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12,13-Epoxy-*C*-nor-*D*-homosteroids. I.[1] The Synthesis and Stereochemistry of 17α-Acetyl-12,13-epoxyetiojervanes

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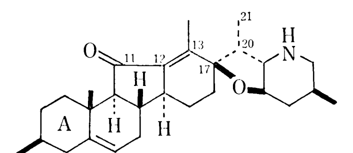
Several 11-substituted 17α-acetyl-12,13-epoxyetiojervanes were prepared from jervine. Jervine was degraded by a known process into (17*E*)-17-ethyletiojerva-4,12,17(20)-triene-3,11-dione, which on epoxidation followed by acid treatment gave 17α-ethyletiojerva-4,12-diene-3,11,20-trione as the main product. Acetalization of the carbonyl groups, at C_3 and C_{20} of the triketone and subsequent hydride reduction produced two 11-epimeric alcohols, which on hydrolysis afforded 17α-ethyl-11α-hydroxyetiojerva-4,12-diene-3,20-dione and its 11β-hydroxy epimer. These alcohols and their acetates were oxidized with perbenzoic acid and/or *t*-butyl hydroperoxide to give the epoxides. The structure and configuration of these epoxides and the synthetic intermediates were determined on the basis of the chemical and spectral evidence.

A number of papers have appeared on the cleavage of an epoxy ring accompanied by the ring skeletal rearrangement in the field of steroid and other closely related compounds.[2] However, only one example[3] seems to be known for the skeletal transformation of a *C*-nor-*D*-homosteroid (etiojervane), *via* the 12,13-epoxy ring opening, into a normal steroid, although the reverse rearrangement (normal to *C*-nor-*D*-homo) has been investigated extensively.[4] In a series of studies aimed at the preparation of biologically active steroids from jervine and other available alkaloids, we have been working on the synthesis and reaction of 12,13-epoxyetiojervanes. In this paper we describe the synthesis and stereochemistry of 17α-acetyl-12,13-epoxyetiojervanes.

Jervine (**1**) was degraded by a known three-step process [*N*-methylation, boron trifluoride etherate (BF_3) treatment and the Oppenauer oxidation][5] into (17*E*)-17-ethyletiojerva-4,12,17(20)-triene-3,11-dione[6] (**2**) in a 70% yield. Compound **2** was then oxidized with perbenzoic acid to give its 17β,20*S*- (**3**) and 17α, 20*R*-epoxy derivatives (**4**), mp 190—192 °C and 176—178 °C, in 73 and 0.4% yields, respectively. The configurations of these compounds were assigned as shown by formulas **3** and **4** mainly by comparison of the NMR spectra with those of the corresponding Δ^5-3-oxo 3-ethylene acetals (**3a**, 17β, 20*S* and **4a**, 17α, 20*R*):[7] δ for 18-C$\underline{H}_3$, $\underline{H}$ at C_{20}, and 21-C$\underline{H}_3$; **3**, 1.98, 3.36, and 1.38; **3a**, 1.96, 3.35, and 1.37; **4**, 1.95, 3.21, and 1.38; **4a**, 1.93, 3.19, and 1.36. The predominant formation[7] of 17β,20*S*-epoxide **3** is understood to be the result of preferential axial attack of the peracid to the 17,20-double bond.[8]



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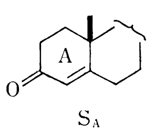
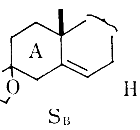
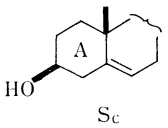


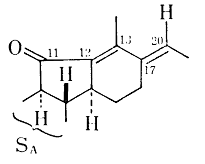
S_A



S_B



S_C



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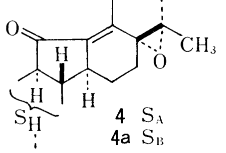
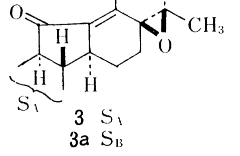
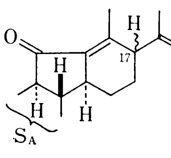


4 S_A
4a S_B

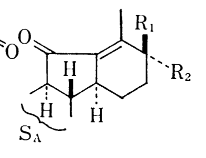


3 S_A
3a S_B

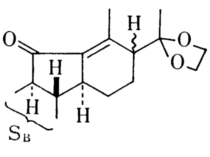
Treatment of 17β,20*R*-epoxide **3** with a large excess of the Lewis acid (BF_3) produced a 5 : 1 (estimated by NMR) mixture of 17βH- and 17αH-methyl ketones (**5**) and (**6**) and 17β-aldehyde (**7**), mp 145—147 °C, in 60 and 7.5% yields, respectively. The mixture of methyl ketones was further separated by fractional recrystallization to yield **5**, mp 151.5—153.5 °C, and **6**, mp 195—197 °C, in pure state. The same treatment of 17α,20*R*-epoxide (**4**) afforded 17α-aldehyde (**8**), mp 148—150 °C, epimeric at C_{17} for **7**, in a 60% yield along with a 30% yield of a 1 : 1 mixture of **5** and **6**. The planar structures of these compounds (**5**—**8**) were completely consistent with the spectral data (see, Experimental). While the configurations at C_{17} of aldehydes **7** and **8** were assigned only by mechanistic consideration, those of methyl ketones **5** and **6** were deduced from the NMR spectra [17βH (pseudo-axial) in **5**, δ 3.33 (br W_H=20 Hz), and 17αH (pseudo-equatorial) in **6**, δ 3.38 (br W_H=11 Hz)], as well as from the relative amplitude in the ORD curves (**5**, $a=+40°$, and **6**, $a=-20°$).[9] In accordance with this assignment, the latter (**6**) with a pseudo-axial 17β-side chain was isomerized to the former (**5**) with *p*-toluenesulfonic acid (*p*-TsOH) in benzene under reflux to give a 2 : 1 equilibrium mixture of **5** and **6**. Each of these methyl ketones (**5**) and (**6**) would be formed by initial cleavage of the 17C–O bond with concomitant hydride shift from C_{20} and/or with subsequent deprotonation at C_{20}. The hydride shift would give only 17αH-methyl ketone (**6**) from 17β-epoxide (**3**) and only 17βH-methyl ketone (**5**) from 17α-epoxide (**4**), while the deprotonation would produce (an) enol intermediate(s), which would then be protonated at C_{17} mainly from the β-side with continued overlap between the p-orbitals of 17-, 13-, and 12-carbon atoms and of the labile donor proton (axial approach), giving 17βH-methyl ketone (**5**) as a major product. The result is explained by assuming that the β-oriented 17C–O bond (pseudo-axial) in **3** would be cleaved more readily and followed mainly by deprotonation, whereas the corresponding α-bond (pseudo-equatorial) in **4** would require the hydride (and also methanide) shift owing to relatively difficult cleavage of the bond. On the other hand, 17-aldehydes (**7**) and (**8**) would result from the 17C–O bond cleavage accompanied by concurrent methyl migration, most probably from the opposite side against the epoxy group. On this premise, the configurations of 17-aldehydes were assigned as shown in formulas **7** and **8**.



5 17βH
6 17αH



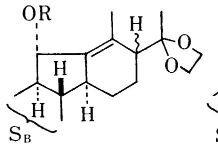
7 R_1=CHO, R_2=CH_3
8 R_1=CH_3, R_2=CHO



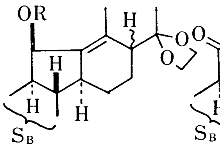
9 17βH
10 17αH

The 5 : 1 mixture of methyl ketones (**5**) and (**6**) was refluxed with ethylene glycol and acid (*p*-TsOH) in benzene for 6 h to give a mixture of the respective 3,20-di(ethylene acetal)s, from which 17βH-3,20-diacetal (**9**), mp 181—183 °C, and 17αH-3,20-diacetal (**10**), mp 143.5-144.5 °C, were isolated in 50 and 10% yields, respectively, by fractional recrystallization. The latter (**10**) was epimerized quantitatively to the former (**9**) by the prolonged acid treatment (28 h).

