The Configuration of 17-Ethyl-3β-hydroxyetiojerva-5,12,17(20)-trien-11-one and Related Compounds[1]

Akio MURAI, Hiroshi SASAMORI, and Tadashi MASAMUNE

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

(Received May 30, 1977)

The title compound, one of the most important starting materials for the synthesis of *C*-nor-*D*-homosteroid and normal steroid hormones, was determined to possess (*E*)-configuration at the 17,20-double bond on the basis of chemical and spectral evidence.

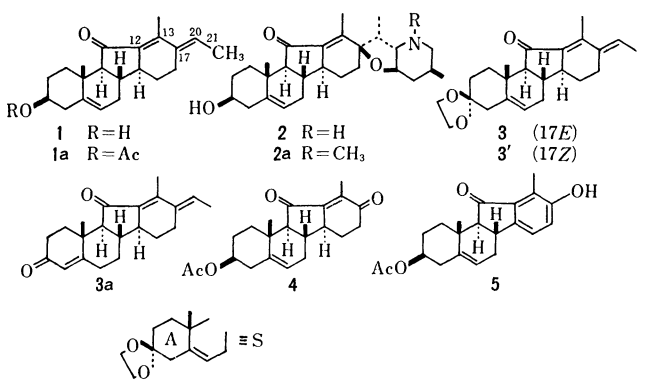
The title compound (**1**), a simple fragmentation product of jervine (**2**), was first obtained by Fried, Wintersteiner and coworkers[2] as a key substance for the structure elucidation of the jerveratrum alkaloids. The compound and its simple derivatives have since been used extensively as one of the most important starting materials for the synthesis of a number of etiojervanes including *C*-nor-*D*-homosteroid hormones[3] and of normal steroid hormones.[4] However, the configuration of the 17,20-double bond in **1** has not been determined yet, and compounds derived therefrom have often been left undecided stereochemically. In this paper, we present evidence indicating that the double bond in question should be assigned the (*E*)-configuration.[5]

Compound (**1**), prepared in good yields by degradation of *N*-methyljervine (**2a**) with boron trifluoride etherate,[6] forms its 3-acetate[2] (**1a**), and is readily converted into 17-ethyletiojerva-5,12,17(20)-triene-3,11-dione 3-ethylene acetal[7] (**3**) *via* the corresponding Δ^4-3-ketone (**3a**). All these compounds (**1**, **1a**, **3**, and **3a**), which are correlated with each other and exhibit the same NMR signals due to the 20-methine, 18- and 21-methyl protons [δ 6.12—6.14 (1H, q J=6 Hz), 2.29—2.31 (3H, s), and 1.79—1.81 (3H, d J=6 Hz)], have been defined completely with respect to the configurations of all asymmetric carbon atoms. In order to decide the configuration of the 17,20-double bond, we first attempted to prepare its geometrical isomer (**3'**) concerning the double bond by the Wittig reaction of a known 17-ketone, 3β-hydroxyetiojerva-5,12-diene-11, 17-dione 3-acetate[7] (**4**) with triphenylethylidenephosphorane. However, no trienones could be obtained, only a known phenol[2b] (**5**), mp 245—247 °C, being isolated in a 50% yield. Preparation of 20- and/or 17-epimeric 20-alcohols, which might undergo dehydration to yield the desired isomer (**3'**), was then undertaken.

