Chem. Pharm. Bull. 15(9)1395~1404(1967)

UDC 547.596.02 : 582.542.2

180. Hiroshi Hikino, Norio Suzuki, and Tsunematsu Takemoto*1 : Synthesis of Cyperolone and 3-*epi*-Cyperolone.*2

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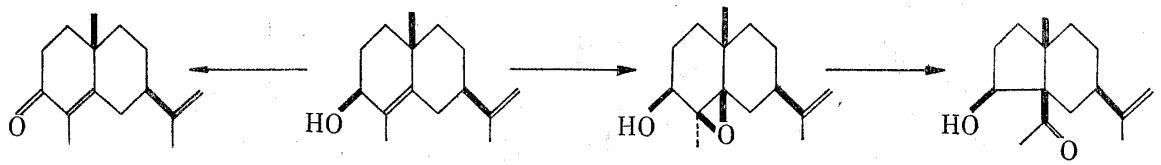
α-Cyperone (II) was reduced to eudesma-4,11-dien-3β-ol (III), which was converted into 4β,5β-oxidoeudesm-11-en-3β-ol (V). Treatment of the epoxide (V) with boron trifluoride gave eudesm-11-en-3-on-5β-ol (IX) but no cyperolone (I). The epoxy-alcohol (V) was acetylated to afford the acetoxy-epoxide (XII) which on treatment with boron trifluoride yielded 5α-fluoro-3β-acetoxyeudesm-11-en-4β-ol (XIV) and 1(*R*)-isopropenyl-3-(1-methyl-4(*S*)-acetoxy-5-oxohexylidene)cyclopentane (XV) but no cyperolone acetate (XXIV). Oxidation of the epoxy-alcohol (V) gave the keto-epoxide (VIII) which was treated with boron trifluoride to yield cyper-11-ene-3,4-dione (XVI). On reduction the dione (XVI) afforded mainly cyper-11-ene-3β,4ξ-diol (XIX) and cyper-11-ene-3α,4ξ-diol (XX). The diol (XIX) was transformed to the 3β-acetoxycyper-11-en-4-one (XXIV) *via* 3β-acetoxycyper-11-en-4ξ-ol (XXII). Alkaline-catalyzed hydrolysis of the acetate (XXIV) furnished cyperolone (I). The diol (XX) was converted into 3β-acetoxycyper-11-en-4-one (XXVII) *via* 3β-acetoxycyper-11-en-4ξ-ol (XXV). When hydrolyzed with an excess of alkali the acetate (XXVII) gave cyperolone (I), while hydrolysis with an insufficient amount of alkali produced 3-*epi*-cyperolone (XXVIII). On alkaline treatment, 3-*epi*-cyperolone (XXVIII) was epimerized to give cyperolone (I).

(Received February 10, 1967)

The sesquiterpenoid cyperolone is one of the bitter principles of nutgrass, *Cyperus rotundus* LINNÉ (Cyperaceae), of Japanese origin. The stereostructure I was recently deduced from analytical studies.[1] The present paper describes a synthesis of this keto-alcohol by a method which confirms both structure and absolute stereochemistry.*3

The planning of our synthetic sequence was influenced by the discovery that cyperolone coexists with α-cyperone (II) in the same oil.[1,2] Biogenetic considerations suggest that cyperolone is constructed from an intermediate of structure A by some version of the pinacolic rearrangement as shown in Chart 1. This postulated rearrangement was considered to be useful in the synthetic work, which has been attempted as described below.



α-cyperone (II) A cyperolone (I)

Chart 1.

α-Cyperone (II) was reduced with lithium aluminum hydride to give eudesma-4,11-dien-3β-ol (III) (quantitative yield). The β-configuration of the C-3 hydroxyl group was deduced from the nuclear magnetic resonance (NMR) signal of the C-3 hydrogen which

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*2 This paper constitutes Part XIV in the series on Sesquiterpenoids. Preceding paper, Part XIII, H. Hikino, Y. Sakurai, H. Takahashi, T. Takemoto : This Bulletin, **15**, 1390 (1967).

*3 Part of the material contained herein formed a preliminary communication, H. Hikino, N. Suzuki, T. Takemoto : *Ibid.*, **14**, 1441 (1966).

1) H. Hikino, K. Aota, Y. Maebayashi, T. Takemoto : *Ibid.*, **14**, 1439 (1966); **15**, 1349 (1967).

2) H. Hikino, K. Aota, T. Takemoto : *Ibid.*, **14**, 890 (1966).

occurs as a broad peak (band width at half height : 15 c.p.s.) and from the more laevorotatory nature ($\Delta[M]_D$ −251°) as compared with its C-3 epimer (Ⅳ).[3] Epoxidation of the alcohol (Ⅲ) with one mole of perbenzoic acid, added at the biginning of the reaction, produced a single mono-epoxide (59% yield) together with a small amount of a di-epoxide (Ⅵ). The mono-epoxide was shown to be the expected product, a 4,5-epoxide, by the infrared and NMR spectra which demonstrated retention of the isopropenyl, disappearance of the allyl methyl, and formation of a tertiary methyl on carbon carrying an oxygen during oxidation. That the epoxy ring had the desired β-configuration was assumed by the directive effect of the 3β-hydroxyl group on epoxidation and established by the positive Cotton effect (a= +75) of the optical rotatory dispersion curve of its oxidation product (Ⅷ),[4] described below. Therefore, the mono-epoxide is represented by formula Ⅴ. The yield of the mono-epoxide (Ⅴ) was later raised to 68% by oxidation with perbenzoic acid which was added gradually until the di-epoxide (Ⅵ) was just formed when formation of the epimeric epoxide, 4α,5α-oxidoeudesm-11-en-3β-ol (Ⅶ) (10% yield), was observed.

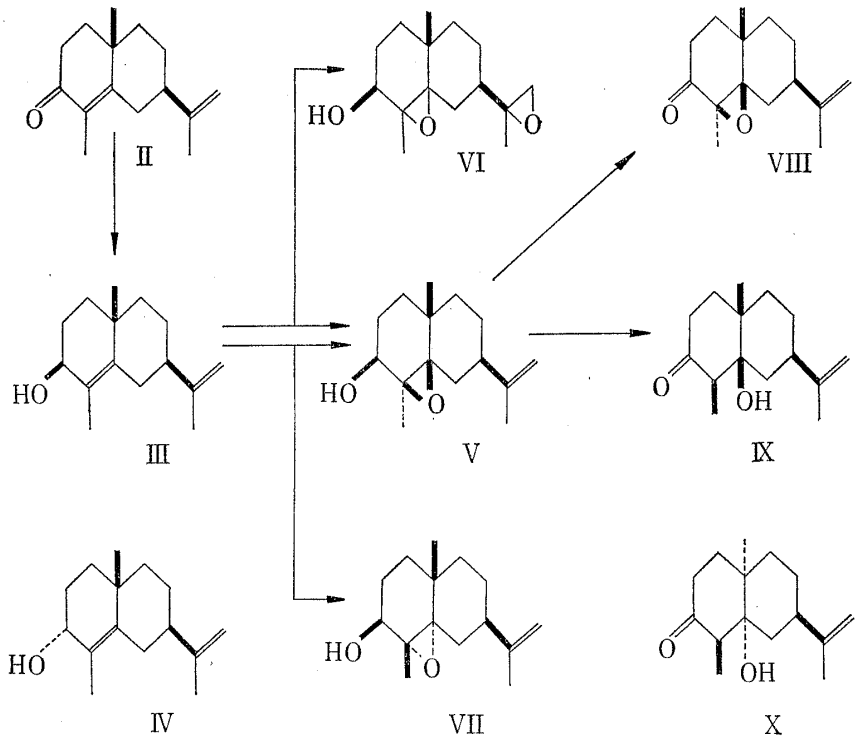

Chart 2.