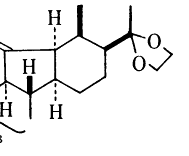
Reduction of 17βH-3,20-diacetal (**9**) with aluminium trihydride followed by chromatographic purification gave 11α-alcohol (**11**), mp 135—137 °C, and 11β-alcohol (**12**), mp 163—164 °C, in 80 and 15% yields, respectively. A similar result was obtained by treatment with lithium aluminium hydride (LAH); alcohols **11** and **12** were produced in 73 and 17% yields, respectively. The configuration at C_{11} of each alcohol was assigned as shown in formulas **11** and **12** on the basis of the following evidence. (i) The 19-methyl protons of **12** were observed as a singlet at a lower field (δ 1.24) than those of **11** (δ 1.06), indicating the 1,3-diaxial-like disposition of the hydroxyl and 19-methyl groups in **12**.[10] (ii) Treatment of 11α-alcohol (**11**) with acetic anhydride at room temperature readily produced the corresponding acetate (**11a**), mp 194—196 °C, in a 95% yield, whereas the same treatment of 11β-alcohol (**12**) led to recovery of the starting alcohol; the corresponding acetate (**12a**), mp 143—145 °C, was obtained in a 94% yield by heating with acetic anhydride at 100 °C. The hydride (LAH) reduction of 17αH-3,20-diacetal (**10**) afforded a mixture of three compounds, from which 11α-alcohol (**13**), mp 194—196 °C, 11β-alcohol (**14**), mp 139—141 °C, and 12αH-11-ketone (**15**), mp 156—157 °C, were isolated in 15, 40, and 22% yields, respectively. The hydroxyl groups at C_{11} of **13** and **14** were assigned α- and β-configurations, respectively, in essentially the same manner as the reduction products of the 17βH-epimer (**9**); 19-methyl protons, δ 1.05 for **13**, and δ 1.24 for **14**. Saturated 11-ketone (**15**) was assigned α-hydrogen configuration at C_{12} and C_{13} on the ORD (a negative Cotton effect, $a=-86°$)[11] and NMR spectral data [19- and 18-methyl protons, δ 1.12 (δ_{calcd} 1.10) and δ 0.88].[10]



11 17βH, R=H
11a 17βH, R=Ac
13 17αH, R=H



12 17βH, R=H
12a 17βH, R=Ac
14 17αH, R=H



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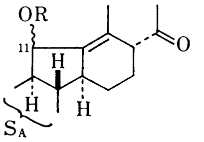
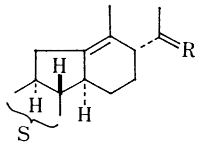
The reduction results for diacetals **9** and **10** deserve the following comments. (i) The hydride reduction of 17αH-3,20-diacetal (**10**) yielded 11β-alcohol (**14**) mainly while that of the 17βH-epimer (**9**) gave 11α-alcohol (**11**) as a major product irrespective of the reagents.[12] The latter result is remarkable as being the first example of the predominant formation of 11α-alcohol by the hydride reduction of 11-oxoetiojervanes. Compound **9** would take a twist-boat form with the pseudo-axial 17α-side chain rather than a half-chair with the pseudo-equatorial bulky substituent. The conformational change in passing from the ketone (**5**) to the acetal (**9**) would result in decrease of steric interaction between the 18-methyl group and the 17-substituent,[13] leading to more facile attack of the reagent from the less-hindered β-side to the carbonyl carbon at C_{11}, contrary to the approach from the α-side as has been illustrated in many 11-oxoetiojervanes. (ii) While no saturated 11-ketone was isolated from the reduction products of **9**, a considerable amount (22%) of saturated 12αH-11-ketone (**15**) was obtained in the reduction of **10**. In view of the slight but definite difference in the absorption maxima [λ_{max} 257 nm (ε 10000) for **9**, and 259 nm (ε 13000) for **10**], it seems that the 12,13-double bond of **9** is conjugated with the carbonyl group at C_{11} to a less extent as compared with that of **10**, suggesting a greater probability of the reduction of the double bond in question in the latter case. It should be emphasized that the 11-ketone (**15**) is the first example of 11-oxo-12α-etiojervanes (13αH) formed by the hydride reduction of 11-oxoetiojerv-12-enes. This is rationalized by assuming the preferential attack of the reagent from the less-hindered α-side to the 13-carbon atom and subsequent axial approach of the donor proton from the less-hindered α-side to the 12-carbon atom of the resulting Δ^{11}-11-olate or Δ^{11}-11-ol, since these intermediates would adopt a twist-boat conformation with both the 18-methyl group and the 17-side chain pseudo-equatorial.[11] As expected for 11-oxo-12α-etiojervanes with a bulky 17-substituent,[10] the 11-ketone (**15**) with C/D *cis*-linkage was recovered unchanged by treatment with base under the usual epimerization conditions (see, Experimental), its 12β-epimer (C/D *trans*) being not detected on TLC.

Treatment of 11α-hydroxy 3,20-diacetal (**11**) and its 11-acetate (**11a**) with acid (*p*-TsOH) in aqueous acetone afforded the corresponding 3,20-diketones (**16**) and (**16a**), mp 178—180 °C and 143—145 °C, in 83 and 99% yields, respectively. Likewise, 11β-hydroxy 3,20-diacetal (**12**) and its acetate (**12a**) were converted into the respective 3,20-diketones (**17**) and (**17a**), mp 158—160 °C and 187—190 °C, in 85 and 99% yields. Naturally the two alcohols (**16**) and (**17**) were acetylated to form the respective acetates (**16a**) and (**17a**) in quantitative yields. It is to be noted that the 12,13-double bond remained unshifted at the original position during the deacetalization, as shown by the UV spectra [λ_{max} 236—238 nm (ε 10,000—11,000) for ketones **16**—**17a**]. 11α-Acetoxy 3,20-diacetal (**11a**) was then submitted to the Birch reduction in ethylamine to give 11-deacetoxy 3,20-diacetal (**18**), mp 139—140 °C in a 90% yield, which was also obtained by the same treatment of 11β-hydroxy 3,20-diacetal (**12**). The diacetal (**18**) underwent deacetalization with acid to give 3,20-diketone (**19**), mp 131—133 °C, in an 80% yield along with a small amount (15%) of 20-oxo 3-acetal (**20**), mp 140—142 °C. The main product (**19**) was also derived in a 70% yield by the Oppenauer oxidation of 3β-hydroxy-17α-ethyletiojerva-5,12-dien-20-one[14) (**21**), a known compound with established configurations. The transformation to correlate compound **11a** with **21** has confirmed the configurations of 17-side chains of a series of the related compounds.

