17. Opening of the Macrocyclic Ring in 5,10:8,9-Disecosteroids (= Steroklastanes)

by **Ljubiuka Lorenc**[a][b], **Lidija Bondarenko-Gheorghiu**[b], **Vladimir Pavlović**[a][b], **Hermann Fuhrer**[c], **Jaroslav Kalvoda**[d]*, and **Mihailo Lj. Mihailović**[a][b]*

[a]) Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 550, YU-11001 Belgrade
[b]) Institute of Chemistry, Technology and Metallurgy, YU-11001 Belgrade
[c]) Central Function Research, *Ciba-Geigy Ltd.*, CH-4002 Basel
[d]) Research Laboratories, Pharmaceuticals Division, *Ciba-Geigy Ltd.*, CH-4002 Basel

Dedicated to Prof. *Vladimir Prelog* on the occasion of his 85th birthday

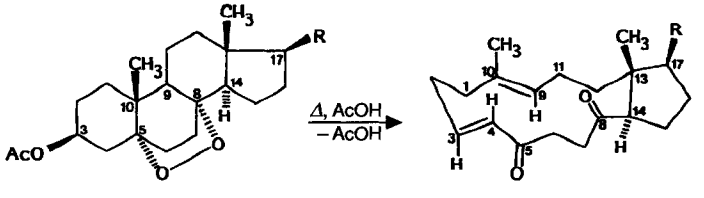
(29.X.91)

Catalytic hydrogenation of the Δ^3-unsaturated (9*R*,10*R*)- and (9*S*,10*S*)-epoxyenol lactones **3a,b** and **4a,b**, respectively, affords, in addition to the expected saturated epoxylactones **5a,b** and **7a,b**, also open-chain products, *i.e.* the diastereoisomeric (9*R*,10*R*)- and (9*S*,10*S*)-9,10-epoxy-8-oxo-4,5-secosteroklastan-5-oic acids **6a,b** and **8a,b**. Alkaline hydrolysis of the lactone ring of compounds **5** and **7** and subsequent acetylation of the corresponding hydroxy derivatives give as the major products the open-chain, diastereoisomeric (9*R*,10*R*)- and (9*S*,10*S*)-4-acetoxy-9,10-epoxy-methyl esters **9a,b** and **11a,b**, respectively, and, but only in the androstane series, the tetrahydropyran derivatives **10a** and **12a**, as the minor components.

Introduction. – As previously reported [1] [2], thermal decomposition of steroidal 5α,8α-peroxides of type **1a,b** in boiling AcOH resulted in a cycloreversion-type reaction [3], accompanied by AcOH elimination, to produce the corresponding 5,10:8,9-diseco compounds **2a,b**, containing a 14-membered ring (fused to ring D) instead of the 'normal' steroid A-B-C ring skeleton (*Scheme 1*)[1]).

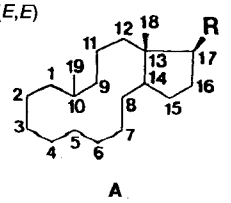
It was suggested that by way of this bis-fragmentation as the key step, it could be possible to correlate steroids with some other naturally occurring products containing a 14-membered ring (*e.g.* cembrenoids, some derivatives of which, isolated from marine organisms, possess significant cytotoxic and antineoplastic activity) or, upon scission of

Scheme 1



1a R = OAc
b R = C_8H_{17}

2a R = AcO (*E,E*)
b R = C_8H_{17} (*E,E*)