On treatment with boron trifluoride etherate in benzene solution at room temperature the hydroxy-epoxide (Ⅴ) gave the isomerized product. However, an NMR study of the product failed to show any signal near 8τ of an intensity sufficient to render possible the presence of cyperolone. Vapor phase chromatography of the product indicated it to be a mixture of a number of components. There was, however, only one peak in the region where keto-alcohols would be expected to appear. The peak had approximately the same retention time as that of cyperolone. The component was isolated and shown to have a carbonyl in a six-membered ring, a tertiary hydroxyl, a secondary methyl, and a hydrogen coupled only with the preceding methyl protons as well as a tertiary

3) H. Hikino, K. Aota, T. Takemoto : This Bulletin, in press.
4) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, E. Klein : Tetrahedron, **21**, 163 (1965).

methyl and an isopropenyl group based on the infrared and NMR evidence. In the mass spectrum, the fragmentation pattern is similar to that of 10-*epi*-eudesm-11-en-3-on-5α-ol (X), prepared by the known method,[5] though there are differences in the relative intensities of certain peaks. On the basis of the above evidence the keto-alcohol is concluded to have the structure IX and to have been formed by the mechanisms as shown in Chart 3. Therefore, the configuration of the C-5 hydroxyl must naturally be β-oriented judged from that of the original epoxide ring. The C-4 methyl group is considered to have the thermodynamically more stable β-configuration from the mechanistic requirements of its genesis, provided that the substance has the all-chair conformation with the isopropenyl group in the equatorial orientation, as is suggested by its negative Cotton curve.

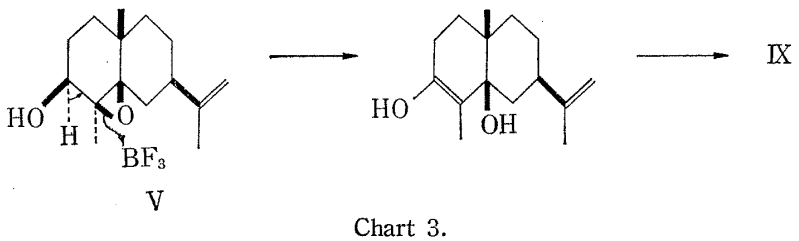

Chart 3.

Thus the one step synthesis of cyperolone from the hydroxy-epoxide (V) was unsuccessful. Therefore, an attempt at direct synthesis of cyperolone acetate from the acetoxy-epoxide (XII) was undertaken.

Acetylation of the alcohol (III) with acetic anhydride in pyridine gave the acetate (XI). On epoxidation with one mole of perbenzoic acid, the acetate (XI) afforded a mono-epoxide. Although the mono-epoxide showed one spot on thin-layer chromatography and a single peak on vapor phase chromatography, its heterogeneous nature was indicated by the NMR spectrum which exhibited a pair of tertiary methyls, tertiary

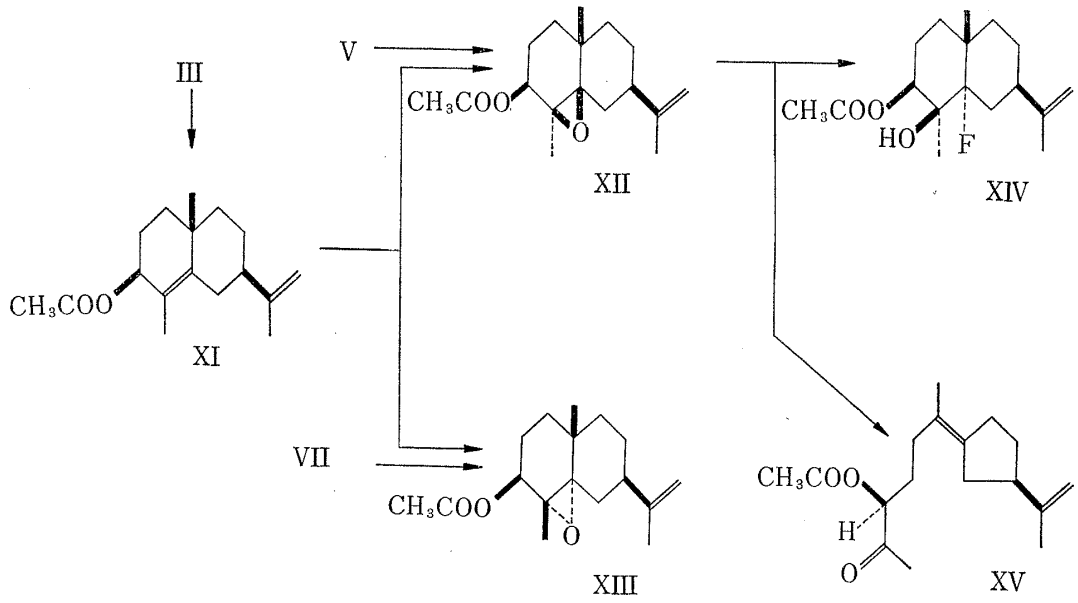

Chart 4.

5) F. J. McQuillin: J. Chem. Soc., **1955**, 528; R. Howe, F. J. McQuillin: *Ibid.*, **1955**, 2423; **1956**, 2671; T. G. Halsall, D. W. Theobald, K. B. Walshaw: *Ibid.*, **1964**, 1029.

methyls on carbons carrying the epoxidic oxygens, allyl methyls, and acetoxy methyls. This was later shown to be a mixture of approximately equal amounts of the β-epoxy-acetate (XII) and the α-epoxy-acetate (XIII), since the previous NMR spectrum was well explained as their resultant. However, attempts to separate the two epimeric epoxides failed. Consequently the epoxy-alcohol (V) was acetylated with acetic anhydride in pyridine yielding the epoxy-acetate (XII).

Treatment of the epoxy-acetate (XII) with boron trifluoride-ether complex in benzene solution at room temperature gave mainly two products. Formation of the expected cyperolone acetate was excluded since vapor phase chromatography showed no peak corresponding to it. One product (36% of the whole calculated by integrating the area of the peak in the vapor phase chromatogram) isolated had the molecular formula $C_{17}H_{27}O_3F$ by elemental analysis and mass spectrometric determination. The infrared and NMR spectra disclosed the presence of a tertiary hydroxyl, a secondary acetoxyl, an isopropenyl, a tertiary methyl, and a tertiary methyl, which was on carbon bearing a hydroxyl and long range coupled with fluorine, but no hydrogen on carbon attached to fluorine. The other product (38% of the whole (vapor phase chromatographically)), isolated but not in a completely pure condition, was shown to have the molecular formula $C_{17}H_{26}O_3$ by mass spectrometry and to possess an acetyl, a secondary acetoxyl, an isopropenyl, an allyl methyl group, and no vinyl hydrogen from the infrared and NMR spectra. Based on this spectral evidence and coupled with the respective molecular formulae, the two products are concluded to have the structure XIV and XV, respectively, and to have been formed by the mechanisms shown in Chart 4.