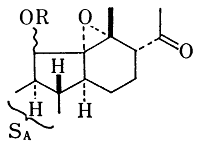


16 11α-OH
16a 11α-OAc
17 11β-OH
17a 11β-OAc

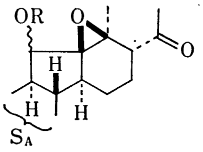


18 R=OCH_2CH_2O-, S=S_B
19 R=O, S=S_A
20 R=O, S=S_B
21 R=O, S=S_C

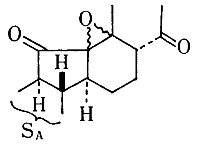
Epoxidation of 11-alcohols and 11-acetates (**16**—**17a**) with perbenzoic acid proceeded smoothly to give the respective 12,13-epoxides. In general, peracid epoxidation of olefins takes place by an electrophilic attack mainly from a less-hindered side.[8) Hence, the epoxidation of these etiojerv-12-enes is expected to proceed from the rear (α) side of the molecules and result in predominant formation of 12α,13α-epoxides. The oxidation of 11α-alcohol (**16**) gave a single product (**22**), mp 206—208 °C, in a quantitative yield, which was assigned 12α, 13α-epoxy configuration on the basis of the above presumption. Compound **22** on acetylation and the Jones oxidation formed the corresponding 11α-acetate (**22a**), mp 200—203 °C, and 11-ketone (**23**), mp 176.5—178 °C, in good yields. On the other hand, the same treatment of 11β-alcohol (**17**) produced two 12,13-epoxides, one (**24**), mp 204—207 °C, in a 60% yield, and the other (**25**), mp 159.5—160.5 °C, in a 36% yield. These 11β-alcohols (**24**) and (**25**) were converted with acetic anhydride at 100 °C into the respective 11β-acetates (**24a**) and (**25a**), mp 209—211 °C and 165—167 °C, in good yields. Oxidation of the major epoxide (**24**) with the Jones reagent gave the 11-ketone (**23**) in an 80% yield, while that of the minor (**25**) afforded a new 11-ketone (**26**), mp 157—159 °C, in an 87% yield. This indicates that the major epoxide (**24**) is 11β-hydroxy 12α,13α-epoxide with the same epoxy configuration as that of epoxide **22**, and the minor (**25**) 11β-hydroxy 12β,13β-epoxide. Likewise, 11α-acetate (**16a**) was oxidized under almost the same conditions as 11α-alcohol (**16**) to give two epimeric epoxides in 45 and 22% yields along with the recovered 11α-acetate (30%). The main epoxide was identified as 11α-acetoxy 12α,13α-epoxide (**22a**), and the minor (**27**), mp 140—142 °C, as the 12β,13β-epoxy epimer. The same epoxidation of 11β-acetate (**17a**) afforded 11β-acetoxy 12α,13α-epoxide (**24a**) as the only isolable 12,13-oxide in a 27% yield, leaving 41% of the starting 11β-acetate (**17a**) unreacted. The formation of 12β, 13β-epoxide (**27**) on the oxidation of 11α-acetate (**16a**) would result from steric hindrance due to the α-acetoxyl group at C_{11}. Finally, compound **19** having no substituent at C_{11} was oxidized with the peracid. The epoxidation proceeded very rapidly, as compared with that of 11-alcohols and 11-acetates (**16**—**17a**), and one major (**28**), mp 161—163 °C, and two minor products (**29** and **30**), mp 175—177 °C and 202—205 °C, were isolated in 65, 24, and 3.5% yields, respectively. In view of the fact that the major compound was the sole isolable 12,13-epoxide, it was assigned formula **28** with a 12α,13α-epoxy group. Moreover, structures **29** and **30** were assigned tentatively to the minor products on the basis of spectral data (see, Experimental).



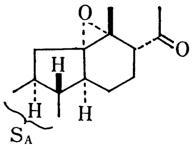
22 11α-OH
22a 11α-OAc
24 11β-OH
24a 11β-OAc



25 11β-OH
25a 11β-OAc
27 11α-OAc



23 12α,13α-O-
26 12β,13β-O-



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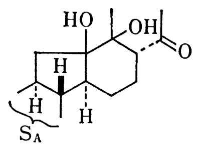

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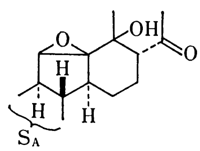

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As mentioned in the preceding section, the configurational assignment of compounds **22**—**28** to the 12,13-epoxy groups was deduced from the same ground, the preferential attack of the peracid from the less-hindered rear (α) side. However, the stereoselectivity of epoxidation is also influenced by nearby polar substituents,[15) as has been illustrated by many allyl alcohols,[16) especially in the presence of transition metal catalysts.[17) In good accord with the prediction, 11β-alcohol (**17**) was oxidized with *t*-butyl hydroperoxide in refluxing benzene containing bis(acetylacetonato)oxovanadium(IV) to give 11β-hydroxy 12β,13β-epoxide (**25**) almost quantitatively. Naturally, 11α-alcohol (**16**) yielded the corresponding 12α,13α-epoxide (**22**) quantitatively by the same treatment. The results are in line with the assigned configurations to the 12,13-epoxy groups, supported also by comparison of the chemical shifts of protons at C_{18} and C_{17}: 18-methyl protons, **22** (11α-OH and 13β-CH_3) δ 1.36: **24** (11β-OH and 13β-CH_3) δ 1.47; **25** (11β-OH and 13α-CH_3) δ 1.33: proton at C_{17}, **25**, **25a**, **26**, and **27** (each 12α,13α-epoxy) 3.14 (br W_H=16 Hz), 3.06 (16), 3.16 (16), and 3.04 (16); **22**, **22a**, **23**, **24**, **24a**, and **28** (each 12α,13α-epoxy), not observed below δ 3.00 as a separated peak.[18]

In a previous paper[10] on the NMR spectra of a number of 12β- and 12α-etiojervanes, it was reported that the effects of many different substituents on the chemical shifts of 19-methyl protons are additive. However, the results for 11-hydroxy, 11-acetoxy and/or 11-oxoetiojervanes with a 12,13-double bond or an 12, 13-epoxy group were not given. We now give the contribution of new functional groups (Table 1) in addition to that given previously.[10] The chemical shift and spectral pattern of a proton at C_{11} in these allyl or β,γ-epoxy alcohol and acetate systems are also summarized in Table 2. These data would be valuable for the confirmation of certain stereochemical conclusions as well as the improvement of the structure determination of new derivatives. The summarized results (Tables 1 and 2) are noteworthy in the following points. (i) Each of the 11-hydroxyl and 11-acetoxyl groups with a 12,13-double bond provides the same deshielding effect as the corresponding group with a 12,13-epoxy group, irrespective of the configuration of the epoxy groups (Table 1). (ii) The 11β-protons of etiojerv-12-en-11-ols and their acetates were observed clearly as a doublet with a large coupling constant of *ca.* 8 Hz, while the 11α-protons appeared as broad peaks with small half-width of *ca.* 12 Hz or doublets with a small coupling constant of *ca.* 4 Hz (Table 2). On the other hand, these protons of 12,13-epoxyetiojervan-11-ols and the acetates were observed as doublets with different coupling constants, depending on the configuration of the epoxy groups.

TABLE 1. CONTRIBUTION (Δδ) OF FUNCTIONAL GROUPS TO THE CHEMICAL SHIFT OF THE 19-METHYL PROTONS OF ETIOJERVANES

Groups	A-T[a]	B-T[a]
Reference shifts	0.74[a]	0.79[a]
Functional groups	Δδ[b]	Δδ[b]
11β-OH, Δ^{12}	0.28	—
11β-OAc, Δ^{12}	0.03	—
11α-OH, Δ^{12}	0.08	—
11α-OAc, Δ^{12}	0.12	—
11β-OH, 12β,13β-O-[c]	0.28	—
11β-OH, 12α,13α-O-[c]	—	0.28
11β-OAc, 12β-13β-O-	0.03	—
11β-OAc, 12α,13α-O-	—	0.03
11α-OH, 12β,13β-O-	0.08	—
11α-OH, 12α,13α-O-	—	0.08
11α-OAc, 12β,13β-O-	0.12	—
11α-OAc, 12α,13α-O-	—	0.12
11=O, 12β,13β-O-	0.11	—
11=O, 12α,13α-O-	—	0.03
12α,13α-O-	—	0.00

a) *Cf.*, Table 2 in Ref. 10. b) "Δδ" means deshielding effect. c) Abbreviations "12β,13β-O- and 12α,13α-O-" denote "12β,13β-epoxy and 12α,13α-epoxy," respectively.

TABLE 2. CHEMICAL SHIFT AND SPECTRAL PATTERN OF THE PROTON AT C_{11} OF Δ^{12}- OR 12,13-EPOXY-ETIOJERVAN-11-OLS AND THE ACETATES

Compound No.	Type C_{11}	C_{12}-C_{13}	C_{17}	Chemical shift (δ)	Coupling constant (Hz)	
11	α-OH	Δ[a]	β-H	4.60	d[b]	J=8
11a	α-OAc	Δ	β-H	5.99	br[b]	W_H=12
12	β-OH	Δ	β-H	4.86	br	W_H=12
12a	β-OAc	Δ	β-H	6.18	d	J=4
13	α-OH	Δ	α-H	4.60	d	J=8
14	β-OH	Δ	α-H	4.84	br	W_H=12
16	α-OH	Δ	β-H	4.54	d	J=8
16a	α-OAc	Δ	β-H	5.88	d	J=8
17	β-OH	Δ	β-H	4.89	d	J=4.5
17a	β-OAc	Δ	β-H	6.18	d	J=4
22	α-OH	α-O[a]	β-H	3.85	d	9
22a	α-OAc	α-O	β-H	5.32	d	8
24	β-OH	α-O	β-H	4.25	d	4
24a	β-OAc	α-O	β-H	5.46	d	4
25	β-OH	β-O[a]	β-H	4.33	d	7.5
25a	β-OAc	β-O	β-H	5.68	d	7
27	α-OAc	β-O	β-H	5.34	d	8

a) "Δ, α-O and β-O" denote "double bond, 12α,13α-epoxy, and 12β,13β-epoxy groups," respectively. b) Abbreviations "d and br" denote "doublet and broad."