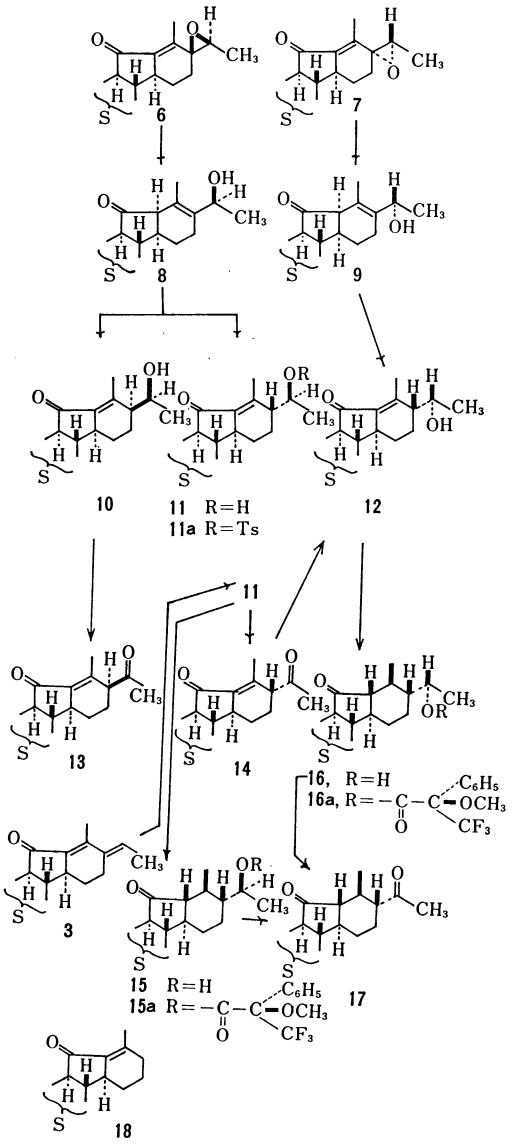
Oxidation of the $\Delta^{5,12,17(20)}$-11-ketone (**3**) with *m*-chloroperbenzoic acid produced a 5:1 (estimated by NMR) mixture of 17,20-monoepoxides in a 50% yield (**3** recovered, 16%), from which major and minor epoxides (**6**) and (**7**), mp 187—189 °C and 160—162 °C, could be separated in pure state by fractional recrystallization. The epoxy groups of **6** and **7** were tentatively assigned β- and α-configurations, respectively, at C_{17} by analogy of the UV spectra [λ_{max} 251 nm (ε 14000) for **6** and 261 nm (ε 11000) for **7**] with those of 17-epimeric 17-hydroxyetiojervanes [λ_{max} 252 nm (ε 14000) for the 17β-hydroxy compound and 261 nm (ε 10300) for the 17α-epimer].[8] The Birch reduction of the mixture of epoxides **6** and **7** followed by chromatography afforded two 20-alcohols (**8**) and (**9**), mp 152—154 °C and 160—162 °C, in 42 and 8% yields, which were naturally obtained from **6** and **7**, respectively, under the same Birch conditions. The 12αH configuration in each of these compounds was deduced from the ORD curves; a=+282° for **8** and a=+300° for **9**.[9] Treatment of **8** with potassium carbonate under mild conditions effected only migration of the 13,17-double bond to give two α,β-unsaturated ketones (**10**) and (**11**), mp 185—187 °C and 175—177 °C, in 66 and 18% yields, respectively. Likewise, compound **9**, when treated under almost the same conditions, was converted into a new α,β-unsaturated ketone (**12**) as an isolable main product (40%). A modification of the Collins oxidation[10] of the 20-alcohols (**10**) and (**11**) gave the corresponding 20-ketones (**13**) and (**14**), mp 160—162 °C and 176—178 °C, in quantitative yields, which were assigned 17αH and 17βH configurations, respectively, on the basis of the ORD and NMR data: **13**, a=−225°,[11] δ 3.33 (1H, br W_H=11 Hz, H at C_{17}); **14**, a=+370°,[11] δ 3.35 (1H, br W_H=20 Hz, H at C_{17}). It is to be noted that the latter (**14**, 17βH) on reduction with lithium aluminium tri-*t*-butoxide hydride formed 20-alcohol **12** as the sole isolable product in a 23% yield (**14** recovered, 61%).

Having available 20- and/or 17-epimeric 20-alcohols (**8**—**11**), we again attempted to prepare the geometrical isomer (**3'**) of **3**. However, 20-epimeric $\Delta^{13(17)}$-20-alcohols (**8**) and (**9**), when treated with tosyl chloride in pyridine (room temp, 22 h), gave rise to only the known trienone (**3**) in good yields. Likewise, 20-alcohol **10** was converted readily into **3** by treatment under the same conditions or with phosphoryl chloride in benzene (room temp, 19 h). Only 20-alcohol **11** formed its tosylate (**11a**), mp 158—160 °C, but attempted base treatment (5% KOH in CH_3OH, reflux, 70 min) of the tosylate led to formation of only **3**, no isomer (**3'**) being detected in the product.

The 20-epimeric Δ^{12}-11-ketones (**11**) and (**12**) were



again submitted to the Birch reduction to give the corresponding saturated 11-ketones (**15**) and (**16**), mp 194—196 °C and 182—184 °C, in 76 and 68% yields, respectively. In accordance with the assigned configurations (12βH and 13αH), each of the ketones exhibited the following spectra: **15**, ORD, $a=-145°$,[9] NMR, δ 1.04 (3H, s, 19-C$\underline{H_3}$);[12] **16**, ORD, $a=-145°$,[9] NMR, δ 1.02 (3H, s, 19-C$\underline{H_3}$).[12] Oxidation of **15** under the afore-mentioned conditions[10] produced the corresponding 20-ketone (**17**), mp 184—186 °C, in a quantitative yield, whose ORD curve with a negative Cotton effect ($a=-86°$) confirmed the 17βH configuration; $a_{calcd}=-72°$ for 17βH and $-227°$ for 17αH.[11] The 11,20-diketone (**17**) was also obtained readily by the same oxidation of **16**. All the results indicate that two pairs of the 20-alcohols (**11**, **12**), and (**15**, **16**) possess the same configuration at C_{17} (17βH). They are diastereoisomers differing only at the configuration at C_{20}.



