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THE CONFIGURATION OF 17-ETHYL-3β-HYDROXYETIOJERVA-5,12,17(20)-TRIEN-11-ONE AND RELATED COMPOUNDS[1)]

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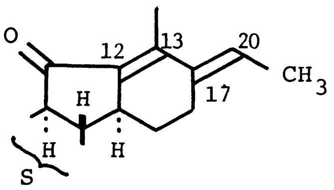
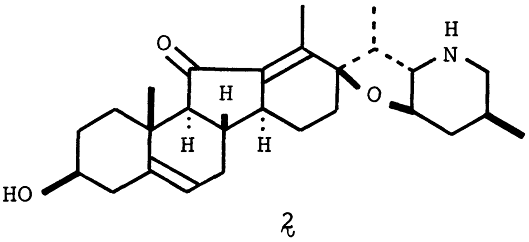
The title compound, one of the most important starting materials for the synthesis of C-nor-D-homosteroid and normal steroid hormones, was determined to possess (E)-configuration at the 17,20-double bond on the basis of the chemical and spectral evidence.

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 hence compounds derived therefrom have often been left undecided stereochemically. We now describe evidence indicating the double bond in question to be assigned (E)-configuration, which also involves the first adaptation of a procedure by Yamaguchi and coworkers[5)] for determination of the absolute configuration of steroidal 20-alcohols.



1 S_A

3 S_B



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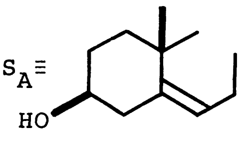
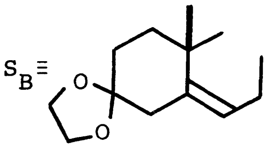
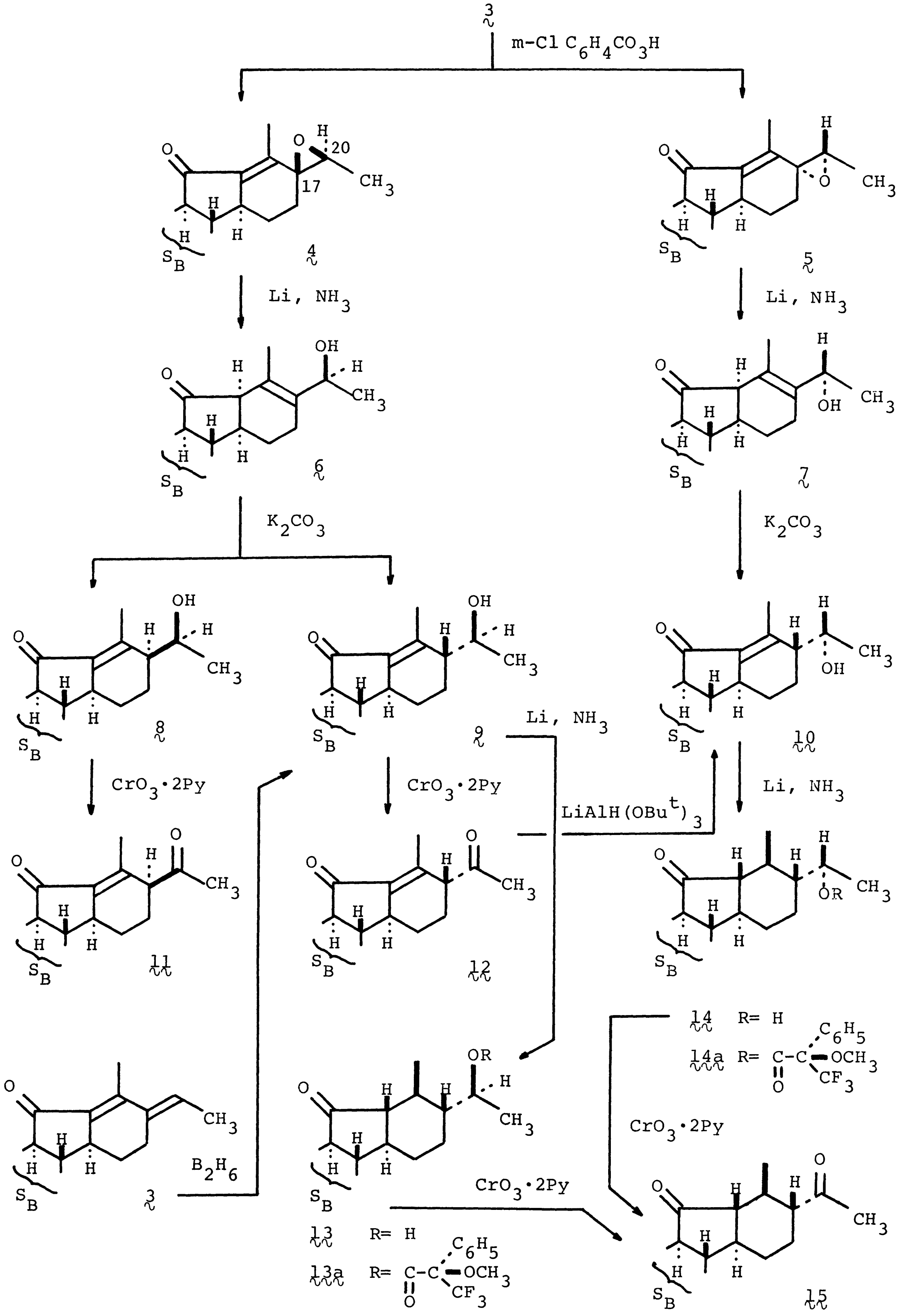