Experimental

All the melting points were uncorrected. The homogeneity of each compound was always checked by TLC on silica gel (Wakogel B-5) with various solvent systems, the spots being developed with cerium(IV) sulfate in dil. sulfuric acid and/or iodine. The optical rotations, ORD curves, UV and IR spectra were measured in chloroform, dioxane, methanol and chloroform, respectively, unless otherwise stated. The NMR spectra were obtained in chloroform-*d* at 60 and/or 100 MHz, and the chemical shifts were given in δ-values, TMS being used as an internal reference. Abbreviations "s, d, q, br, and do" in the NMR spectra denote "singlet, doublet, quartet, broad, and double", respectively.

(20S)-17,20-Epoxy-17α-ethyletiojerva-4,12-diene-3,11-dione (3) and Its 17-Epimer (4). To a solution of (17*E*)-17-ethyletiojerva-4,12,17(20)-triene-4,11-dione[6] (**2**, 20 g) in chloroform (1.2 l) cooled with ice was added perbenzoic acid (10 g, purity, 97.3%) in chloroform (100 ml) under stirring for 10 min. The resulting solution was allowed to stand at room temp for 3 h, and treated with 5% aq sodium thiosulfate to decompose excess of the perbenzoic acid. The chloroform layer was separated, washed with 5% aq sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate, and evaporated to leave an oily residue (21.5 g), which crystallized on trituration with acetone-diisopropyl ether (5 : 1) and was recrystallized from the same solvent mixture to give **3** (14.6 g), mp 190—192 °C; $[\alpha]_D$ +57.0°; MS, *m/e* 326 (M^+); UV, λ_{max} 253 nm (ε 17000) and λ_{max} (dioxane) 254 nm (ε 15000); IR, ν_{max} (Nujol) 1705, 1677, and 1625 cm^{-1}; NMR, δ 1.25 (3H, s, 19-C$\underline{H}_3$), 1.38 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 1.98 (3H, s, 18-C$\underline{H}_3$), 3.36 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), and 5.81 (1H, s, $\underline{H}$ at C_4). Found: C, 77.23; H, 8.03%. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%.

The mother liquors obtained on crystallization of crude **3** were evaporated to give a resinous material, which was crystallized and recrystallized from ethyl acetate-hexane (5 : 1) to yield **4** (80 mg), mp 176—178 °C; $[\alpha]_D$ +203.5 °C; MS, *m/e* 326 (M^+), UV, λ_{max} 253 nm (ε 17000) and λ_{max} (dioxane) 257 nm (ε 16000); IR, ν_{max} (Nujol) 1714, 1664, and 1628 cm^{-1}; NMR, δ 1.25 (3H, s, 19-$C\underline{H}_3$), 1.38 (3H, d J=6 Hz, 21-$C\underline{H}_3$), 1.95 (3H, s, 18-$C\underline{H}_3$), 3.21 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), and 5.78 (1H, s, $\underline{H}$ at C_4). Found: C, 77.41; H, 8.04%. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%.

*17α-Ethyletiojerva-4,12-diene-3,11,20-trione (**5**), Its 17β-Epimer (**6**), and 17β-Formyl-17α-methyletiojerva-4,12-diene-3,11-dione (**7**), and Its 17-Epimer (**8**).* (i) A solution of **3** (1.0 g) in benzene (50 ml), dried over sodium and then LAH, was stirred with BF_3 (2.0 ml), freshly distilled over calcium hydride, at room temp for 60 s. The benzene solution was mixed with ether, washed with 5% aq sodium hydrogencarbonate and water, dried and evaporated to leave a resinous substance (1.0 g), which was purified by chromatography over silica gel (Merck, 70—230 mesh, 50 g) with benzene and ether. Eluates with benzene-ether (5 : 1) crystallized on trituration with ether. Recrystallization from ether gave **7** (75 mg), mp 145-147 °C; $[\alpha]_D$ +17°; ORD, $[\Phi]^{\text{trough}}_{338}$ −352°, $[\Phi]^{\text{peak}}_{280}$ +2280°, a=−26°; MS, *m/e* 326 and 297 (M^+ −CHO); UV, λ_{max} (dioxane) 250 nm (ε 18000); IR, ν_{max} 1717, 1703, and 1658 cm^{-1}; NMR, δ 1.24, 1.30, and 2.12 (each 3H, s, 19-, 17-, and 18- $C\underline{H}_3$), 5.76 and 9.44 (each 1H, s, $\underline{H}$ at C_4 and $C\underline{H}O$).

Eluates with a 3 : 1 mixture of benzene and ether afforded a mixture (600 mg) of **5** and **6**. A part of the mixture was separated by fractional recrystallization to give the respective compounds in pure state. Compound **5**, mp 151.5—153.5 °C (from ether–acetone); $[\alpha]_D$ +95°; ORD, $[\Phi]^{\text{peak}}_{312}$ +2710°, $[\Phi]^{\text{trough}}_{298}$ −1320°, a=+40°; MS, *m/e* 326 (M^+) and 284 (base); UV, λ_{max} (dioxane) 249 nm (ε 15,000); IR, ν_{max} 1718, 1708, and 1670 cm^{-1}; NMR, δ 1.24, 2.11, and 2.17 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.33 (1H, br W_H=20 Hz, $\underline{H}$ at C_{17}), and 5.76 (1H, s, $\underline{H}$ at C_4). Found: C, 76.95; H, 8.04%. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%. Compound **6**, mp 195—197 °C (from acetone–diisopropyl ether); $[\alpha]_D$ +25°; ORD, $[\Phi]^{\text{trough}}_{314}$ −960°, $[\Phi]^{\text{peak}}_{294}$ +1080°, a=−20°; MS, *m/e* 326 (M^+) and 284; UV, λ_{max} (dioxane) 251 nm (ε 16000); IR, ν_{max} 1714, 1699, and 1674 cm^{-1}; NMR, δ 1.30, 2.13, and 2.32 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.38 (1H, br W_H=11 Hz, $\underline{H}$ at C_{17}), and 5.08 (1H, s, $\underline{H}$ at C_4). Found: C, 77.24; H, 7.97%. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%.

(ii) 17α,20*R*-Epoxide (**4**, 1.0 g) in dry benzene (50 ml) was treated with dry BF_3 (2.0 ml) at room temp for 60 s and then worked up in the same manner as **3** to give a resinous substance (1.0 g), which was separated by chromatography (silica gel, 50 g). Fractions eluted with benzene-ether (5 : 1) crystallized on trituration with ether and were recrystallized from ether to yield **8** (600 mg), mp 148—150 °C; $[\alpha]_D$ +204°; ORD, $[\Phi]^{\text{peak}}_{328}$ +2140°, $[\Phi]^{\text{trough}}_{272}$ −3970°; a=+61°; MS, *m/e* 326 (M^+) and 297 (M^+−CHO); UV, λ_{max} (dioxane) 250 nm (ε 18,000); IR, ν_{max} 1725, 1706, and 1668 cm^{-1}; NMR, δ 1.25, 1.32, and 2.08 (each 3H, s, 19-, 17-, and 18-$C\underline{H}_3$), 5.78 and 9.30 (each 1H, s, $\underline{H}$ at C_4 and $C\underline{H}O$). Found; C, 77.24; H, 7.97%. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%. Fractions eluted with a 3 : 1 mixture of benzene and ether afforded a 1 : 1 mixture (300 mg) of **5** and **6** which were isolated by fractional recrystallization as described in part (i).

(iii) A solution of **6** (22 mg) in benzene (4 ml) was stirred with *p*-TsOH (25 mg) under reflux for 2 h. The solution was worked up as mentioned above to leave a crystalline residue, showing a single spot on TLC, which was identified as a 1 : 2 mixture of **6** and **5** on the basis of the NMR spectrum. When compound **5** was submitted to the same treatment, almost the same equilibrium mixture was obtained. However, none of these ketones (**5** and **6**) was isomerized under the conditions (BF_3, room temp, 60 s) as described in parts (i) and (ii).