Recently Yamaguchi and co-workers[13] reported a procedure for the determination of the absolute configurations of epimeric secondary alcohols, which involves measurement of the relative magnitude of the lanthanoid induced shift (LIS) by the shift reagent Eu(fod)$_3$ for the NMR signals for the methoxy protons of diastereoisomeric (*R*)-α-methyl-α-trifluoromethyl-α-phenylacetate (MTPA ester) of the epimeric alcohols. The 20-alcohols (**15** and **16**) were then converted by treatment with (*S*)-(+)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride[14] (MTPA-Cl) in pyridine into the respective MTPA esters (**15a**) and (**16a**), mp 176—178 °C and 138—140 °C, respectively, in good yields, showing the methoxy protons at δ 3.56 and 3.45 in the respective NMR spectra in chloroform-*d* solutions. Addition of the shift reagent Eu(fod)$_3$ to the solutions caused down-field shift of the relevant protons, and the LIS values for the protons were found to be larger for ester **16a** than for **15a** (Fig. 1 and Table 1). The result indicates that **15** with smaller LIS values has an (*S*)-configuration at C_{20} and its epimer (**16**) with larger LIS values an (*R*)-configuration.[13] This assignment not only confirms the tentatively assigned configurations for epoxides **6** and **7**, but also indicates that all

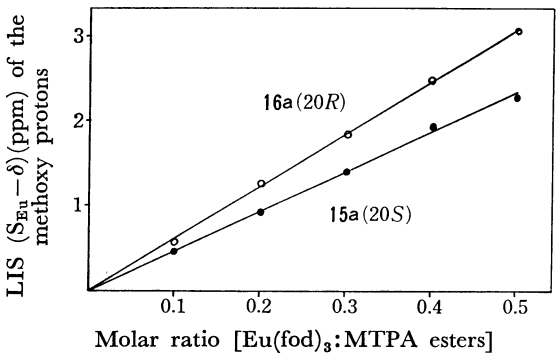


Fig. 1. LIS values of the methoxyprotons of MTPA esters **15a** and **16a**.

Table 1. Chemical shifts (δ, $CDCl_3$) of methoxyl, 19- and 18-methyl, and ethylenedioxy groups of diastereomeric MTPA esters **15a** and **16a** induced by Eu(fod)$_3$

Molar ratio Eu(fod)$_3$/MTPA ester	**15a**				**16a**			
	OCH_3	19-CH_3	18-CH_3	-OCH_2CH_2O-	OCH_3	19-CH_3	18-CH_3	-OCH_2CH_2O-
0.0	3.56	1.05	1.37	3.96	3.47	1.03	1.29	3.93
0.1	4.01	1.06	1.37	3.97	4.03	1.06	1.30	3.96
0.2	4.47	1.09	1.37	3.99	4.70	1.07	1.37	4.00
0.3	4.96	1.09	1.36	4.00	5.31	1.06	1.44	4.01
0.4	5.48	1.12	1.39	4.04	5.94	1.08	1.44	4.04
0.5	5.83	1.14	1.42	4.08	6.52	1.09	1.45	4.07

the other compounds (**8**—**17**) are represented correctly by the respective formulas. On the other hand, hydroboration of the relevant $\Delta^{5,12,17(20)}$-11-ketone (**3**) followed by oxidation resulted in hydration at the 17,20-double bond to give the (20*S*)-alcohol (**11**) as the only isolable product (25%) (**3** recovered, 48%). Since hydroboration usually proceeds in a *cis*-addition manner,[15] the present result leads to the conclusion that the 17,20-double bond in question in **3** and hence in related compounds (**1**, **1a**, and **3a**) should be assigned the (*E*)-configuration. It should be emphasized that the epoxidation and hydroboration of the 17,20-double bond take place preferentially at the β-side (axial approach), suggesting that the hydroxylation with osmium tetraoxide[7] would also lead to formation of (20*R*)-17α,20-glycol (equatorial attack).[16]

Experimental

All the melting points were uncorrected. The homogeneity of each compound was 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, IR, and NMR (100 MHz) spectra were measured in chloroform, dioxane, methanol, chloroform, and chloroform-*d*, respectively. Abbreviations "s, d, q, qui, br, and do" in the NMR spectra denote "singlet, doublet, quartet, quintet, broad, and double," respectively.

The Witting Reaction of ***4***. A solution of dry dimethyl sulfoxide (DMSO, 2 ml) containing sodium hydride (157 mg) was heated at 72—80 °C (bath temp) for 20 min and then cooled. To the solution was added ethyltriphenylphosphonium bromide (1.07 g, 2.88 mmol) in dry DMSO (5 ml) and compound **4**[7] (240 mg, 0.71 mmol) in dry tetrahydrofuran (THF, 3 ml) at room temp under stirring. The mixture was stirred at room temp for 20 min and then at 50—56 °C for 15 h. After being cooled, the mixture was poured into ice-water (100 ml) and extracted with dichloromethane. The dichloromethane solution was washed with water, dried over sodium sulfate, and evaporated to leave an amorphous residue (300 mg), which was separated by chromatography over silica gel (Merck, 70—230 mesh, 26 g) with benzene and ether (3 : 1) to give 3β,17-dihydroxyetiojerva-5,12,14,16-tetraen-11-one 3-acetate[2b] (**5**, 120 mg), mp 245—247 °C (from ether) (lit,[2b] 245—247 °C): MS, *m/e* 280 (M^+−AcOH), 265, and 247; NMR, δ 1.22, 2.52, and 2.07 (each 3H, s, 19- and 18-C$\underline{H}_3$, and OCOC$\underline{H}_3$), 4.64 and 5.51 (each 1H, br W_H=22 and 10 Hz, 2$\underline{H}$ at C_3 and C_6), 5.84 (1H, s, O$\underline{H}$), 7.08 and 7.27 (each 1H, ABq J=8 Hz, 2$\underline{H}$ at C_{15} and C_{16}).