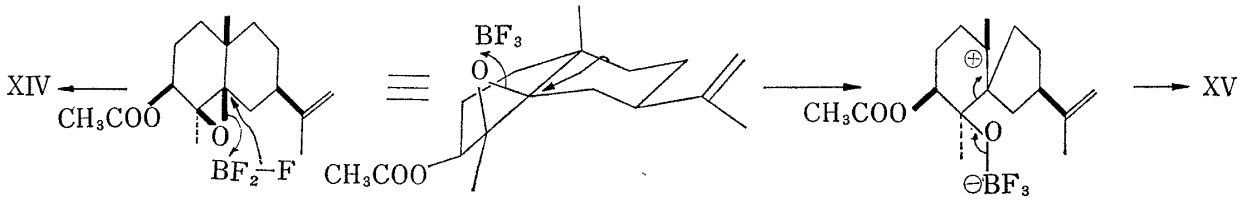

Chart 5.

Since the desired cyperolone acetate could not be obtained by isomerization of the epoxy-acetate (XII), another route for synthesis of cyperolone was tried.

The epoxy-alcohol (V) was, therefore, oxidized with chromium trioxide-pyridine complex to furnish 4β,5β-oxidoeudesm-11-en-3-one (VIII) (88% yield). The keto-epoxide (VIII) was treated with boron trifluoride etherate in benzene solution at room temperature to give the isomerized product. This was shown by vapor phase chromatography to be a mixture of a number of components in which a major one had the same retention time as that of the desired cyper-11-ene-3,4-dione (XVI), previously prepared from cyperolone (I) by oxidation.[1] The component was, therefore, isolated and identified as the dione (XVI). The yield of the dione (XVI) varied from lot to lot presumably depending upon the delicate change of the reaction conditions and the maximum reached 26% of the product, calculated by integration of the area of the peak in the vapor phase chromatogram. Since the epoxy ring has the β-configuration in the epoxide (VIII), the newly formed acetyl group in the dione (XVI) must also on mechanistic grounds be β-oriented; this conclusion is compatible with the previous conclusion from the structural studies.[1] If treatment of the dione (XVI) with a quarter mole of lithium aluminum hydride resulted in the partial reduction of the C-3 carbonyl group, this could lead to the completion of the synthesis of cyperolone (I). However, since this treatment was previously observed to give exclusively the other ketol (XVII),[1] an alternative route had to be devised. Thus the dione (XVI) was reduced with an excess of lithium aluminum hydride yielding a mixture of four products. The first one

(8% yield) was identified as the monoketone (XVIII), which was formed by partial reduction of the C-4 carbonyl group followed by the retroaldol loss of acetaldehyde from the C-5 tertiary carbon.[1] The second (39% yield) was a diol which was identified as cyper-11-ene-3β,4ξ-diol (XIX) previously obtained form cyperolone by reduction.[1] The third (33% yield) was also a diol which was concluded to be cyper-11-ene-3α,4ξ-diol (XX) since its infrared spectrum indicated the absence of an intramolecular hydrogen bond. The α-configuration of the C-3 hydroxyl group was later confirmed by its transformation to 3-*epi*-cyperolone (XXVIII). The last (6% yield) was the third diol (XXI) whose stereochemistry at C-3 and C-4 is so far unknown. The diol (XIX) was then acetylated with acetic anhydride in pyridine at room temperature. The reaction was stopped just after the starting diol (XIX) had been exhausted to give a mono-acetate (84% yield) and the diacetate (XXIII). The NMR spectrum of the mono-acetate revealed that the

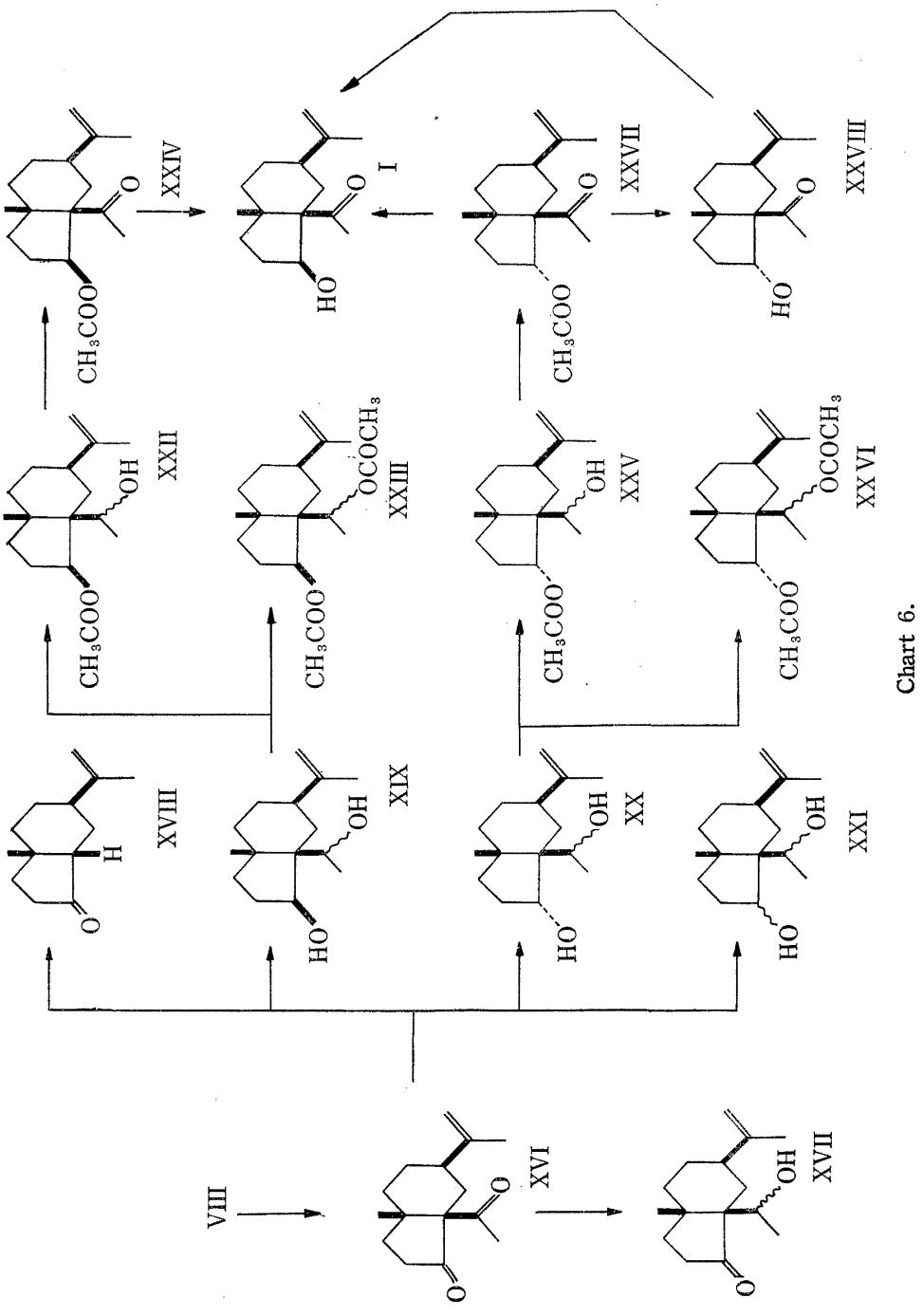

Chart 6.