*17α-Ethyletiojerva-5,12-diene-3,11,20-trione 3,20-Di(ethylene Acetal) (**9**) and Its 17-Epimer (**10**).* The afore-mentioned 5 : 1 mixture (6.0 g) of **5** and **6** was refluxed with ethylene glycol (60 ml) and *p*-TsOH (0.6 g) in benzene (600 ml) for 6 h, water being removed with a Dean-Stark apparatus. After being cooled, the solution was worked up as usual to leave crystalline acetals (7.5 g), which on recrystallization from ether gave **9** (3.3 g), mp 181—183 °C; $[\alpha]_D$ −77°; MS, *m/e* 414 (M^+), 399, 99, and 87; UV, λ_{max} 257 nm (ε 10000); IR, ν_{max} 1710 and 1623 cm^{-1}; NMR, δ 1.09, 1.23, and 2.30 (each 3H, s, 19-, 21-, and 18-$C\underline{H}_3$), 3.97 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), and 5.39 (1H, br W_H=10Hz, $\underline{H}$ at C_6). Found: C, 72.04; H, 8.45%. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27%.

The mother liquors on recrystallization from ether were evaporated and purified by chromatography over silica gel (80 g). Eluates with benzene gave crystals (1.3 g), which on recrystallization from ether yielded **10** (0.75 g), mp 143.5—144.5 °C; $[\alpha]_D$ −128°; MS, *m/e* 414 (M^+), 399, 99, and 87; UV, λ_{max} 259 nm (ε 13000); IR, ν_{max} 1708 and 1623 cm^{-1}; NMR, δ 1.08, 1.28, and 2.32 (each 3H, s, 19-, 21-, and 18-$C\underline{H}_3$), 3.96 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), and 5.39 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 72.03; H, 8.04%. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27%. Eluates with benzene-ether (10 : 1) afforded an additional sample of **9** (1.0 g).

17αH-Di(ethylene acetal) (**10**, 30 mg) was treated with ethylene glycol (1 ml) and *p*-TsOH (10 ml) in benzene (10 ml) under reflux for 28 h. The reaction mixture was worked up as usual to leave a crystalline residue (28 mg), showing essentially the same NMR spectrum and TLC spot as those of **9**.

*17α-Ethyl-11α-hydroxyetiojerva-5,12-diene-3,20-dione 3,20-Di(ethylene Acetal) (**11**), Its 11-Acetate (**11a**), and Their 11β-Epimers (**12** and **12a**).* (i) To a solution of **9** (5.2 g) in dry tetrahydrofuran (THF, 260 ml) was added dropwise aluminium trihydride (0.57 g) in dry THF (29 ml) under cooling with ice and stirring in a stream of nitrogen during 20 min, the whole mixture being stirred at room temp for 3 h. After addition of methanol to decompose excess hydride, the mixture was mixed with 6M aq ammonia and then filtered. The filtrate was dried and evaporated to leave an amorphous residue (5.9 g), which was separated by chromatography over silica gel (150 g). Eluates with benzene-ether (3 : 1) were crystallized and recrystallized from ether to give **12** (0.8 g), mp 163—164 °C; $[\alpha]_D$ +32°; MS, *m/e* 416 (M^+); IR, ν_{max} 3580 and 3440 cm^{-1}; NMR, δ 1.18, 1.24, and 1.90 (each 3H, s, 21-, 19-, and 18-$C\underline{H}_3$), 3.88 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), 4.86 (1H, br W_H=12 Hz, $\underline{H}$ at C_{11}), and 5.24 (1H, br W_H=8 Hz, $\underline{H}$ at C_6). Found: C, 71.77; H, 8.75%. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%.

Eluates with benzene-ether (1 : 2), crystallized on trituration with acetone-diisopropyl ether, were recrystallized from the same solvent mixture to yield **11** (4.2 g), mp 135—137 °C; $[\alpha]_D$ +10°; MS, *m/e* 416 (M^+); IR, ν_{max} 3580 and 3440 cm^{-1}; NMR, δ 1.06, 1.18 and 1.82 (each 3H, s, 19-, 21-, and 18-$C\underline{H}_3$), 3.90 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), 4.60 (1H, d J=8 Hz, $\underline{H}$ at C_{11}), and 5.36 (1H, br W_H=8 Hz, $\underline{H}$ at C_6). Found: C, 72.00; H, 8.70%. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%.

(ii) 11α-Alcohol (**11**, 200 mg) was stirred with acetic anhydride (Ac_2O, 0.55 ml) in pyridine (Py, 5 ml) at room temp for 24 h. The mixture was worked up as usual to give an amorphous residue, which was crystallized and recrystallized from diisopropyl ether-acetone to give **11a** (210 mg), mp 194—196 °C; $[\alpha]_D$ −6.5°; MS, *m/e* 443 (M^+−CH_3), 398 (M^+ −AcOH), 383, 99, and 87; IR, ν_{max} 1725 cm^{-1}; NMR, δ 1.11. 1.15, 1.62, and 1.94 (each 3H, s, 19-, 21-, 18-$C\underline{H}_3$, and $OCOC\underline{H}_3$), 3.90 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), 5.38 (1H, br W_H=8 Hz, $\underline{H}$ at C_6), and 5.99 (1H, br W_H=12 Hz, $\underline{H}$ at C_{11}). Found: C, 70.62; H, 8.32%. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35%.

11β-Alcohol (**12**, 630 mg) was heated with Ac_2O (1.7 ml) in Py (16 ml) at 100 °C for 11h. The mixture, after being worked up as usual, was purified by chlomatography over silica gel (6 g) to give benzene–ether (1 : 1) eluates (650 mg), which crystallized from ether to give **12a**, mp 143—145 °C; $[\alpha]_D$ −6.0°; MS, 443 (M^+ $-CH_3$) and 398 (M^+ −AcOH); IR, ν_{max} 1720 cm^{-1}; NMR, δ 0.98, 1.16, 1.62, and 1.96 (each 3H, s, 19-, 21-, 18-$C\underline{H}_3$, and $OCOC\underline{H}_3$), 3.88 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), 5.28 (1H, br W_H=8 Hz, $\underline{H}$ at C_6), and 6.18 (1H, d J=4 Hz, $\underline{H}$ at C_{11}). Found: C, 70.67; H, 8.30%. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35%.

*17β-Ethyl-11α-hydroxyetiojerva-5,12-diene-3,20-dione 3,20-Di(ethylene Acetal) (**13**), Its 11β-Epimer (**14**), and 17β-Ethyl-12α-etiojerv-5-ene-3,11,20-trione 3,20-Di(ethylene Acetal) (**15**).*

(i) A solution of **10** (3.2 g) in THF (162 ml) was treated with aluminium trihydride (0.35 g) in THF (18 ml) at room temp for 5 h in the same manner as **9**. After addition of methanol, the mixture was treated with 6 M aq ammonia and then filtered. The filtrate was dried, evaporated and shaken with water and chloroform repeatedly. The chloroform solutions were combined and worked up as usual to give a resinous material (3.3 g), which was separated by chromatography over silica gel (100 g). Eluates with benzene–ether (8 : 1) gave a crystalline substance, which was recrystallized from diisopropyl ether to yield **15** (690 mg), mp 156—157 °C; $[\alpha]_D$ −56°; ORD, $[\Phi]_{334}^{trough}$ −5200°, $[\Phi]_{300}^{peak}$ +3370°, a=−86°; MS, m/e 416 (M^+), 401, 99, and 87; IR, ν_{max} 1730 cm^{-1}; NMR, δ 0.88 (3H, d J=7 Hz, 18-$C\underline{H}_3$), 1.12 and 1.26 (each 3H, s, 19- and 21-$C\underline{H}_3$), 3.94 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), and 5.35 (1H, br W_H=8 Hz, $\underline{H}$ at C_6). Found: C, 71.76; H, 8.64%. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%.

Eluates with benzene–ether (5 : 1) gave **14** (1.3 g), mp 139—141 °C (from ether); $[\alpha]_D$ −57°; MS, m/e 416 (M^+), 401, and 383; IR, ν_{max} 3608 and 3480 cm^{-1}; MNR, δ 1.24, 1.28, and 1.92 (each 3H, s, 19-, 21-, and 18-$C\underline{H}_3$), 3.95 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), 4.84 (1H, br W_H=12 Hz, $\underline{H}$ at C_{11}), 5.24 (1H, br W_H=8 Hz, $\underline{H}$ at C_6). Found: C, 71.80; H, 8.68%. Calcd for $C_{25}H_{36}O_5$: C, 72.08: H, 8.71%.