*(20S)-17,20-Epoxy-17α-ethyletiojerva-5,12-diene-3,11-dione 3-Ethylene Acetal (****6****) and Its 17,20-Epimer (****7****).* A solution of **3**[7] (14 g) in chloroform (680 ml) was mixed with *m*-chloroperbenzoic acid (9.7 g, 1.2 mol equiv) in chloroform (140 ml) under cooling with stirring, the whole solution being stirred for 20 min under cooling with ice. After addition of 5% aq sodium thiosulfate to decompose excess of the peracid, the chloroform solution was washed with 5% aq sodium hydrogencarbonate and water, dried and evaporated to leave a resinous material (16.5 g), which was separated by chromatography over silica gel (500 g). Eluates with benzene and ether (10 : 1) yielded **3** (2.3 g), mp 130—132 °C, (from diisopropyl ether). Eluates with benzene and ether (5 : 1) afforded a 5 : 1 (estimated by NMR) mixture of **6** and **7**, which on crystallization from diisopropyl ether gave **6** (3.8 g), mp 187—189 °C. The mother liquors were evaporated, crystallized on trituration with acetone to give **7** (340 mg), mp 160—162 °C (from acetone). **6**, $[\alpha]_D$ −154°; MS, *m/e* 370 (M^+); UV, λ_{max} 251 nm (ε 14000); IR, ν_{max} 1708 and 1625 cm^{-1}; NMR, δ 1.09 and 1.95 (each 3H, s, 19- and 18-C$\underline{H}_3$), 1.37 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 3.35 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), 3.97 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), and 5.40 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 74.63; H, 8.14%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%. **7**, $[\alpha]_D$ −28°; MS, *m/e* 370 (M^+); UV, λ_{max} 261 nm (ε 11000); IR, ν_{max} 1707 and 1623 cm^{-1}; NMR, δ 1.08 and 1.93 (each 3H, s, 19- and 18-C$\underline{H}_3$), 1.36 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 3.19 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), 3.95 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), and 5.40 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 74.85; H, 8.20%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%.

*(20S)-17-Ethyl-20-hydroxy-12α-etiojerva-5,13(17)-diene-3,11-dione 3-Ethylene Acetal (****8****), and Its 20-Epimer (****9****).* (i) To liquid ammonia (350 ml), distilled over sodium, containing lithium (880 mg) was added the afore-mentioned mixture (880 mg) of **6** and **7** in dry THF (20 ml), and the mixture was stirred at −70 °C for 15 min. After addition of ammonium chloride (8.8 g), the reaction mixture was stirred for 5 min and evaporated to leave an amorphous material, which was mixed with water (400 ml) and extracted with chloroform repeatedly. The chloroform solution was worked up as usual to give an amorphous residue (925 mg), which was purified by chromatography over silica gel (30 g). Eluates with benzene-ether (3 : 1) gave etiojerva-5,12-diene-3,11-dione 3-ethylene acetal (**18**, 70 mg), mp 177—179 °C (from diisopropyl ether); MS, *m/e* 328 (M^+); NMR, δ 1.08 and 2.15 (each 3H, s, 19- and 18-C$\underline{H}_3$), 3.96 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), and 5.42 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Eluates with benzene-ether (1 : 1) afforded **8** (365 mg), mp 152—154 °C (from diisopropyl ether) and then **9** (65 mg), mp 160—162 °C (from diisopropyl ether). **8**, $[\alpha]_D$ −8.5°; ORD, $[\Phi]_{340}^{peak}$ +11700°, $[\Phi]_{289}^{trough}$ −16500°, a=+282°; MS, *m/e* 372 (M^+) and 354; IR, ν_{max} 3630, 3370, and 1735 cm^{-1}; NMR, δ 1.00 and 1.78 (each 3H, s, 19- and 18-C$\underline{H}_3$), 1.21 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 2.82 (1H, br W_H=10 Hz, $\underline{H}$ at C_{12}), 3.94 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), 4.81 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), and 5.38 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 73.99; H, 8.68%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%. **9**, $[\alpha]_D$ +38°; ORD, $[\Phi]_{340}^{peak}$ +13000°, $[\Phi]_{289}^{trough}$ −17000°, a=+300°; IR, ν_{max} 3630, 3370, and 1735 cm^{-1}; NMR, δ 0.94 and 1.85 (each 3H, s, 19- and 18-C$\underline{H}_3$), 1.17 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 2.83 (1H, br W_H=10 Hz, $\underline{H}$ at C_{12}), 3.95 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), 4.87 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), and 5.41 (1H, br W_H=10 Hz, $\underline{H}$ at C_6). Found: C, 73.86; H, 8.42%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.