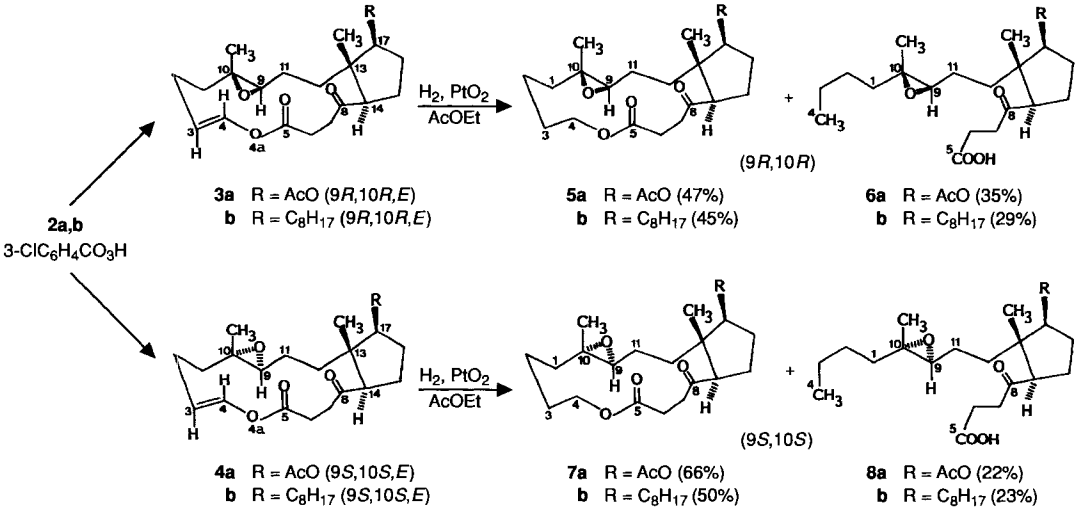
A

[1]) Compounds of the structural type **A**, *i.e.* 5,10:8,9-disecosteroids, were named 'steroklastanes' [2].

the appropriate bond in the 14-membered ring, with prostaglandin-like compounds containing a substituted 5-membered ring[2]). In the present paper, we wish to describe reactions of some 5,10:8,9-disecosteroidal derivatives which resulted in opening of the macrocyclic ring of these bicyclic systems.

Results and Discussion. – The substrates used in the present study, *i.e.* the (9*R*,10*R*)- and (9*S*,10*S*)-epoxyenol lactones **3a,b** and **4a,b**, respectively, were obtained by treatment of the diseco-diketones **2a,b** with an excess of 3-chloroperbenzoic acid [1] [2] which resulted in a non-stereospecific epoxidation of the C(9)=C(10) bond of **2a,b**, followed by *Baeyer-Villiger* oxidation (*Scheme 2*)[3]). The aim was to open these macrocyclic rings by

Scheme 2



alkaline hydrolysis which was expected to proceed readily. However, since hydrolysis of enol lactones of type **3** and **4** would produce formyl-carboxylic acids, which, under alkaline conditions, could undergo undesired reactions, these compounds were first subjected to catalytic hydrogenation.

Hydrogenation of the epoxyenol lactones **3a,b** and **4a,b** over PtO_2 in AcOEt at room temperature and atmospheric pressure afforded, in addition to the expected saturated

---

[2]) Actually, since the configuration at C(13) and C(14) in the usual 14α-steroid molecules is opposite to that at the corresponding prostaglandin C-atoms containing the side chains, such ring-D-substituted steroidal analogues would be stereoisomeric to the naturally occurring prostaglandin systems. In spite of this fact, these synthetic analogues of prostaglandins could be of pharmacological interest.

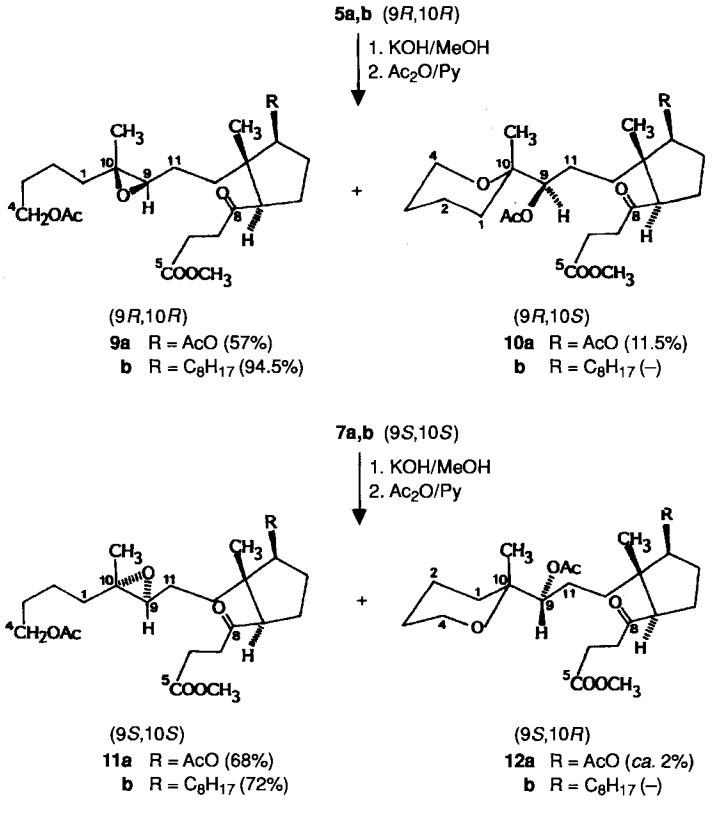
[3]) The X-ray determination of the molecular structure (including the solid-state conformation) of (9*S*,10*S*,*E*)-epoxyenol lactone **4a** was described previously [2], while the molecular structure of the (9*R*,10*R*,*E*)-diastereoisomer **3a** was established (also by X-ray diffraction) only recently [4].