Eluates with benzene–ether (3 : 1) afforded **13** (0.5 g), mp 194—196 °C (from diisopropyl ether–acetone); $[\alpha]_D$ −53°; MS, m/e 416 (M^+), 401, and 383; IR, ν_{max} 3606 and 3480 cm^{-1}; NMR, δ 1.05, 1.22, and 1.91 (each 3H, s, 19-, 21-, and 18-$C\underline{H}_3$), 3.94 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), 4.60 (1H, d J=8 Hz, $\underline{H}$ at C_{11}), and 5.33 (1H, br W_H=8 Hz, $\underline{H}$ at C_6). Found: C, 71.89; H, 8.70%. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%.

(ii) 11-Ketone (**15**, 100 mg) was refluxed with 5% aq potassium hydroxide in methanol (20 ml) for 7 h under nitrogen. The solution was cooled, neutralized with acetic acid, evaporated, and shaken with water and chloroform. The chloroform solution, after being worked up as usual, gave a crystalline residue (104 mg), showing a single spot on TLC, which displayed the same NMR spectrum as that of the starting ketone and had mp 158—159°C on recrystallization from diisopropyl ether.

*17α-Ethyl-11α-hydroxyetiojerva-4,12-diene-3,20-dione (**16**) and Its 11-Acetate (**16a**).* (i) A solution of **11** (5.1 g) in acetone (1.4 l) and water (220 ml) was refluxed with *p*-TsOH (1.0 g) for 3 h. After being cooled, the solution was evaporated and shaken with water and chloroform, and the chloroform solution was washed with 5% aq sodium hydrogencarbonate and water, dried and evaporated to leave a crystalline residue. The residue was recrystallized from ether to give **16** (3.4 g), mp 178—180 °C; $[\alpha]_D$ +198°; MS m/e 328 (M^+); UV, λ_{max} 238 nm (ε 11000); IR, ν_{max} 3447, 1705, and 1660 cm^{-1}; NMR, δ 1.22, 1.71, and 2.14 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.16 (1H, br W_H=22 Hz, $\underline{H}$ at C_{17}), 4.54 (1H, d J=8 Hz, $\underline{H}$ at C_{11}), and 5.79 (1H, s, $\underline{H}$ at C_4). Found: C, 76.57; H, 8.67%. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%.

(ii) 11α-Acetate (**11a**, 0.5 g) was treated with *p*-TsOH (105 mg) in acetone (140 ml) and water (21 ml) under reflux for 9 h. The reaction mixture was worked up as usual to give a crystalline residue, which was recrystallized from ether to give **16a** (390 mg), mp 143—145 °C; $[\alpha]_D$ +203°; MS, m/e 310 (M^+ −AcOH), 295 (310−CH_3), and 267 (310 −$COCH_3$); UV, λ_{max} 236 nm (ε 10000); IR, ν_{max} 1724, 1710, and 1660 cm^{-1}; NMR, δ 1.24, 1.50, 2.04, and 1.97 (each 3H, 19-, 18-, 21-$C\underline{H}_3$, and $OCOC\underline{H}_3$), 3.10 (1H, br W_H=20 Hz, $\underline{H}$ at C_{17}), and 5.75 (1H, s, $\underline{H}$ at C_4), 5.88 (1H, d J=8 Hz, $\underline{H}$ at C_{11}). Found: C, 74.28; H, 8.02%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%.

*17α-Ethyl-11β-hydroxyetiojerva-4,12-diene-3,20-dione (**17**) and Its 11-Acetate (**17a**).* (i) 3,20-Di(ethylene acetal) (**12**, 207 mg) was refluxed with *p*-TsOH (60 mg) in acetone (60 ml) and water (9 ml) for 2.5 h. The mixture on the usual work-up gave a crystalline substance, which was recrystallized from ether–acetone to yield **17** (139 mg), mp 158—160 °C; $[\alpha]_D$ +256°; MS, m/e 328 (M^+); UV, λ_{max} 238 nm (ε 11000); IR, ν_{max} 3444, 1700, and 1675 cm^{-1}; NMR, δ 1.44, 1.75, and 2.12 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.20 (1H, br W_H=22 Hz, $\underline{H}$ at C_{17}), 4.89 (1H, d J=4.5 Hz, $\underline{H}$ at C_{11}), and 5.73 (1H, s $\underline{H}$ at C_4). Found: C, 76.57; H, 8.67%. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%.

(ii) 11β-Acetate (**12a**, 0.3 g) was deacetalized in the same manner [*p*-TsOH (63 mg), acetone (84 ml), water (13 ml), reflux, 9 h] as **12** and gave **17a** (230 mg) on recrystallization from ether, mp 187—190 °C; $[\alpha]_D$ +204°; MS, m/e 310 (M^+ −AcOH), 295 (310−CH_3), and 267 (310−$COCH_3$); UV, λ_{max} 237 nm (ε 10000); IR, ν_{max} 1724, 1710, and 1660 cm^{-1}; NMR, δ 1.20, 1.48, 2.07, and 2.01 (each 3H, s, 19-, 18-, 21-$C\underline{H}_3$, and $OCOC\underline{H}_3$), 3.18 (1H, br W_H=20 Hz, $\underline{H}$ at C_{17}), 5.75 (1H, s, $\underline{H}$ at C_4), and 6.18 (1H, d J=4 Hz, $\underline{H}$ at C_{11}). Found: C, 74.28; H, 8.02%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%.

*17α-Ethyletiojerva-5,12-diene-3,20-dione 3,20-Di(ethylene Acetal) (**18**).* (i) To ethylamine (5 ml), dried over potassium hydroxide, containing lithium lump (20 mg) was added **11a** (100 mg) in THF (4 ml), and the blue-colored mixture was refluxed for 50 min. On addition of ammonium chloride (1 g), the mixture became colorless. It was then evaporated, mixed with water and extracted with chloroform repeatedly. The chloroform solution, after being worked up as usual, left a crystalline residue, which was recrystallized from acetone–diisopropyl ether to yield **18** (78 mg), mp 139—140 °C; $[\alpha]_D$ −12°; MS, m/e 400 (M^+), 385, 99, and 87; IR, no absorption maximum near 1700 cm^{-1}; NMR, δ 1.00, 1.22, and 1.71 (each 3H, s, 19-, 21-, and 18-$C\underline{H}_3$), 4.00 (8H, s, $2OC\underline{H}_2C\underline{H}_2O$), and 5.42 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 74.73; H, 9.02%. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06%.

(ii) 11β-Alcohol (**12**, 90 mg) was submitted to the Birch reduction under almost the same conditions [ethylamine (5 ml), lithium (30 mg), THF (4 ml), reflux, 60 min] as **11a**. The mixture was worked up as mentioned above to leave an amorphous residue (92 mg), showing two spots on TLC. The residue was separated by chromatography over silica gel (5 g) into two fractions, one (53 mg) being eluted with benzene–ether (10 : 1) and the other (39 mg) with benzene–

ether (3 : 1). The former with mp 138—140 °C (from acetone-diisopropyl ether) was identified as **18** (TLC, IR and NMR), and the latter with mp 164—166 °C (from acetone-diisopropyl ether) proved to be the starting material (**12**).

*17α-Ethyletiojerva-4,12-diene-3,20-dione (**19**) and 17α-Ethyletiojerva-5,12-diene-3,20-dione 3-Ethylene Acetal (**20**).* (i) 3,20-Di(ethylene acetal) (**18**, 1.95 g) was refluxed with *p*-TsOH (600 mg) in acetone (600 ml) and water (90 ml) for 2 h. The solution, after being worked up as usual, afforded an amorphous substance (1.90 g), which was separated by chromatography over silica gel (40 g). Eluates with benzene-ether (5 : 1) gave **20** (270 mg), mp 140—142 °C (from diisopropyl ether); MS, *m/e* 356 (M^+) and 313 (M^+-COCH_3); IR, ν_{max} 1705 cm^{-1}; NMR, δ 1.01, 1.56, and 2.12 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.10 (1H, br W_H=20 Hz, $\underline{H}$ at C_{17}), 3.98 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), and 5.41 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 77.20; H, 9.18%. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05%. Eluates with benzene-ether (3 : 1) afforded **19** (1.17 g), mp 131—133 °C (from diisopropyl ether-acetone); $[\alpha]_D$ +198°; MS, *m/e* 312 (M^+) and 269 (M^+-COCH_3); UV, λ_{max} 238 nm (ε 12000); IR, ν_{max} 1700, 1655, and 1603 cm^{-1}; NMR, δ 1.18, 1.57, and 2.13 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.10 (1H, br W_H=20 Hz, $\underline{H}$ at C_{17}), and 5.08 (1H, s, $\underline{H}$ at C_4). Found: C, 80.90; H, 9.15%. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03%.