C-3 hydrogen signal (4.49τ) suffered an appreciable lowfield shift (−1.26 p.p.m.) on passing from the diol to the mono-acetate, while the C-4 hydrogen signal (6.35τ) remained unchanged (−0.16 p.p.m.). Therefore, the diol (XIX) was shown to have been partially acetylated giving a single monoacetate, 3β-acetoxycyper-11-en-4ξ-ol (XXII). Oxidation of the diol monoacetate (XXII) with chromium trioxide-pyridine complex afforded the ketol acetate, 3-acetoxycyper-11-en-4-one (XXIV) (88% yield), which was identical with the acetate of the natural cyperolone (I).[1] Although cyperolone, a β-keto-alcohol, is sensitive to alkali, hydrolysis of the ketol acetate (XXIV) using one mole of alkali furnished cyper-11-en-4-on-3β-ol (91% yield) which was identified as the natural cyperolone (I).

In the previous structural studies, the benzoate rule was applied for determination of the absolute configuration at C-3 in cyperolone.[1] For this purpose preparation of the C-3 epimers was required as a reference substance. This was achieved by a similar sequence, as described below. Thus, the diol (XX) was acetylated with acetic anhydride in pyridine at room temperature and the reaction stopped just after the starting diol had disappeared yielding, together with the diacetate (XXVI), a single monoacetate (64% yield), which was shown to have the structure XXV from NMR evidence similar to that discussed in the diol monoacetate (XXII). Acetylation of the diol (XX) under the similar conditions, *i.e.*, interruption of the reaction just after the diacetate (XXVI) was observed to form, furnished in improved yield (72% yield) the monoacetate (XXV) as well as the unreacted diol (XX) (22% yield). On oxidation with chromium trioxide-pyridine complex the diol monoacetate (XXV) gave the ketol acetate (XXVII) (97% yield) whose infrared and NMR spectra indicated the formation of an acetyl group. Hydrolysis of the ketol acetate (XXVII) with a small excess of alkali resulted in the formation of a free ketol which was however, not the expected 3-*epi*-cyperolone, but cyperolone (I). Therefore, the ketol acetate (XXVII) was treated with an amount of alkali insufficient for complete hydrolysis, whereupon the free ketol obtained was the desired 3-*epi*-cyperolone (XXVIII). As above mentioned, the epimerization at C-3 during the hydrolysis of 3-*epi*-cyperolone acetate (XXVII) with an excess alkali was unexpectedly observed. In confirmation, 3-*epi*-cyperolone (XXVIII) was treated with alkali to yield the epimerized product, cyperolone (I). Since a Walden inversion involving nucleophilic displacement of the hydroxyl group at C-3 seems to be highly improbable, this transformation is certainly an example of the epimerization of a less stable substituent to a more stable one in consequence of retroaldolization and realdolization.

The benzoate of 3-*epi*-cyperolone (XXVIII) was not prepared by direct benzoylation of the ketol (XXVIII) but by partial benzoylation of the diol (XX) followed by oxidation in a manner similar to the preparation of 3-*epi*-cyperolone acetate (XXVII). The pair of the free alcohol (XXVIII) and its benzoate (XXX) then employed for application of the benzoate rule.[1]

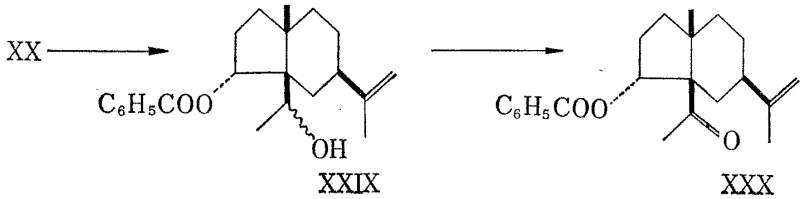

Chart 7.

Experimental*4

Reduction of α-Cyperone with Lithium Aluminum Hydride——α-Cyperone (Ⅱ) (0.50 g.) in ether (10 ml.) was stirred with an excess of $LiAlH_4$ at room temperature for 30 min. The residue (0.51 g.) obtained after ether extraction was distilled under reduced pressure to give eudesma-4,11-dien-3β-ol (Ⅲ) as a colorless oil, $[\alpha]_D$ +10.9° (c=4.1), *Anal.* Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.59; H, 10.77, IR (liquid) cm^{-1}: 3106, 1616, 887 (vinylidene), 3390 (hydroxyl), NMR: singlet (3H) at 8.92 τ ($C\underline{H}_3$-C≤), unresolved singlet (3H) at 8.34 τ ($C\underline{H}_3$-C=C), unresolved singlet (3H) at 8.29 τ ($C\underline{H}_3$-C=C), broad peak (1H) at 6.13 τ (band width at half height: 15 c.p.s., $-CH_2-C\underline{H}(OH)-C=C$), unresolved singlet (2H) at 5.35 τ ($C\underline{H}_2$=C-CH_3).

Epoxidation of the Alcohol with Perbenzoic Acid——a) The alcohol (Ⅲ) (888 mg.) was allowed to react with BzO_2H (534 mg.) in $CHCl_3$ (10 ml.) at room temperature for 20 min. and yielded a product (1106 mg.) which was chromatographed over silica gel (15 g.).

Elution with light petroleum-benzene (1:1) gave an oil (547 mg.) which on distillation under reduced pressure afforded 4β,5β-oxidoeudesm-11-en-3β-ol (Ⅴ) as a colorless oil, $[\alpha]_D$ −23.5° (c=5.6), *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.95; H, 10.03, IR (liquid) cm^{-1}: 3016, 1647, 889 (vinylidene), 3472 (hydroxyl), NMR: singlet (3H) at 8.96 τ ($C\underline{H}_3$-C≤), singlet (3H) at 8.62 τ ($C\underline{H}_3$-C(O)-C<), triplet (3H) at 8.29 τ (J=1, $C\underline{H}_3$-C=CH_2), broad peak (1H) at 6.40 τ ($-CH_2-C\underline{H}(OH)-C\leq O-$), quadruplet (2H) at 5.36 τ (J=1, $C\underline{H}_2$=C-CH_3).

Elution with benzene-ether (1:1) furnished the hydroxy-diepoxide (Ⅵ) as a colorless oil, $[\alpha]_D$ +11.8° (c=3.4), *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.42, IR (liquid) cm^{-1}: 3484 (hydroxyl), NMR: singlet (3H) at 8.97 τ ($C\underline{H}_3$-C≤), singlet (3H) at 8.78 τ ($C\underline{H}_3$-C(O)-C<), doublet (3H) at 8.63 τ (J=1, $C\underline{H}_3$-C(O)-C<), unresolved singlet (2H) at 7.58 τ ($\underline{H}$-C(O)-C<), broad peak (1H) at 6.38 τ ($-CH_2-C\underline{H}(OH)-C\leq O-$).

b) To the alcohol (Ⅲ) (1.38 g.) in $CHCl_3$ (3 ml.), BzO_2H solution (60 mg. in $CHCl_3$ 1 ml.) was added every 15 min. by 1~3 ml. at room temperature. After 1.5 hr., the product (1.45 g.) isolated in the customary manner was chromatographed over silica gel (15 g.).