(ii) Compound **6** (300 mg) was reduced under the same Birch conditions as mentioned above to give **8** (125 mg) and **18** (30 mg). Likewise, the same treatment of **7** (300 mg) afforded **8** (113 mg) and **18** (20 mg).

*(20S)-17β-Ethyl-20-hydroxyetiojerva-5,12-diene-3,11-dione 3-Ethylene Acetal (****10****) and Its 17-Epimer (****11****).* A solution of **8** (185 mg) in methanol (48 ml) and water (18 ml), containing potassium carbonate (1.85 g), was stirred at room temp for 30 min under nitrogen. The solution was worked up as usual to give an amorphous residue (195 mg), showing four spots on TLC, which was separated in the order of decreasing R_f value into four fractions by preparative TLC over silica gel (Wakogel B-5F, 20×20 cm^2, 0.75 mm, 10 plates), with benzene and ether (1 : 1), a UV lamp being used as a detector. Compounds **3** (13 mg), mp 128—130 °C, (from acetone-diisopropyl ether), and **18** (11 mg), mp 178—180 °C (from diisopropyl ether), were obtained from the first two fractions. The third fraction (123 mg) was crystallized and recrystallized from diisopropyl ether to yield **10** (77 mg),

mp 185—187 °C; $[\alpha]_D$ −109°; MS, *m/e* 372 (M^+); UV, λ_{max} 258 nm (ε 10000); IR, ν_{max} 3626, 3406, 1706, and 1626 cm^{-1}; NMR, δ 1.10 and 2.27 (each 3H, s, 19- and 18-CH_3), 1.32 (3H, d J=6 Hz, 21-CH_3), 3.97 (4H, s, OCH_2CH_2O), 4.36 (1H, q J=6 Hz, H at C_{20}), and 5.40 (1H, br W_H=10 Hz, H at C_6). Found: C, 74.29; H, 8.51%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%. The least mobile fraction (34 mg) was recrystallized from diisopropyl ether to give **11** (25 mg), mp 175—177 °C; $[\alpha]_D$ −130°; MS, *m/e* 372 (M^+); UV, λ_{max} 255 nm (ε 16000); IR, ν_{max} 3626, 3406, 1706, and 1626 cm^{-1}; NMR, δ 1.08 and 2,14 (each 3H, s, 19-, and 18-CH_3), 1.04 (3H, d J=6 Hz, 21-CH_3), 3.95 (4H, s, OCH_2CH_2O), 4.39 (1H, q J=6 Hz, H at C_{20}), and 5.38 (1H, br W_H=10 Hz, H at C_6). Found: C, 73.73; H, 8.71%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.

*(20R)-17α-Ethyl-20-hydroxyetiojerva-5,12-diene-3,11-dione 3-Ethylene Acetal (**12**).* Compound **9** (172 mg) was stirred with potassium carbonate (1.72 g) in methanol (45 ml) and water (35 ml) at room temp for 1.5 h under nitrogen. The solution was worked up as usual to leave an amorphous residue (185 mg), showing two main spots, which was separated into two fractions by preparative TLC over silica gel (10 plates) with benzene and ether (1 : 1). A more polar fraction (68 mg) gave a crystalline substance (68 mg), which was recrystallized from diisopropyl ether to yield **12** (50 mg), mp 148—150 °C; $[\alpha]_D$ −124°; MS, *m/e* 372 (M^+); UV, λ_{max} 255 nm (ε 14000); IR, ν_{max} 3626, 3445, 1705, and 1629 cm^{-1}; NMR, δ 1.10 and 2.24 (each 3H, s, 19- and 18-CH_3), 1.26 (3H, d J=6 Hz, 21-CH_3), 3.94 (4H, s, OCH_2CH_2O), 4.36 (1H, q J=6 Hz, H at C_{20}), and 5.40 (1H, br W_H=10 Hz, H at C_6). Found: C, 74.41; H, 8.60%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%. A more mobile fraction was found to be a 1 : 1 (estimated by NMR) mixture of a new 17β-ethyl epimer and **9**, but was not further purified.

*17β-Ethyletiojerva-5,12-diene-3,11,20-trione 3-Ethylene Acetal (**13**) and Its 17-Epimer (**14**).* (i) To a stirred suspension of chromium (VI) oxide (33 mg) in dichloromethane (0.81 ml), distilled over phosphorus pentaoxide, and pyridine (0.051 ml), distilled over calcium hydride, was added a solution of **10** (20 mg) in dichloromethane (1 ml). The mixture was stirred at room temp for 15 min and filtered. The resulting ppt was washed with ether. The filtrate and ether washings were combined, washed with 5% aq sodium hydroxide and saturated aq sodium chloride, dried and evaporated to leave a crystalline substance (19 mg), which was recrystallized from diisopropyl ether to yield **13** (15 mg), mp 160—162 °C; $[\alpha]_D$ −198 °; ORD, $[\Phi]_{316}^{trough}$ −6100°, $[\Phi]_{284}^{peak}$ +16400°, a=−225°; MS, *m/e* 370 (M^+); UV, λ_{max} 254 nm (ε 13000); IR, ν_{max} 1714 and 1629 cm^{-1}; NMR, δ 1.10, 2.07, and 2.23 (each 3H, s, 19-, 18-, and 21-CH_3), 3.33 (1H, br W_H=11 Hz, H at C_{17}), and 3.94 (4H, s, OCH_2CH_2O).