(ii) A solution of 3β-hydroxy-17α-ethyletiojerva-5,12-diene-20-one[14] (**21**, 34 mg) in toluene (20 ml) and dry cyclohexanone (0.5 ml) was heated to distil *ca.* 12 ml of toluene to dry the system by azeotropization. To the stirred solution was added aluminium isopropoxide (34 mg), and the suspended mixture was again heated to distil *ca.* 6 ml of toluene and then refluxed for 2.5 h. After being cooled, the mixture was submitted to distillation with steam, until most of the solvents were removed, and the residue was treated with water and chloroform. The chloroform solution was worked up as usual to leave an amorphous substance, which was purified by preparative TLC to give an α,β-unsaturated ketone (14 mg), mp 126—128 °C (from diisopropyl ether). This was found to be identical with **19** (TLC, IR, NMR, and mixed mp).

*12α,13α-Epoxy-17α-ethyl-11α-hydroxyetiojerv-4-ene-3,20-dione (**22**) and Its 11-Acetate (**22a**).* (i) To a chloroform solution (4 ml) of **16** (25 mg) was added perbenzoic acid (15 mg, purity, 84%) in chloroform (1.2 ml), and the whole solution was allowed to stand at room temp for 24 h. After addition of 5% aq sodium thiosulfate (5 ml) to decompose excess peracid, the solution was washed with 5% aq sodium hydrogencarbonate and water, dried, and evaporated to leave a crystalline residue. The residue was recrystallized from diisopropyl ether-acetone to yield **22** (24 mg), mp 206—208 °C; $[\alpha]_D$ +192°; MS, *m/e* 344; UV, λ_{max} 239 nm (ε 11000); IR, ν_{max} 3400, 1708, and 1663 cm^{-1}; NMR δ 1.28, 1.36, 2.24 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.85 (1H, d J=9 Hz, $\underline{H}$ at C_{11}), and 5.78 (1H, s, $\underline{H}$ at C_4). Found: C, 73.44; H, 8.38%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

(ii) Compound **22** (460 mg) was treated Ac_2O (4.6 ml) and Py (9.2 ml) at room temp for 25 h under stirring. The mixture was worked up as usual to give an amorphous residue (530 mg), which was separated by chromatography over silica gel (11 g). Eluates with benzene-ether (3 : 1) afforded **22a** (430 mg), mp 200—203 °C (from ether); $[\alpha]_D$ +189°; MS, *m/e* 386 (M^+); UV, λ_{max} (EtOH) 238 nm (ε 10,000); IR, ν_{max} 1734, 1706, and 1674 cm^{-1}; NMR, δ 1.24, 1.29, 2.20, and 2.07 (19-, 18-, 21-$C\underline{H}_3$, and $COC\underline{H}_3$), 5.32 (1H, d J=8 Hz, $\underline{H}$ at C_{11}), and 5.78 (1H, s, $\underline{H}$ at C_4). Found: C, 71.10; H, 7.84%. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82%. Eluates with ether gave the starting alcohol (**22**, 50 mg), mp 204—206 °C.

(iii) To a refluxing greenish solution of **16** (100 mg) in dry benzene (3 ml) containing bis(acetylacetonato)oxovanadium (IV) [VO(acac)$_2$] (1.35 mg) was added rapidly *t*-butyl hydroperoxide (0.06 ml), when the solution became red-colored. The solution was further refluxed for 30 min and cooled. The resulting yellow mixture was washed with 5% aq sodium thiosulfate, 5% aq sodium hydrogencarbonate, water, dried and evaporated to give a crystalline residue, which on recrystallization from diisopropyl ether-acetone to give **22** (94 mg), mp 204—206 °C, identical with the sample (**22**) in part (i).

*12α,13α-Epoxy-17α-ethyl-11β-hydroxyetiojerv-4-ene-3,20-dione (**24**), Its 12β,13β-Epoxy Epimer (**25**), and Their 11-Acetates (**24a** and **25a**).* (i) A chloroform solution (29.5 ml) of **17** (118 mg) was treated with perbenzoic acid (65 mg, purity, 84%) at room temp for 21 h. The solution was worked up as usual to give an amorphous residue (138 mg), which was separated by chromatography over silica gel (3.5 g). Eluates with benzene-ether (5 : 1) gave **25** (44 mg), mp 159.5—160.5 °C (from ether); $[\alpha]_D$ +118°; MS, *m/e* 344 (M^+); UV, λ_{max} 238 nm (ε 8000); IR, ν_{max} 3500, 1718, and 1673 cm^{-1}; NMR, δ 1.33, 1.44, and 2.22 (18-, 19-, and 21-$C\underline{H}_3$), 3.14 (1H, br W_H=16 Hz, $\underline{H}$ at C_{17}), and 4.33 (1H, d J=7.5 Hz, $\underline{H}$ at C_{11}), and 5.70 (1H, s, $\underline{H}$ at C_4). Found: C, 73.28; H, 8.24%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

Eluates with benzene-ether (2 : 1) gave **24** (74 mg), mp 204—207 °C (from ether-acetone); $[\alpha]_D$ +174°; MS, *m/e* 344 (M^+); IR, ν_{max} 3470, 1695, and 1675 cm^{-1}; NMR, δ 1.45 and 1.47 (each 3H, s, 19- and 18-$C\underline{H}_3$ or *vice versa*), 2.20 (3H, s, 21-$C\underline{H}_3$), 4.25 (1H, d J=4 Hz, $\underline{H}$ at C_{11}), and 5.75 (1H, s, $\underline{H}$ at C_4). Found: C, 73.24; H, 8.10%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

(ii) Compound **24** (33 mg) was heated with Ac_2O and Py at 100 °C for 4 h. The reaction mixture was worked up as usual to yield an amorphous residue, which was purified by preparative TLC followed by recrystallization from ether to give **24a** (18 mg), mp 209—211 °C; $[\alpha]_D$ +140°; MS, *m/e* 386 (M^+) and 326 (M^+-AcOH); UV, λ_{max} (EtOH) 237 nm (ε 14500); IR, ν_{max} 1733, 1713, 1673, and 1613 cm^{-1}; NMR, δ 1.22 (6H, s, 19- and 18-$C\underline{H}_3$), 2.07 and 2.00 (each 3H, s, $OCOC\underline{H}_3$ and 21-$C\underline{H}_3$), 5.46 (1H, d J=4 Hz, $\underline{H}$ at C_{11}). Found: C, 71.10; H, 7.84%. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82%. The starting alcohol (**24**, 7 mg) was also recovered unchanged by preparative TLC.

Compound **25** (50 mg) was acetylated under the same conditions as **24** to give an amorphous residue (48 mg), showing a single spot, which was crystallized and recrystallized from ether to yield **25a** (22 mg), mp 165—167 °C; $[\alpha]_D$ +131°; MS, *m/e* 386 (M^+), 344, and 326; UV, λ_{max} (EtOH) 237 nm (ε 12000); IR, ν_{max} 1737, 1715, 1667, 1616, and 1242 cm^{-1}; NMR, δ 1.32, 1.36, 2.20, and 2.10 (each 3H, s, 19-, 18-, 21-$C\underline{H}_3$, and $OCOC\underline{H}_3$), 3.06 (1H, br W_H=16 Hz, $\underline{H}$ at C_{17}), 5.68 (1H, d J=7 Hz, $\underline{H}$ at C_{11}), and 5.72 (1H, s, $\underline{H}$ at C_4).