Elution with light petroleum-benzene (1:1) gave the starting alcohol (Ⅲ) (68 mg.), identified in the usual criteria.

Successive elution with benzene afforded 4β,5β-oxidoeudesm-11-en-3β-ol (Ⅴ) (975 mg.), identified in the usual criteria.

Further elution with benzene-ether (5:1) yielded an oil (145 mg.) which was distilled under reduced pressure to give 4α,5α-oxidoeudesm-11-en-3β-ol (Ⅶ) as a colorless oil, $[\alpha]_D$ +36.4° (c=7.3), IR (liquid) cm^{-1}: 3060, 1644, 888 (vinylidene), 3410 (hydroxyl), NMR: singlet (3H) at 8.90 τ ($C\underline{H}_3$-C≤), singlet (3H) at 8.71 τ ($C\underline{H}_3$-C(O)-C<), slightly spliting singlet (3H) at 8.27 τ ($C\underline{H}_3$-C=CH_2), triplet (1H) at 6.26 τ (J=8, $-CH_2-C\underline{H}(OH)-C\leq O-$), singlet (2H) at 5.33 τ ($C\underline{H}_2$=C-CH_3).

Rearrangement of the Hydroxy-epoxide with Boron Trifluoride Etherate——The hydroxy-epoxide (Ⅴ) (562 mg.) was treated with $BF_3 \cdot Et_2O$ (1 ml.) in benzene (5 ml.) at room temperature for 3 min. The mixture was worked up in the usual way and the product (649 mg.) was chromatographed over silica gel (15 g.). Elution with benzene gave a crystalline mass (99 mg.), which was crystallized from AcOEt to yield eudesm-11-en-3-on-5β-ol (Ⅸ) as colorless needles, m.p. 138~139°, $[\alpha]_D$ +57.1° (c=5.2), ORD (c=0.099, MeOH): $[\phi]_{302}^{trough}$ −240°, $[\phi]_{254}^{peak\,(inflection)}$ +2840°, CD (c=0.099, MeOH): $[\theta]_{275}$ −1080, MS (*m/e*): 236 (M^+), 218, 203, 161, 152, 147, 137, 133, 121, 119, 109, 107, 105, 95, 93, 91, 81, 79, 77, 69, 67, 57, 55, 53, 44, 43, 41 (base), IR (KBr) cm^{-1}: 3091, 1645, 899 (vinylidene), 3413 (hydroxyl), 1718 (cyclohexanone), NMR: doublet (3H) at 8.99 τ (J=7, $C\underline{H}_3$-CH<), singlet (3H) at 8.92 τ ($C\underline{H}_3$-C≤), triplet (3H) at 8.27 τ (J=1, $C\underline{H}_3$-C=CH_2), quadruplet (1H) at 7.02 τ (J=7, $-CO-C\underline{H}(CH_3)-C\leq$), quadruplet (2H) at 5.23 τ (J=1, $C\underline{H}_2$=C-CH_3).

Acetylation of the Alcohol——The alcohol (Ⅲ) (1.29 g.) in pyridine (4 ml.) was treated overnight at room temperature with Ac_2O (1.7 ml.). Upon isolation, the product (1.41 g.) was distilled under reduced pressure to give 3β-acetoxyeudesma-4,11-diene (Ⅺ) as a colorless oil, $[\alpha]_D$ +52.1° (c=3.8), *Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.97; H, 9.93, IR (liquid) cm^{-1}: 3106, 1649, 887 (vinylidene), 1740, 1239 (acetoxyl), NMR: singlet (3H) at 8.90 τ ($C\underline{H}_3$-C≤), singlet (3H) at 8.44 τ ($C\underline{H}_3$-C=C<), triplet (3H) at 8.27 τ (J=1, $C\underline{H}_3$-C=CH_2), singlet (3H) at 8.02 τ ($C\underline{H}_3$-CO-O-), quadruplet (2H) at 5.33 τ (J=1, $C\underline{H}_2$=C-CH_3), broad peak (1H) at 4.82 τ ($-CH_2-C\underline{H}(OCOCH_3)-C=C$).

Epoxidation of the Acetate with Perbenzoic Acid——The acetate (Ⅺ) (190 mg.) was allowed to stand at room temperature for 6 hr. in $CHCl_3$ (1.7 ml.) and BzO_2H (106 mg.). The product (207 mg.) isolated as usual was distilled under reduced pressure to afford the mixture of 3β-acetoxy-4β,5β-oxidoeudesm-11-ene

*4 Melting points are uncorrected. Specific rotations were determined using $CHCl_3$ as solvent. NMR spectra were obtained at 60 Mc.p.s. in CCl_4 solution with Me_4Si as internal reference unless otherwise specified. Chemical shifts are expressed in τ units and coupling constants (J) in c.p.s.

(XII) and 3β-acetoxy-4α,5α-oxidoeudesm-11-ene (XIII) as a colorless oil, IR (liquid) cm^{-1}: 3106, 1647, 870 (vinylidene), 1741, 1238 (acetoxyl), NMR: singlets at 8.94, 8.72, 8.28 (unresolved), 7.95, 5.34 (unresolved), broad peak at *ca.* 5.1 τ (3β-acetoxy-4β,5β-oxidoeudesm-11-ene (XII)), singlets at 8.89, 8.82, 8.28 (unresolved), 8.00, 5.34 (unresolved), broad peak at *ca.* 5.1 τ (3β-acetoxy-4α,5α-oxidoeudesm-11-ene (XIII)).

Acetylation of the Epoxy-alcohol——The hydroxyepoxide (V) (400 mg.) was allowed to react with Ac_2O (1 ml.) in pyridine (3 ml.) at room temperature for 6 hr. After isolation, the product (438 mg.) was distilled under diminished pressure to yield 3β-acetoxy-4β,5β-oxidoeudesm-11-ene (XII) as a colorless oil, $[\alpha]_D$ +3.2° (c=2.5), *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 72.56; H, 9.74, IR (liquid) cm^{-1}: 3106, 1647, 870 (vinylidene), 1741, 1238 (acetoxyl), NMR: singlet (3H) at 8.94 τ (CH_3-C$\leqslant$), singlet **(3H)** at 8.72 τ (CH_3-C(O)-C$\langle$), unresolved singlet (3H) at 8.28 τ (CH_3-C=CH_2), singlet (3H) at 7.95 τ (CH_3-CO-O-), unresolved singlet (2H) at 5.34 τ (CH_2=C-CH_3), unresolved triplet (1H) at 5.06 τ (J=5, -CH_2-CH(OCOCH_3)-C$\leqslant$O-).

Acetylation of the Epimeric Epoxy-alcohol——The epimeric epoxy-alcohol (VII) (35 mg.) and Ac_2O (0.05 ml.) in pyridine (0.1 ml.) were set aside at room temperature for 1 day. The product (41 mg.) isolated in the usual way was distilled under reduced pressure to give 3β-acetoxy-4α,5α-oxidoeudesm-11-ene (XIII) as a colorless oil, $[\alpha]_D$ +36.1° (c=5.9), IR (liquid) cm^{-1}: 3100, 1646, 884 (vinylidene), 1741, 1235 (acetoxyl), NMR: singlet (3H) at 8.89 τ (CH_3-C$\leqslant$), singlet (3H) at 8.82 τ (CH_3-C(O)-C$\langle$), slightly splitting singlet (3H) at 8.28 τ (CH_3-C=CH_2), singlet (3H) at 8.00 τ (CH_3-CO-O-), singlet (2H) at 5.35 τ (CH_2=C-CH_3), triplet (1H) at 5.13 τ (J=7, -CH_2-CH(OCOCH_3)-C$\leqslant$O-).