Oxidation of 17-ethyletiojerva-5,12,17(20)-triene-3,11-dione 3-ethylene acetal[6)] (**3**), obtained readily from **1**, with m-chloroperbenzoic acid (in $CHCl_3$, 0°C, 20 min) produced a 5:1 (NMR) mixture of 17,20-monoepoxides[7)] in a 50% yield, from which major and minor epoxides (**4** and **5**), mp 187-189°C and 160-162°C; $[\alpha]_D$ -154° and -28°; λ_{max} 251 nm (ε 14,000) and 261 nm (ε 11,000), could be isolated. The epoxy groups of **4** and **5** were tentatively assigned β- and α-configurations at C_{17}

by analogy with the UV spectra of 17-epimeric 17-hydroxyetiojervanes.[8] The Birch reduction (Li in NH_3, -70°C, 30 min) of the mixture of **4** and **5** afforded a mixture, which was separated by chromatography to give two 20-alcohols (**6** and **7**), mp 152-154°C and 160-162°C; $[\alpha]_D$ -8.5° and +38°; ORD, a = +282° and 300°,[9] in 42 and 8% yields. Naturally, compounds **6** and **7** were obtained from epoxides **4** and **5** under the same conditions, respectively. Treatment of **6** with base (K_2CO_3 in aq CH_3OH, room temp, 0.5 h) effected only migration of the 13,17-double bond to give two α,β-unsaturated ketones (**8** and **9**), mp 185-187°C and 175-177°C; $[\alpha]_D$ -109° and -130°; λ_{max} 258 nm (ε 10,000) and 255 nm (ε 16,000), in 66 and 18% yields. Likewise, compound **7**, when treated under the same basic conditions (2.5 h), yielded a new α,β-unsaturated ketone (**10**), mp 148-150°C; $[\alpha]_D$ -124°; λ_{max} 255 nm (ε 14,000), as an isolable main product (40%). A modification of the Collins oxidation[10] of **8** and **9** (CrO_3 and C_5H_5N in CH_2Cl_2, room temp, 15 min) gave the respective 20-ketones (**11** and **12**), mp 160-162°C and 176-178°C; $[\alpha]_D$ -198° and -12°, in quantitative yields, which were assigned 17αH and 17βH configurations, respectively, on the basis of the ORD and NMR data: **11**, a = -225°;[11] δ 3.33 (1H, br W_H = 11 Hz, H at C_{17}): **12**, a = +370°;[11] δ 3.35 (1H, br W_H = 20 Hz, H at C_{17}). It is to be noted that the 20-ketone (**12**) on hydride reduction [$LiAlH(t\text{-}C_4H_9O)_3$ in THF, room temp, 23 h] formed the 20-alcohol (**10**) as a sole product in a 23% yield (**12** recovered, 61%). These α,β-unsaturated ketones (**9** and **10**) were again submitted to the Birch reduction to give their C/D trans-fused saturated ketones (**13** and **14**), mp 194-196°C and 182-184°C; $[\alpha]_D$ -106° and -102°; ORD, a = -145° and -145°;[9] NMR, δ 1.04 and 1.02 (each 3H, s, 19-CH_3),[12] in 76 and 68% yields, respectively. Oxidation of the former (**13**) under the aforementioned conditions[10] afforded a 20-ketone (**15**), mp 184-186°C; $[\alpha]_D$ -108°; ORD, a = -86°,[11] which was also obtained by the same treatment of the latter (**14**). These data indicate that two pairs of the 20-alcohols (**9**, **10**, and **13**, **14**) possess the same configuration at C_{17} (17βH) and are diastereoisomers differing only at C_{20}, respectively.