epoxylactones **5a,b** and **7a,b**, respectively (isolated in 45–66% yield), also open-chain products, *i.e.* the diastereoisomeric (9*R*,10*R*)- and (9*S*,10*S*)-9,10-epoxy-8-oxo-4,5-seco-steroklastan-5-oic acids **6a,b** and **8a,b** (22–35% yield; *Scheme 2*). The latter compounds arise from hydrogenolysis of the C(4)–O bond and saturation of the vinyl group in the substrate molecules. In that way, compounds with prostaglandin-like structures were already formed at this stage.

To get more insight into the way of hydrogenolytic opening of the lactone ring, the saturated epoxy-lactones **5a**, **b** and **7a**, **b** were resubmitted to the conditions of catalytic hydrogenation. Since their recovery was 100%, hydrogenolysis of the C(4)–O bond in the epoxyenol lactones **3a**, **b** and **4a**, **b** must precede saturation of the olefinic double bond, thus implying that hydrogenation and hydrogenolysis in these compounds are competing processes[4]).

Compounds **5**–**8** were fully characterized by analytical and spectral data (^{1}H-NMR, ^{13}C-NMR, and IR). In their ^{1}H-NMR spectra, the original olefinic protons are missing. Instead, **5a**, **b** and **7a**, **b** show *m*'s (for 2 H) between 3.90 and 4.50 ppm which can be assigned to H_α–C(4) and H_β–C(4), while in **6a**, **b** and **8a**, **b**, a *t* (for 3 H) appears at

Scheme 3



[4]) Hydrogenolysis of an ester to give an acid (–COOR→–COOH) is possible only when the R–O bond is weakened due to the presence of some activating group, as in the case of R = benzyl, vinyl, or allyl [5].

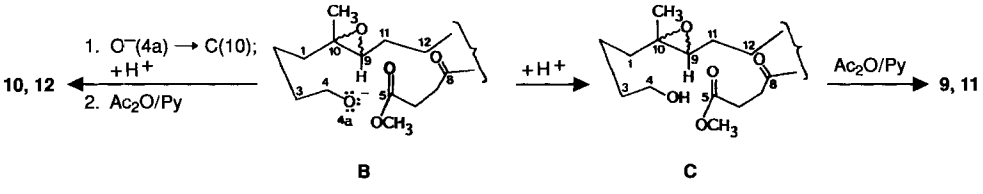
ca. 0.90 ppm, which corresponds to a CH_3 group (CH_3(4)) next to a CH_2 group. The *s* at *ca.* 1.25 ppm (for CH_3(19)) and the *m* at *ca.* 2.70 ppm (for H–C(9)), which are also present in the ^{1}H-NMR spectra of the starting compounds **3** and **4**, indicate that the 9,10-epoxide ring survived hydrogenation and hydrogenolysis to compounds **5**–**8**. The carboxylic-acid group in **6a, b** and **8a, b** was confirmed by the ^{13}C-NMR signal between 176.5 and 178.1 ppm and the broad IR band between 3500 and 2500 cm^{-1}. For additional spectral characteristics of **5**–**8**, see *Exper. Part.*

Hydrolysis of the lactone ring in the saturated epoxy-lactones **5a, b** and **7a, b** was carried out with a 5% KOH/MeOH solution at room temperature for 30 min. The resulting crude mixtures were acetylated and separated by column chromatography (SiO_2). The predominant products (57–94% yield) were the open-chain, diastereoisomeric (9*R*,10*R*)- and (9*S*,10*S*)-4-acetoxy-9,10-epoxy-methyl esters **9a, b** and **11a, b**, respectively. In addition, in the androstane series **a**, the corresponding tetrahydropyran derivatives **10a** and **12a** were also isolated, albeit in low yield (11 and 2%, resp.).