Rearrangement of the Acetoxy-epoxide with Boron Trifluoride Etherate——The acetoxy-epoxide (XII) (250 mg.) in benzene (1 ml.) was treated with $BF_3 \cdot Et_2O$ (0.5 ml.) at room temperature for 7 min. Upon isolation, the product (296 mg.) was chromatographed over silica gel (10 g.).

Elution with light petroleum-benzene (5:1) and crystallization from light petroleum gave 5α-fluoro-3β-acetoxyeudesm-11-en-4β-ol (XIV) as colorless needles, m.p. 58.5~59.5°, $[\alpha]_D$ +5.8° (c=2.1), *Anal.* Calcd. for $C_{17}H_{27}O_3F$: C, 68.45; H, 9.06. Found: C, 68.00; H, 9.38, IR (KBr) cm^{-1}: 3106, 1645, 895 (vinylidene), 3534 (hydroxyl), 1721, 1255 (acetoxyl), NMR: doublet (3H) at 8.85 τ (J=2, CH_3-C$\leqslant$CF-), singlet (3H) at 8.80 τ (CH_3-C$\leqslant$), triplet (3H) at 8.27 τ (J=1, CH_3-C=CH_2), singlet (3H) at 7.98 τ (CH_3-CO-O-), quadruplet (2H) at 5.32 τ (J=1, CH_2=C-CH_3), multiplet (1H) at *ca.* 5.1 τ (CH_2-CH(OCOCH_3)-C$\leqslant$CF-).

Successive elution with the same solvent afforded 1(*R*)-isopropenyl-3-(1'-methyl-4'(*S*)-acetoxy-5'-oxohexylidene)cyclopentane (XV) as a colorless oil, MS (*m/e*): 278 (M^+), IR (CCl_4) cm^{-1}: 3096, 1644, 880 (vinylidene), 1740, 1228 (acetoxyl), 1732 (acetyl with α-oxygen substitution), NMR: broadened singlet (3H) at 8.41 τ (CH_3-C=C$\langle$), triplet (3H) at 8.29 τ (J=1, CH_3-C=CH_2), singlets (3H each) at 7.94 and 7.92 τ (CH_3-CO-C, CH_3-CO-O-), quadruplet (2H) at 5.38 τ (J=1, CH_2=C-CH_3), triplet (1H) at 5.23 τ (J=6, -CH_2-CH(OCOCH_3)-CO-CH_3).

Oxidation of the Hydroxy-epoxide with Chromium Trioxide-Pyridine Complex——The hydroxy-epoxide (V) (116 mg.) in pyridine (3 ml.) was added to CrO_3 (150 mg.) in pyridine (4 ml.) and allowed to stand overnight at room temperature. Isolation of the product (101 mg.) followed by distillation under reduced pressure yielded 4β,5β-oxidoeudesm-11-en-3-one (VIII) as a colorless oil, ORD (c=0.113, MeOH): $[\phi]_{325}^{peak}$ +3640°, $[\phi]_{275}^{trough}$ −3860°, *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.58; H, 9.34, IR (liquid) cm^{-1}: 3096, 1645, 889 (vinylidene), 1712 (cyclohexanone), NMR: singlet (3H) at 8.82 τ (CH_3-C$\leqslant$), singlet (3H) at 8.63 τ (CH_3-C(O)-C$\langle$), unresolved singlet (3H) at 8.26 τ (CH_3-C=CH_2), unresolved singlet (2H) at 5.32 τ (CH_2=C-CH_3).

Rearrangement of the Keto-epoxide with Boron Trifluoride Etherate——The keto-epoxide (VIII) (226 mg.) was treated at room temperature with $BF_3 \cdot Et_2O$ (0.2 ml.) in benzene (2 ml.) for 5 min. The mixture was worked up in the customary manner and the product (215 mg.) obtained was chromatographed over silica gel (10 g.). Elution with light petroleum and distillation under diminished pressure gave cyper-11-ene-3,4-dione (XVI) as a colorless oil, IR (liquid) cm^{-1}: 3096, 1642, 886 (vinylidene), 1742 (cyclopentanone), 1692 (acetyl), 1406 (methylene adjacent to carbonyl), NMR: singlet (3H) at 8.84 τ (CH_3-C$\leqslant$), triplet (3H) at 8.26 τ (J=1, CH_3-C=CH_2), singlet (3H) at 7.97 τ (CH_3-CO-C), quadruplet (2H) at 5.31 τ (J=1, CH_2=C-CH_3). This was shown by Rt on VPC, Rf on TLC, and IR and NMR spectra to be identical with the dione (XVI) obtained by oxidation of cyperolone.

Reduction of the Diketone with Lithium Aluminum Hydride——The dione (XVI) (2.50 g.) in ether (25 ml.) was treated at room temperature with $LiAlH_4$ (0.79 g.) for 2 hr. The product (2.57 g.) isolated in the usual way was chromatographed over silica gel (70 g.).

Elution with light petroleum-benzene (1:1) yielded a crystalline mass (0.14 g.), which on crystallization from light petroleum furnished the monoketone (XVIII)[1] as colorless needles, m.p. 37~37.5°, IR (KBr) cm^{-1}: 3086, 1642, 885 (vinylidene), 1730 (cyclopentanone), identified by mixed m.p. and comparison of IR spectra.

Elution with benzene-ether (5:1) gave a crystalline mass (0.99 g.), which was crystallized from AcOEt to yield cyper-11-ene-3β,4ξ-diol (XIX) as colorless needles, m.p. 112~112.5°, IR (KBr) cm^{-1}: 3077, 1642, 891 (vinylidene), 3448, 3311 (hydroxyl), NMR: singlet (3H) at 9.01 τ (CH_3-C$\leqslant$), doublet (3H) at 8.47 τ (J=7, CH_3-CH(OH)-), triplet (3H) at 8.24 τ (J=1, CH_3-C=CH_2), quadruplet (1H) at 6.51 τ (J=7, $\geqslant$C-CH(OH)-CH_3),

broad peak (1H) at 5.75 τ (-CH_2-C$\underline{H}$(OH)-C$\lessdot$), slightly multiplying singlet (2H) at 5.33 τ (C$\underline{H}_2$=C-CH_3), showing no m.p. depression on admixture with an authentic sample and having IR and NMR spectra identical with those of the authentic material prepared from cyperolone by reduction.[1]

Successive elution with the same solvent afforded a crystalline mass (0.85 g.), which on crystallization from AcOEt gave cyper-11-ene-3α,4ξ-diol (XX) as colorless needles, m.p. 110~111°, $[\alpha]_D$ +31.6° (c=3.5), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.54; H, 10.75, IR (KBr) cm^{-1}: 3125, 1647, 886 (vinylidene), 3425 (hydroxyl), IR (0.01*M*, CCl_4): 3624 (free hydroxyl), NMR ($CHCl_3$): singlet (3H) at 8.92 τ (C$\underline{H}_3$-C$\lessdot$), doublet (3H) at 8.84 τ (J=7, C$\underline{H}_3$-CH(OH)-), unresolved singlet (3H) at 8.27 τ (C$\underline{H}_3$-C=CH_2), quadruplet (1H) at 6.24 τ (J=7, CH_3-C$\underline{H}$(OH)-), quadruplet (1H) at 5.60 τ (J_1=4, J_2=9, -CH_2-C$\underline{H}$(OH)-C$\lessdot$), unresolved singlet (2H) at 5.33 τ (C$\underline{H}_2$=C-CH_3).