(iii) A benzene solution (3 ml) of **17** (100 mg) was refluxed with *t*-butyl hydroperoxide (0.06 ml) in the presence of VO(acac)$_2$ (1.35 mg) for 30 min. The reaction mixture was worked up in the same manner as that of **16** to give a crystalline residue (110 mg) showing a single spot, which on recrystallization from ether gave **25** (83 mg), mp 162—164 °C, identical with **25** obtained in part (i).

*12α,13α-Epoxy-17α-ethyletiojerv-4-ene-3,11,20-trione (**23**) and Its 12β,13β-Epimer (**26**).* (i) A solution of **22** (30 mg) in dry acetone (5 ml) was stirred with a few drops of the Jones reagent under cooling with ice for 1 h. After addition of ethanol to decompose the reagent, the mixture was evaporated and shaken with water and chloroform. The chloroform solution was worked up as usual to leave an amorphous residue (29 mg), which was separated into two fractions by preparative TLC (Wakogel B-5F), ether being used as a solvent. A more mobile fraction gave **23** (10 mg), mp 176.5—178 °C (from diisopropyl ether-acetone); $[\alpha]_D$ +200°; ORD, $[\Phi]^{\text{trough}}_{351}$ −1900°; $[\Phi]^{\text{peak}}_{310}$ +16100°; *a*=−180°; MS, *m/e* 342 (M^+) and 299 (M^+-COCH_3); UV, λ_{max} (EtOH) 234 nm (ε 13000); IR, ν_{max} 1750, 1710, 1665, and 1618 cm^{-1}; NMR, δ 1.22, 1.55, and 2.21 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), and 5.80 (1H, s, $\underline{H}$ at C_4). Found: C, 73.57; H, 7.65%. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66%. A less mobile fraction afforded the starting alcohol (**22**, 12 mg).

Compound **24** (28 mg) was oxidized with the Jones reagent in the same manner as **22** and gave epoxy ketone (22 mg), mp 178—180 °C (from ether), which was identical with the sample (**23**) described above.

(ii) Compound **25** (8 mg) in dry acetone (1 ml) was stirred with one drop of the Jones reagent under ice-cooling for 1 h. The reaction mixture, after addition of ethanol, was worked up as usual to leave a crystalline residue, which was recrystallized from ether to give **26** (7 mg), mp 157—159 °C; $[\alpha]_D$ −25°; ORD, $[\Phi]^{\text{trough}}_{345}$ −6900°; $[\Phi]^{\text{peak}}_{305}$ +9600°; *a*=−165°; MS, *m/e* 342 (M^+) and 299 (M^+-COCH_3); UV, λ_{max} (EtOH) 233 nm (ε 7000); IR, ν_{max} 1750, 1718, 1665, and 1615 cm^{-1}; NMR, δ 1.26, 1.55, and 2.24 (each 3H, s, 19-, 18-, and 21- $C\underline{H}_3$), 3.16 (1H, br W_H=16 Hz, $\underline{H}$ at C_{17}), and 5.82 (1H, s, $\underline{H}$ at C_4). Found: C, 73.31; H, 7.53%. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66%.

*Epoxidation of 11α-Acetate (**16a**).* A chloroform solution (30 ml) of **16a** (150 mg) was stirred with perbenzoic acid (75 mg) at room temp for 26 h. The chloroform solution was washed with 5% aq sodium thiosulfate, 5% aq sodium hydrocarbonate and water, dried and evaporated to leave a resinous residue (183 mg), which was separated into three fractions by preparative TLC (Wakogel B-5), a 2 : 1 mixture of benzene and ether being used as solvent. The most mobile fraction (51 mg) was found to be the unchanged starting acetate (**16a**, 51 mg), mp 141—143 °C. A middle fraction was crystallized and recrystallized from ether to yield 12β,13β-epoxy-17α-ethyl-11α-hydroxyetiojerv-4-ene-3,20-dione 11-acetate (**27**, 27 mg), mp 140—142 °C; $[\alpha]_D$ +102°; MS, *m/e* 386 (M^+), 344, and 326; UV, λ_{max} (EtOH) 237 nm (ε 10000); IR, ν_{max} 1734, 1714, 1664, 1612, and 1244 cm^{-1}; NMR, δ 1.24, 1.26, 2.22, and 2.05 (19-, 18-, 21-$C\underline{H}_3$, and $OCOC\underline{H}_3$), 3.04 (1H, br W_H=16 Hz, $\underline{H}$ at C_{17}), 5.34 (1H, d *J*=8 Hz, $\underline{H}$ at C_{11}), and 5.76 (1H, s, $\underline{H}$ at C_4). Found: C, 71.74; H, 7.89%. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82%.

The least mobile fraction gave crystalline epoxide (71 mg), mp 200—202 °C (from ether), which was identical with the sample (**22a**), obtained by acetylation of **22**.

*Epoxidation of 11β-Acetate (**17a**).* A chloroform solution (20 ml) of **17a** (100 mg) was treated with perbenzoic acid (50 mg) at room temp for 26 h under stirring. The chloroform solution, after being worked up as usual, gave an amorphous residue (122 mg), which was separated into two fractions by preparative TLC (Wakogel B-5), a 2 : 1 mixture of benzene and ether being used as solvent. The starting acetate (**17a**, 41 mg), mp 190—192 °C (from ether) was recovered unchanged from a more mobile fraction. A less mobile fraction yielded epoxy acetate (28 mg), mp 205—207 °C (from ether), which was identified as **24a** described above by comparison of the spectral data.

*Epoxidation of 17α-Ethyletiojerva-4,12-diene-3,20-dione (**19**).* A chloroform solution (192 ml) of **19** (1.04 g) was treated with perbenzoic acid (536 mg) at room temp under stirring. The reaction proceeded rapidly as compared with those of other etiojerv-12-enes and the starting material (**19**) disappeared on TLC after 3 h. The chloroform solution, after being worked up as usual, left a resinous residue (1.15 g), which was separated by chromatography over silica gel (30 g). Eluates with benzene-ether (5 : 1) afforded crystalline epoxide, which on recrystallization from acetone-diisopropyl ether gave **28** (700 mg), mp 161—163 °C; $[\alpha]_D$ +176°; MS, *m/e* 328 (M^+) and 285 (M^+-COCH_3); UV, λ_{max} (EtOH) 237 nm (ε 12000); IR, ν_{max} 1702 and 1663 cm^{-1}; NMR, δ 1.18, 1.28, and 2.21 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), and 5.78 (1H, s, $\underline{H}$ at C_4). Found: C, 76.57; H, 8.59%. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%.

Eluates with benzene-ether (3 : 1) afforded a crystalline substance, which on recrystallization from ether gave **30** (39 mg), mp 202—205 °C; $[\alpha]_D$ +57°; MS, *m/e* 344 (M^+), 326 (M^+-H_2O), 311 ($326-CH_3$), 301 (M^+-COCH_3), and 283 ($326-COCH_3$); UV, λ_{max} 238 nm (ε 15000); IR, ν_{max} (Nujol) 3405, 1705, 1658, and 1611 cm^{-1}; NMR, δ 1.24, 1.33, and 2.32 (each 3H, s, 19-, 18-, 21-$C\underline{H}_3$), 2.66 (1H, s, $O\underline{H}$), 3.68 (1H, br s, $\underline{H}$ at C_{11}), and 5.80 (1H, s, $\underline{H}$ at C_4). Found: C, 73.00; H, 8.25%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

Eluates with benzene-ether (1 : 1) gave a crystalline substance, which was recrystallized from acetone-diisopropyl ether to yield **29** (318 mg), mp 175—177 °C; $[\alpha]_D$ +61°; MS, 346 (M^+), 328 (M^+-H_2O), 310 ($328-H_2O$), 303 (M^+-COCH_3), and 285 ($328-COCH_3$); UV, λ_{max} 239 nm (ε 10000); IR, ν_{max} (Nujol) 3385, 3285, 1693, 1675, and 1612 cm^{-1}; NMR, δ 1.16, 1.26, and 2.33 (each 3H, s, 19-, 18-, and 21- $C\underline{H}_3$), 2.16 and 5.06 (each 1H, s, $2O\underline{H}$), 3.14 (1H, br W_H=18 Hz, $\underline{H}$ at C_{17}), 5.77 (1H, s, $\underline{H}$ at C_4). Found: C, 72.71; H, 8.71%. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73%.

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