Treatment of the 20-alcohols (**13** and **14**) with "(S)-(+)-α-methoxy-α-trifluoromethyl-α-phenylacetyl chloride" [(+)-MTPA-Cl] (in C_5H_5N, room temp, 6 h)[13] gave the corresponding MTPA esters (**13a** and **14a**), mp 176-178°C and 138-140°C; $[\alpha]_D$ -67° and -87°; MS, m/e each 590 (M^+); NMR, δ 3.56 and 3.45 (each 3H, s, OCH_3), in 93 and 93% yields. Addition of the shift reagent $Eu(fod)_3$ into the chloroform-d solutions of **13a** and **14a** caused down-field shift of the methoxy protons in the respective NMR spectra, and the LIS values for the protons were larger for ester **14a** than for that **13a**, as shown in Fig. 1. The result indicates that one (**13**) of the 20-alcohols has (S)-configuration at C_{20}, while another (**14**) (R)-configuration.[5] This assignment not only confirms the tentatively assigned configurations for epoxides **4** and **5**, but also indicates all other compounds (**6** ∿ **15**) to be represented correctly by the respective formulas. Hydroboration of the relevant compound (**3**) followed by oxidation resulted in hydration at the 17,20-double bond to yield the (20S)-alcohol (**9**) as a sole isolable product (25%) (**3** recovered, 50%). Since hydroboration usually proceeds in a cis-addition manner,[14] all the results lead to conclusion that the 17,20-double bond in question in **3** and hence in **1** must possess (E)-configuration.


3
m-Cl $C_6H_4CO_3H$
4
20
17
CH_3
5
Li, NH_3
Li, NH_3
6
7
K_2CO_3
K_2CO_3
8
9
10
Li, NH_3
$CrO_3 \cdot 2Py$
$CrO_3 \cdot 2Py$
$LiAlH(OBu^t)_3$
Li, NH_3
11
12
14 R= H
14a R= $C(=O)-C(C_6H_5)(OCH_3)CF_3$
$CrO_3 \cdot 2Py$
3
B_2H_6
13 R= H
13a R= $C(=O)-C(C_6H_5)(OCH_3)CF_3$
$CrO_3 \cdot 2Py$
15
S_B

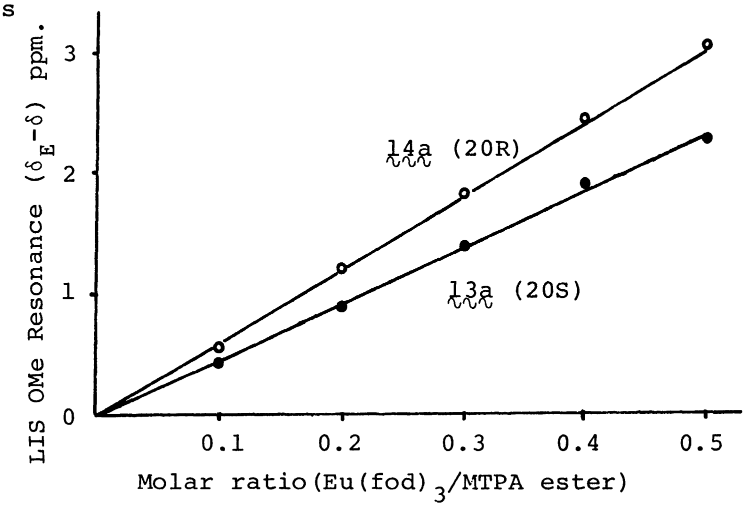


Fig. 1. Representative plots of lanthanide induced shift (LIS) of the methoxy proton resonance *vs*. molar ratio of Eu(fod)$_3$ for the diastereomeric MTPA esters (**13a** and **14a**): "δ_E", the chemical shift in ppm for the OMe signal in the presence of a specified molar ratio of Eu(fod)$_3$ in $CDCl_3$ solutions: "δ", the normal chemical shift.

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