Further elution with the same solvent gave a crystalline mass (0.15 g.), which was crystallized from light petroleum to yield cyperane-3ξ,4ξ-diol (XXI) as colorless needles, m.p. 117~118°, $[\alpha]_D$ +26.0° (c=2.5), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.56; H, 10.70, IR (KBr) cm^{-1}: 3106, 1647, 880 (vinylidene), 3448 (hydroxyl), NMR ($CHCl_3$): singlet (3H) at 8.97 τ (C$\underline{H}_3$-C$\lessdot$), doublet (3H) at 8.81 τ (J=7, C$\underline{H}_3$-CH(OH)-), triplet (3H) at 8.25 τ (J=1, C$\underline{H}_3$-C=CH_2), quadruplet (1H) at 6.29 τ (J=7, CH_3-C$\underline{H}$(OH)-), quadruplet (1H) at 5.70 τ (J_1=8, J_2=5, -CH_2-C$\underline{H}$(OH)-C$\lessdot$), quadruplet (2H) at 5.30 τ (J=1, C$\underline{H}_2$=C-CH_3).

Partial Acetylation of the Diol——The diol (XIX) (300 mg.) in pyridine (2.5 ml.) was treated with Ac_2O (3 ml.) at room temperature for 3 hr. The product (338 mg.) isolated by ether extraction was chromatographed over silica gel (10 g.).

Elution with light petroleum-benzene (1:1) afforded 3β,4ξ-diacetoxycyper-11-ene (XXIII)[1] as a colorless oil (108 mg.), IR (liquid) cm^{-1}: 3106, 1647, 890 (vinylidene), 1742, 1248 (acetoxyl), identified by behavior upon VPC and TLC and by IR spectrum.

Succesive elution with the same solvent gave an oil (174 mg.), which was distilled under reduced pressure to yield 3β-acetoxycyper-11-en-4ξ-ol (XXII) as a colorless oil, $[\alpha]_D$ +56.8° (c=5.5), *Anal.* Calcd for $C_{17}H_{28}O_3$: C, 72.92; H, 10.57. Found: C, 73.21; H, 10.35, IR (liquid) cm^{-1}: 3106, 1645, 887 (vinylidene), 3521 (hydroxyl), 1730, 1239 (acetoxyl), NMR: singlet (3H) at 8.97 τ (C$\underline{H}_3$-C$\lessdot$), doublet (3H) at 8.61 τ (J=7, C$\underline{H}_3$-CH(OH)-), triplet (3H) at 8.28 τ (J=1, C$\underline{H}_3$-C=CH_2), singlet (3H) at 7.97 τ (C$\underline{H}_3$-CO-O-), quadruplet (1H) at 6.35 τ (J=7, $\gtrdot$C-C$\underline{H}$(OH)-CH_3), quadruplet (2H) at 5.34 τ (J=1, C$\underline{H}_2$=C-CH_3), quadruplet (1H) at 4.49 τ (J_1=7, J_2=9, -CH_2-C$\underline{H}$(OCOCH_3)-C$\lessdot$).

Oxidation of the Monoacetate with Chromium Trioxide-Pyridine Complex——The monoacetate (XXII) (50 mg.) in pyridine (2 ml.) was added to CrO_3 (100 mg.) in pyridine (1 ml.) and let stand at room temperature for 2 hr. The reaction mixture was diluted with H_2O and extracted with ether. The product (44 mg.) was distilled under diminished pressure to give 3β-acetoxycyper-11-en-4-one (XXIV) as a colorless oil, $[\alpha]_D$ +62.1° (c=5.2), *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.20; H, 9.42, IR (liquid) cm^{-1}: 3096, 1646, 888 (vinylidene), 1742, 1235 (acetoxyl), 1701 (acetyl), NMR: singlet (3H) at 9.08 τ (C$\underline{H}_3$-C$\lessdot$), triplet (3H) at 8.27 τ (J=1, C$\underline{H}_3$-C=CH_2), singlet (3H) at 8.06 τ (C$\underline{H}_3$-CO-O-), singlet (3H) at 7.96 τ (C$\underline{H}_3$-CO-C), unresolved singlet (2H) at 5.30 τ (C$\underline{H}_2$=C-CH_3), triplet (1H) at 4.47 τ (J=9, -CH_2-C$\underline{H}$(OCOCH_3)-C$\lessdot$). The identity with cyperolone acetate[1] was confirmed by behaviors on VPC and TLC, by IR and NMR spectra, and rotation.

Hydrolysis of Cyperolone Acetate——The ketol acetate (XXIV) (150 mg.) was allowed to stand at room temperature with ethanolic NaOH (1%, 2.1 ml.) for 3 hr. The mixture was worked up as usual and the product (116 mg.) was distilled under reduced pressure to yield the synthetic cyperolone (I) as a colorless oil, $[\alpha]_D$ +32.4° (c=4.2), IR (liquid) cm^{-1}: 3086, 1642, 885 (vinylidene), 3436 (hydroxyl), 1695 (acetyl), NMR: singlet (3H) at 9.06 τ (C$\underline{H}_3$-C$\lessdot$), triplet (3H) at 8.25 τ (J=1, C$\underline{H}_3$-C=CH_2), singlet (3H) at 7.93 τ (C$\underline{H}_3$-CO-C), broad peak (1H) at 5.70 τ (-CH_2-C$\underline{H}$(OH)-C$\lessdot$), quadruplet (2H) at 5.32 τ (J=1, C$\underline{H}_2$=C-CH_3). Identification with the natural cyperolone[1] was carried out by identical behaviors on VPC and TLC, and by identical IR and NMR spectra.

Partial Acetylation of the Epimeric Diol——a) The diol (XX) (350 mg.) in pyridine (2 ml.) was treated with Ac_2O (1.2 ml.) at room temperature for 4 hr., when the starting diol disappeared judged by TLC. The product (373 mg.) isolated in the usual manner was chromatographed over silica gel (10 g.).

Elution with light petroleum-benzene gave 3α,4ξ-diacetoxycyper-11-ene (XXVI) as a colorless oil (84 mg.), IR (liquid) cm^{-1}: 3096, 1647, 887 (vinylidene), 1742, 1242 (acetoxyl), NMR: singlet (3H) at 9.06 τ (C$\underline{H}_3$-C$\lessdot$), doublet (3H) at 8.83 τ (J=7, C$\underline{H}_3$-CH(OCOCH_3)-), triplet (3H) at 8.33 τ (J=1, C$\underline{H}_3$-C=CH_2), singlet (3H) at 8.06 τ (C$\underline{H}_3$-CO-O-), singlet (3H) at 8.01 τ (C$\underline{H}_3$-CO-O-), quadruplet (2H) at 5.42 τ (J=1, C$\underline{H}_2$=C-CH_3), quadruplet (1H) at 5.33 τ (J=6, $\gtrdot$C-C$\underline{H}$(OCOCH_3)-CH_3, quadruplet (1H) at 4.48 τ (J_1=9, J_2=4, -CH_2-C$\underline{H}$(OCOCH_3)-C$\lessdot$).

