.

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