(ii) Compound **11** (20 mg) was oxidized in the same way as above to give **14** (17 mg), mp 176—178 °C (from diisopropyl ether); $[\alpha]_D$ −12°; ORD, $[\Phi]_{312}^{peak}$ +14700°, $[\Phi]_{286}^{trough}$ −22300°, a=+370°; MS, *m/e* 370 (M^+); UV, λ_{max} 253 nm (ε 13000); IR, ν_{max} 1713 and 1629 cm^{-1}; NMR, δ 1.12, 2.14, and 2.19 (each 3H, s, 19-, 18-, and 21-CH_3), 3.35 (1H, br W_H=20 Hz, H at C_{17}), and 4.00 (4H, s, OCH_2CH_2O).

*Hydride Reduction of **14** to **12**.* To a stirred solution of **14** (26 mg) in dry THF (6 ml) was added dropwise a suspension of lithium alminium tri-*t*-butoxide hydride (35 mg) in dry THF (5 ml) under cooling with ice. The mixture was stirred at room temp. for 23 h under nitrogen and filtered, after addition of aq ammonium sulfate. The filtrate was evaporated and shaken with water and chloroform. The chloroform extracts were washed with water, dried and evaporated to leave an amorphous residue (25 mg), showing two spots, which was separated into two fractions by preparative TLC over silica gel (one plate) with benzene and ether (1 : 1). While a less polar fraction (16 mg) gave **14**, mp 176—178 °C (from diisopropyl ether), a more polar fraction (8 mg) was crystallized and recrystallized from diisopropyl ether to yield **12** (4 mg), mp 148—150 °C, which was identical with the afore-mentioned sample (MS, IR, NMR, and TLC).

*Dehydration of Alcohols **8**, **9**, **10**, and **11**.* (i) A solution of **8** (20 mg) in pyridine (0.2 ml), distilled over potassium hydroxide, was stirred with tosyl chloride (*p*-TsCl, 25 mg) at room temp for 22 h. The mixture was worked up as usual to leave an amorphous material (18 mg), which was purified by preparative TLC over silica gel (one plate) with benzene and ether (5 : 1) to give **3** (9 mg), mp 130—132 °C.

The same treatment of **9** (20 mg) gave **3** (8 mg), mp 131—133 °C, and that of **10** (20 mg) afforded **3** (8 mg), mp 128—130 °C, and **10** (4 mg), mp 183—186 °C.

(ii) To a stirred and ice-cooled solution of **10** (20 mg) in benzene was added phosphoryl chloride (0.02 ml). The mixture was stirred at room temp. for 19 h, poured into ice-water, and extracted with chloroform. The extracts were washed with 5% aq sodium hydrogencarbonate and water, dried and evaporated to leave a tarry residue (19 mg), which was purified in the same manner as described above to yield **3** (4 mg), mp 130—132 °C, as a sole detectable product.

(iii) Compound **11** (15 mg) was treated with *p*-TsCl (18 mg) in pyridine (0.15 ml) at room temp for 22 h under stirring. The reaction mixture was worked up as usual to yield its tosylate (**11a**, 7 mg), mp 158—160 °C (from diisopropyl ether); $[\alpha]_D$ −102°; MS, *m/e* 354 ($M^+ - CH_3C_6H_4SO_3H$); UV, λ_{max} 252 nm (ε 12000) and 228 (13,500); IR, ν_{max} 1708, 1630, 1352, 1170, 1095, 912, and 893 cm^{-1}; NMR, δ 1.05 and 2.03 (each 3H, s, 19- and 18-CH_3), 1.08 (3H, d J=6 Hz, 21-CH_3), 2.46 (3H, s, $CH_3C_6H_4SO_2$), 3.96 (4H, s, OCH_2CH_2O), 5.06 (1H, qui J=6 Hz, H at C_{20}), 5.38 (1H, br W_H=10 Hz, H at C_6), 7.34 and 7.81 (each 2H, ABq J=8 Hz, $CH_3C_6H_4SO_2$). The starting material (**11**; 3 mg), mp 176—178 °C, was recovered.

Compound **11a** (10 mg) was refluxed with 5% potassium hydroxide in methanol (2 ml) for 70 min under nitrogen. The solution was neutralized with 10% acetic acid, evaporated, mixed with water and extracted with chloroform. The chloroform extracts, after being worked up as usual, gave an amorphous residue (8 mg), which was purified by preparative TLC over silica gel (one plate) with benzene and ether (5 : 1) to give **3** (4 mg), mp 131—133 °C, as the sole isolable product.