The structures of these products were deduced from the analytical and spectral data. Thus, **9**–**12** contain a COOMe group (^{1}H-NMR: *s* at *ca.* 3.70 ppm) and a newly introduced AcO function (^{1}H-NMR: *s* at *ca.* 2.05 ppm). In **9** and **11**, which still contain the oxirane ring present also in the starting lactones **5** and 7 (^{1}H-NMR: *m* at *ca.* 2.70 ppm) (H–C(9)), this AcO function is attached to a CH_2 group (^{1}H-NMR: *t* at *ca.* 4.10 ppm), whereas in **10a** and **12a**, the proton of the oxirane ring is missing. Instead appears a *dd* at *ca.* 5.00 ppm (characteristic for a *H*–C–OAc next to a CH_2) and a *m* at *ca.* 3.60–3.65 ppm (indicative of a tetrahydropyran ring). The other physical data, consistent with the proposed structures, are given in the *Exper. Part.*

The formation of compounds **9**–**12** can be rationalized by assuming initial attack of MeOH (or MeO^-) at the lactone carbonyl C-atom (C(5)) of the saturated epoxy-lactones **5** and **7**, followed by opening of the lactone ring to give *via* the open-chain primary alkoxide anions **B** the corresponding alcohols **C** which are acetylated to **9** and **11**, respectively.

Scheme 4



By-products **10a** and **12a** containing a six-membered ether ring can also be formed *via* **B**, but with participation of the 9,10-epoxide ring[5]): internal backside attack by the alkoxide ion in **B** at C(10) results in the formation of a tetrahydropyran ring and a secondary OH group at C(9), which is subsequently acetylated to **10a** and **12a**. The reaction is stereospecific, *i.e.* (9*R*,10*R*)-diastereoisomer **5a** and (9*S*,10*S*)-diastereoisomer **7a** yield the tetrahydropyran derivatives **10a** and **12a** with the (9*R*,10*S*)- and (9*S*,10*R*)-configuration, respectively.

The results presented above and in our previous publications [1] [2] show that it is possible to correlate chemically steroids with prostaglandin-like derivatives and that such transformations may be of importance for preparing interesting and useful structures from readily available natural products.

---

[5]) Intramolecular participation of the oxirane ring was also observed in some reactions of the macrocyclic rings contained in 9,10-epoxy-ansa-secosteroids [6].

The authors from Yugoslavia are grateful to the *Serbian Academy of Sciences and Arts* and to the *Serbian Republic Research Fund* for financial support.

Experimenal Part

1. *General*[6]). Evaporation of solvents was carried out under reduced pressure. Prep. column chromatography: silica gel 0.063–0.200 mm. TLC: control of reactions and separation of products on silica gel *G* (*Stahl*) with benzene/AcOEt 9:1 or 7:3, detection with 50% aq. H_2SO_4 soln. M.p.: uncorrected. IR spectra: *Perkin-Elmer-337* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR spectra: *Brucker AM-360* (^1H at 360 MHz, ^{13}C at 90.55 MHz); $CDCl_3$ soln. at r.t., TMS as internal standard; chemical shifts in ppm as δ values, J in Hz.

2. *Hydrogenation of (9R,10R,E)-9,10-Epoxy-5,8-dioxo-4a-oxa-4a-homo-5,10:8,9-disecoandrost-3-en-17β-yl Acetate* (= *(9R,10R,E)-9,10-Epoxy-5,8-dioxo-4a-oxa-4a-homoandroklast-3-en-17β-yl Acetate*; **3a**). A soln. of **3a** (513 mg) in AcOEt (70 ml) was hydrogenated at r.t./1 atm over prereduced PtO_2 (100 mg) with stirring, until no more H_2 was absorbed (*ca.* 1 h). After removal of the catalyst and solvent, the residue was chromatographed on silica gel (15 g). Elution with benzene/Et_2O 8:2 afforded *(9R,10R)-9,10-epoxy-5,8-dioxo-4a-oxa-4a-homo-5,10:8,9-disecoandrostan-17β-yl acetate* (= *(9R,10R)-9,10-epoxy-5,8-dioxo-4a-oxa-4a-homoandroklastane-17β-yl acetate*; **5a**; 240 mg, 46.5%). Oil. $[\alpha]_D^{20} = -34.1$ ($c = 1.00$, $CHCl_3$). IR (film): 2920*m*, 1725*s*, 1710*s*, 1365*m*, 1238*s*. ^1H-NMR: 1.01 (*s*, $CH_3(18)$); 1.26 (*s*, $CH_3(19)$); 2.06 (*s*, AcO); 2.38–2.88 (*m*, $CH_2(6)$, $CH_2(7)$, H–C(9), H–C(14)); 4.12 (*t*, $J = 6.5$, $CH_2(4)$); 4.82 (*t*, $J = 9$, H–C(17)). ^{13}C-NMR: 209.0 (*s*, C(8)); 172.2 (*s*, C(5)); 170.6 (*s*, CH_3COO); 79.2 (*d*, C(17)); 63.9 (*t*, C(4)); 63.8 (*d*, C(9)); 60.7 (*s*, C(10)); 56.4 (*d*, C(14)); 46.5 (*s*, C(13)); 39.4 (*t*, C(7)); 37.2 (*t*, C(6)); 35.3 (*t*, C(1)); 29.0 (*t*, C(12)); 28.1 (*t*, C(3)); 27.3 (*t*, C(16)); 22.6 (*t*, C(15)); 22.4 (*t*, C(11)); 22.0 (*t*, C(2)); 21.2 (*q*, CH_3COO); 16.7 (*q*, C(19)); 14.7 (*q*, C(18)). Anal. calc. for $C_{21}H_{32}O_6$ (380.487): C 66.29, H 8.48; found: C 66.47, H 8.45.