Successive elution with the same solvent yielded a crystalline mass (237 mg.), which on crystallization from light petroleum gave 3α-acetoxycyper-11-en-4ξ-ol (XXV) as colorless needles, m.p. 80.5~81.5°, $[\alpha]_D$ +29.6° (c=2.7), *Anal.* Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.64; H, 10.30, IR (KBr) cm^{-1}: 3096, 1647, 885 (vinylidene), 3546 (hydroxyl), 1721, 1279 (acetoxyl), NMR: singlet (3H) at 8.91 τ (C$\underline{H}_3$-C$\lessdot$), doublet (3H) at 8.82 τ (J=6, C$\underline{H}_3$-CH(OH)-), triplet (3H) at 8.34 τ (J=1, C$\underline{H}_3$-C=CH_2), singlet (3H) at 8.00 τ (C$\underline{H}_3$-CO-O-), quadruplet (1H) at 6.32 τ (J=6, $\gtrdot$C-C$\underline{H}$(OH)-CH_3), quadruplet (2H) at 5.44 τ (J=1, C$\underline{H}_2$=C-CH_3), quadruplet (1H) at 4.60 τ (J_1=7, J_2=5, -CH_2-C$\underline{H}$(OCOCH_3)-C$\lessdot$).

b) The diol (XX) (1.19 g.) was acetylated with Ac_2O (0.7 ml.) in pyridine (5 ml.) by standing 4 hr. at room temperature, when the diacetate just started to form. The product was separated by silica gel chromatography into the monoacetate (XXV) (1.00 g.) and the recovered diol (XX) (265 mg.).

Oxidation of the Epimeric Diol Monoacetate with Chromium Trioxide-Pyridine Complex——3α-Acetoxycyper-11-en-4ξ-ol (XXV) (1.00 g.) in pyridine (3 ml.) was added to CrO_3 (1.5 g.) in pyridine (3 ml.) and kept at room temperature for 7 hr. The oxidation product (961 mg.) isolated in the customary way was distilled under diminished pressure to afford 3α-acetoxycyperan-4-one (XXVII), 3-*epi*-cyperolone acetate, as a colorless oil, $[\alpha]_D$ +22.6°(c=5.9), *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found : C, 73.12; H, 9.29, IR (liquid) cm^{-1} : 3106, 1647, 887 (vinylidene), 1742, 1242 (acetoxyl), 1698 (acetyl), NMR : singlet (3H) at 9.01 τ (CH_3-C$\leqslant$), triplet (3H) at 8.30 τ (J=1, CH_3-C=CH_2), singlet (3H) at 8.01 τ (CH_3-CO-O-), singlet (3H) at 7.89 τ (CH_3-CO-C), quadruplet (2H) at 5.37 τ (J=1, CH_2=C-CH_3) quadruplet (1H) at 4.64 τ (J_1=8, J_2=4, -CH_2-CH(OCOCH_3)-C$\leqslant$).

Hydrolysis of 3-*epi*-Cyperolone Acetate——a) The epimeric ketol acetate (XXVII) (90 mg.) was dissolved in ethanolic NaOH solution (12 mg. in 1.5 ml.) and stirred at room temperature for 5 hr. Isolation in the usual manner gave the epimerized product, cyperolone (I), as a colorless oil (monohydrate : m.p. 41~42°), $[\alpha]_D$ +31.5°(c=6.7), which was identical in every respect with the natural cyperolone (I).

b) The ketol acetate (XXVII) (456 mg.) in an ethanolic NaOH solution (55 mg. in 7 ml.) was stirred at room temperature for 20 min., when about a half of the starting acetate (XXVII) had been hydrolyzed, judging by TLC. The product (442 mg.) isolated in the customary way was chromatographed over silica gel (10 g.).

Elution with light petroleum-benzene (1:1) gave the recovered acetate (XXVII) as a colorless oil (230 mg.), which was identified by usual criteria.

Elution with benzene afforded an oil (204 mg.), which was distilled under reduced pressure to furnish cyper-11-en-4-on-3α-ol (XXVIII), 3-*epi*-cyperolone, as a colorless oil, $[\alpha]_D$ +23.7°(c=3.2), *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 67.22, H, 10.24. Found : C, 67.22; H, 10.35, IR (liquid) cm^{-1} : 3096, 1645, 887 (vinylidene), 3448 (hydroxyl), 1689 (acetyl), NMR : singlet (3H) at 9.04 τ (CH_3-C$\leqslant$), triplet (3H) at 8.23 τ (J=1, CH_3-C=CH_2), singlet (3H) at 7.90 τ (CH_3-CO-C), quadruplet (1H) at 5.65 τ (J_1=10, J_2=5, -CH_2-CH(OH)-C$\leqslant$), quadruplet (2H) at 5.27 τ (J=1, CH_2=C-CH_3).

Alkali Treatment of 3-*epi*-Cyperolone——3-*epi*-Cyperolone (XXVIII) (40 mg.) was treated with ethanolic NaOH solution (8 mg. in 1 ml.) at 0° for 3hr. Isolation in the customary manner gave cyperolone (I), which was identical in every respect with an authentic specimen.

Partial Benzoylation of the Epimeric Diol——The diol (XX) (265 mg.) in pyridine (3 ml.) was treated with BzCl (0.3 g.) at room temperature for 3.5 hr. After extraction with ether, the product was chromatographed over silica gel (6 g.). The fraction (272 mg.) eluted with light petroleum-benzene (1:1) was distilled under diminished pressure to give cyper-11-ene-3α,4ξ-diol 3-benzoate (XXIX) as a colorless oil, $[\alpha]_D$ −33.3°(c=5.4), *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found : C, 77.51; H, 8.43, IR (liquid) cm^{-1} : 3086, 1645, 887 (vinylidene), 3521 (hydroxyl), 1706 (ester), 1605, 1112, 710 (phenyl).

Oxidation of the Epimeric Diol Monobenzoate with Chromium Trioxide-Pyridine Complex——The diol monobenzoate (XXIX) (91 mg.) in pyridine (1 ml.) was added to CrO_3 (150 mg.) in pyridine (1 ml.) and let stand 4 hr. at room temperature. The oxidation product (87 mg.) was isolated in the usual way and distilled under reduced pressure to give 3-*epi*-cyperolone benzoate (XXX) as a colorless oil, $[\alpha]_D$ −38.1°(c=1.9), *Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found : C, 77.20; H, 8.92, IR (liquid) cm^{-1} : 3096, 1647, 890 (vinylidene), 1724 (ester), 1701 (acetyl), 1109, 711 (phenyl).

We are indebted to Professor K. Nakanishi, this University, for the ORD curve, and to Analytical Laboratory, Department of Chemistry, this University, and International Flavors & Fragrances Inc., Union Beach, for the mass spectra. The IR and NMR measurements and microanalyses were carried out in Analytical Laboratories, this Institute, to whom thanks are also due.