*(20S)-17α-Ethyl-20-hydroxy-12β-etiojerv-5-ene-3,11-dione 3-Ethylene Acetal (**15**), Its 20-Epimer (**16**), and Their MTPA Esters (**15a** and **16a**).* (i) To liquid ammonia (20 ml), cooled with dry ice-acetone, containing lithium (70 mg), was added **11** (50 mg) in dry THF (1 ml). The mixture was stirred at −78 °C (bath temp) for 30 min, and then worked up as described before to give an amorphous residue (57 mg), which was purified by chromatography over silica gel (5 g) with benzene-ether (1 : 1) to yield **15** (38 mg), mp 194—196 °C (from diisopropyl ether); $[\alpha]_D$ −106°; ORD, $[\Phi]_{334}^{trough}$ −7900°, $[\Phi]_{290}^{peak}$ +6600°, a=−145°; MS, *m/e* 374 (M^+); IR, ν_{max} 3630, 3444, and 1734 cm^{-1}; NMR, δ 1.04 (3H, s, 19-CH_3), 1.06 and 1.26 (each 3H, d J=4 and 6 Hz, 21- and 18-CH_3), 3.94 (4H, s, OCH_2CH_2O), 4.22 (1H, q J=6 Hz, H at C_{20}), and 5.40 (1H, br W_H=8 Hz, H at C_6).

(ii) Compound **12** (50 mg) was reduced under the same Birch conditions as described above to give **16** (34 mg), mp 182—184 °C (from diisopropyl ether); $[\alpha]_D$ −102°; ORD, $[\Phi]_{334}^{trough}$ −7900°, $[\Phi]_{290}^{peak}$ +6600°, a=−145°; MS, *m/e* 374 (M^+); IR, ν_{max} 3630, 3440, and 1734 cm^{-1}; NMR, δ 1.02

(3H, s, 19-C$\underline{H}_3$), 1.16 and 1.28 (each 3H, d J=6 Hz, 21- and 18-C$\underline{H}_3$), 3.91 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), 4.18 (1H, q J=6 Hz, $\underline{H}$ at C_{20}), and 5.37 (1H, br W_H=8 Hz, $\underline{H}$ at C_6).

(iii) A solution of **15** (15 mg, 0.04 mmol) in dry pyridine (0.12 ml) and carbon tetrachloride (0.12 ml) was stirred with MTPA-Cl[14] (10.4 μl, 0.056 mmol) at room temp for 6 h.[13] After addition of *N,N*-dimethyl-1,3-propanediamine (9.6 μl), the mixture was allowed to stand for 5 min, diluted with ether, washed with dil hydrochloric acid, saturated aq sodium carbonate and saturated aq sodium chloride, dried and evaporated to leave an amorphous residue, which was passed through a small column packed with silica gel (Merck, 70—230 mesh, 2g) with benzene to yield its crude MTPA ester (22 mg). This was recrystallized from hexane to give **15a** (18 mg), mp 176—178 °C; $[\alpha]_D$ −67°; MS, *m/e* 590 (M^+); IR, ν_{max} 1740, 1170, 710, and 690 cm^{-1}; NMR, δ 1.05 (3H, s, 19-C$\underline{H}_3$), 1.21 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 1.37 (3H, br W_H=6 Hz, 18-C$\underline{H}_3$), 3.56 (3H, s, OC$\underline{H}_3$), 3.96 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), 5.38 (1H, br W_H=10 Hz, $\underline{H}$ at C_6), and 5.53 (1H, q J=6 Hz, $\underline{H}$ at C_{20}). Found: C, 67.36; H, 7.17%. Calcd for $C_{33}H_{41}O_6F_3$: C, 67.12; H, 6.95%.

Compound **16** (15 mg) was converted in the same manner as **15** into its MTPA ester (**16a**, 17 mg), mp 138—140 °C (from aq methanol); $[\alpha]_D$ −87°; MS, *m/e* 590 (M^+); IR, ν_{max} 1738, 1175, 710, and 694 cm^{-1}; NMR, δ 1.03 (3H, s, 19-C$\underline{H}_3$), 1.23 and 1.29 (each 3H, d J=6 Hz, 21- and 18-C$\underline{H}_3$), 3.45 (3H, s, OC$\underline{H}_3$), 3.94 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), 5.36 (1H, br W_H=10 Hz, $\underline{H}$ at C_6), and 5.42 (1H, q J=6 Hz, $\underline{H}$ at C_{20}). Found: C, 67.38; H, 7.25%. Calcd for $C_{33}H_{41}O_6F_3$: C, 67.12; H, 6.95%.