Elution with Et_2O gave *(9R,10R)-17β-acetoxy-9,10-epoxy-8-oxo-4,5:5,10:8,9-trisecoandrostan-6-oic acid* (= *(9R,10R)-17β-acetoxy-9,10-epoxy-8-oxo-4,5-seconandroklastan-5-oic acid*; **6a**; 179 mg, 34.5%). Oil. $[\alpha]_D^{20} = -24.1$ ($c = 0.97$, $CHCl_3$). IR (film): 3500–2500*w*, 2970*m*, 1740*s*, 1715*s*, 1378*m*, 1250*s*. ^1H-NMR: 0.82 (*s*, $CH_3(18)$); 0.84 (*t*, $J = 8.5$, H–C(4)); 1.18 (*s*, $CH_3(19)$); 1.99 (*s*, AcO); 2.51–2.68 (*m*, $CH_2(6)$, $CH_2(7)$, H–C(14)); 2.67 (*t*, $J = 6.5$, H–C(9)); 4.81 (*t*, $J = 7$, H–C(17)). ^{13}C-NMR: 208.6 (*s*, C(8)); 176.8 (*s*, C(5)); 170.3 (*s*, CH_3COO); 79.2 (*d*, C(17)); 63.1 (*d*, C(9)); 61.0 (*s*, C(10)); 56.0 (*d*, C(14)); 46.6 (*s*, C(13)); 38.1 (*t*, C(6)); 38.0 (*t*, C(7)); 36.0 (*t*, C(1)); 27.7 (*t*, C(12)); 27.2 (*t*, C(16)); 27.0 (*t*, C(2)); 23.4 (*t*, C(11)); 23.1 (*t*, C(3)); 22.4 (*t*, C(15)); 20.7 (*q*, CH_3COO); 16.1 (*q*, C(18)); 14.9 (*q*, C(19)); 13.6 (*q*, C(4)). Anal. calc. for $C_{21}H_{34}O_6$ (382.503): C 65.94, H 8.96; found: C 65.81, H 8.97.