17α-Ethyl-12β-etiojerv-5-ene-3,11,20-trione 3-Ethylene Acetal (17). To a stirred suspension of chromium(VI) oxide (17 mg) in dry dichloromethane (0.41 ml) and dry pyridine (0.026 ml) was added **15** (11 mg) in dry dichloromethane (0.1 ml). The mixture was stirred at room temp for 15 min and filtered, when ppts formed were washed with ether. The filtrate and ether washings were combined, washed with 5% aq sodium hydroxide and saturated aq sodium chloride, dried and evaporated to leave an amorphous residue, showing a single spot, which crystallized on trituration with diisopropyl ether and was recrystallized from the same solvent to yield **17** (10 mg), mp 184—186 °C; $[\alpha]_D$ −108°; ORD, $[\Phi]_{334}^{trough}$ −3000°, $[\Phi]_{302}^{peak}$ +5600°, a=−86°; MS, *m/e* 372 (M^+); IR, ν_{max} 1735 and 1713 cm^{-1}; NMR, δ 1.07 and 2.17 (each 3H, s, 19- and 21-C$\underline{H}_3$), 1.20 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 3.97 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O), and 5.41 (1H, br W_H=10 Hz, $\underline{H}$ at C_6).

Compound **16** (14 mg) was oxidized in the same manner as described above to give **17** (13 mg), mp 183—185 °C.

*Hydroboration of **3** Followed by Oxidation.* To a stirred solution of **3** (2.0 g, 6 mmol) in THF (90 ml) was added diborane in THF (3.6 ml, 2.2 M) under cooling with ice. The solution was stirred at the temp for 50 min under nitrogen. After dropwise addition of water (14.4 ml) to decompose excess of the diborane, the reaction mixture was stirred with 1 M aq sodium hydroxide (43 ml) and 30% aq hydrogen peroxide (29 ml) at room temp for 1 h and then treated with 5% aq sodium thiosulfate (60 ml) under cooling to decompose excess hydrogen peroxide. The THF layer was separated and the aqueous layer was extracted with THF. All the THF solutions were combined, washed with water, dried and evaporated to leave a resinous material (2.4 g), which was separated by chromatography over silica gel (70 g). Eluates with benzene and ether (5 : 1) afforded the starting compound (**3**, 950 mg), mp 130—132 °C. Eluates with benzene and ether (1 : 1) gave a crystalline substance (0.5 g), which on recrystallization from diisopropyl ether afforded **11** (0.44 g), mp 174—176 °C, identical with a sample obtained from **8** (TLC, IR, and NMR).

References

1) Part XXXII of "*C*-Nor-*D*-homosteroids and Related Alkaloids," Part XXXI, Ref. 4a.

2) a) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin, and A. Klingsberg, *J. Am. Chem. Soc.*, **73**, 2970 (1951); b) J. Fried and A. Klingsberg, *ibid.*, **75**, 4929 (1953).

3) For a recent review, see, T. Masamune, "MTP International Review of Science, Organic Chemistry Series Two," Vol. 8, ed by W. F. Johns, Butterworth & Co., London (1976), p. 237.

4) a) A. Murai, N. Iwasa, and T. Masamune, *Chem. Lett.*, **1977**, 235; b) A. Murai, H. Sasamori, and T. Masamune, *Bull. Chem. Soc. Jpn.*, **50**, 437 (1977).

5)A preliminary communication: A. Murai, H. Sasamori, and T. Masamune, *Chem. Lett.*, **1977**, 669.

6) S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.*, **86**, 701 (1964).

7) S. M. Kupchan, T. Masamune, and C. W. A. Milne, *J. Org. Chem.*, **29**, 755 (1964).

8) O. Wintersteiner and M. Moore, *J. Org. Chem.*, **29**, 262 (1964). *Cf.*, S. M. Kupchan and M. I. Suffness, *J. Am. Chem. Soc.*, **90**, 2730 (1968).

9) T. Masamune, A. Murai, K. Orito, H. Ono, S. Numata, and H. Suginome, *Tetrahedron*, **25**, 4853 (1969).

10) R. Ratcliffe and T. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

11) A. Murai, T. Nishimura, and T. Masamune, *Bull. Chem. Soc. Jpn.*, **49**, 1602 (1976). *Cf.*, footnote 15 in Ref. 4b, p. 442.

12) T. Masamune, A. Murai, K. Nishizakura, T. Orito, S. Numata, and H. Sasamori, *Bull. Chem. Soc. Jpn.*, **49**, 1622 (1976).

13) S. Yamaguchi, F. Yasuhara, and K. Kabuto, *Tetrahedron*, **32**, 1363 (1976). The authors wish to express their thanks to Professor Shozo Yamaguchi, Tohoku University, for his kind suggestion on the procedure.

14) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

15) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin Inc., Menlo Park, California (1972), p. 106.

16) a) H. B. Henbest, *Proc. Chem. Soc.*, **1963**, 159; J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **23**, 3511 (1967); J. Bascoul, C. Reliand, A. Guinot, and A. Crastes de Paulet, *Bull. Soc. Chim. Fr.*, **1968**, 4074. The authors wish to express their thanks to the referee for his suggestion on the hydroxylation; b) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier Publ. Comp., Amsterdam (1968), p. 70.