3. *Hydrogenation of (9R,10R,E)-9,10-Epoxy-4a-oxa-4a-homo-5,10:8,9-disecocholest-3-ene-5,8-dione* (= *(9R,10R,E)-9,10-Epoxy-4a-oxa-4a-homocholeklast-3-ene-5,8-dione*; **3b**). As described in *Exper. 2*, **3b** (531 mg) in AcOEt (50 ml) was hydrogenated (PtO_2 (50 mg)) and the product mixture chromatographed (silica gel (15 g), benzene/AcOEt 95:5 and 9:1): *(9R,10R)-9,10-epoxy-4a-oxa-4a-homo-5,10:8,9-disecocholestane-5,8-dione* (= *(9R,10R)-9,10-epoxy-4a-oxa-4a-homocholeklastane-5,8-dione*; **5b**; 239 mg, 44.8%). Oil. $[\alpha]_D^{20} = -16.6$ ($c = 1.35$, $CHCl_3$). IR (film): 2920*s*, 1735*s*, 1710*s*, 1470*m*, 1385*m*, 1255*m*. ^1H-NMR: 0.86 (*s*, $CH_3(18)$); 0.88 (*d*, $CH_3(26)$, $CH_3(27)$); 0.96 (*d*, $CH_3(21)$); 1.35 (*s*, $CH_3(19)$); 2.36–2.92 (*m*, $CH_2(6)$, $CH_2(7)$, H–C(9), H–C(14)); 4.03 (*dt*, $J = 6, 12$, H–C(4)); 4.13 (*dt*, $J = 6, 12$, H–C(4)). ^{13}C-NMR: 209.5 (*s*, C(8)); 171.8 (*s*, C(5)); 63.9 (*d*, C(9)); 63.6 (*t*, C(4)); 60.6 (*s*, C(10)); 57.3 (*d*, C(17)); 49.3 (*d*, C(14)); 47.0 (*s* C(13)); 39.3 (*t*, C(24)); 38.9 (*t*, C(7)); 36.7 (*t*, C(6)); 35.1 (*t*, C(22)); 34.5 (*t*, C(1)); 33.5 (*d*, C(20)); 28.2 (*t*, C(16)); 27.5 (*d*, C(25)); 27.0 (*t*, C(12)); 25.9 (*t*, C(11)); 23.7 (*t*, C(23)); 23.3 (*t*, C(3)); 22.3 (*q*, C(27)); 22.0 (*q*, C(26)); 21.5 (*t*, C(15)); 18.0 (*q*, C(21)); 16.9 (*q*, C(19)); 16.7 (*q*, C(18)). Anal. calc. for $C_{27}H_{46}O_4$ (434.665): C 74.61, H 10.67; found: C 74.52, H 10.65.

Elution with AcOEt afforded *(9R,10R)-9,10-epoxy-8-oxo-4,5:5,10:8,9-trisecocholestan-5-oic acid* (= *(9R,10R)-9,10-epoxy-8-oxo-4,5-secocholeklastan-5-oic acid*; **6b**; 157 mg, 29.3%). Oil. $[\alpha]_D^{20} = -2.2$ ($c = 0.93$, $CHCl_3$). IR (film): 3500–2500*w*, 2920*s*, 1735*m*, 1710*s*, 1470*m*, 1385*m*. ^1H-NMR: 0.82 (*s*, $CH_3(18)$); 0.86 (*d*, $CH_3(26)$, $CH_3(27)$); 0.90 (*t*, $J = 8$, $CH_3(4)$); 0.95 (*d*, $CH_3(21)$); 1.26 (*s*, $CH_3(19)$); 2.55–2.72 (*m*, $CH_2(6)$, $CH_2(7)$, H–C(14)); 2.77 (*t*, $J = 9$, H–C(9)). ^{13}C-NMR: 210.6 (*s*, C(8)); 178.1 (*s*, C(5)); 63.9 (*d*, C(9)); 61.4 (*s*, C(10)); 58.1 (*d*, C(17)); 51.2 (*d*, C(14)); 47.9 (*s*, C(13)); 39.6 (*t*, C(24)); 38.7 (*t*, C(7)); 38.6 (*t*, C(6)); 35.7 (*t*, C(22)); 35.6 (*t*, C(1));

---

[6]) IR measurements and elemental microanalyses were carried out in the Laboratories for Instrumental Analysis of the Faculty of Chemistry, Belgrade. NMR measurements were performed at *Ciba-Geigy Ltd.*, Basel, Switzerland.

33.5 (*d*, C(20)); 28.1 (*d*, C(25)); 27.9 (*t*, C(16)); 27.5 (*t*, C(12)); 26.6 (*t*, C(11)); 24.9 (*t*, C(2)); 24.6 (*t*, C(15)); 23.6 (*t*, C(23)); 22.9 (*t*, C(3)); 22.9 (*q*, C(27)); 22.7 (*q*, C(26)); 19.6 (*q*, C(21)); 17.5 (*q*, C(19)); 16.7 (*q*, C(18)); 14.2 (*q*, C(4)). Anal. calc. for $C_{27}H_{48}O_4$ (436.681): C 74.26, H 11.08; found: C 74.08, H 10.99.

4. *Hydrogenation of (9S,10S,E)-Isomer* **4a**. As described in *Exper. 2*, **4a** (347 mg; see **3a**) was hydrogenated and the product mixture chromatographed (silica gel (10 g), benzene/Et_2O 8:2): (9*S*,10*S*)-isomer **7a** (230 mg, 65.9%; see **5a**). M.p. 131–132°. $[\alpha]_D^{20} = +41.8$ ($c = 1.00$, $CHCl_3$). IR (KBr): 2935*m*, 1720*s*, 1710*s*, 1695*s*, 1365*m*, 1250*s*. ^{1}H-NMR: 0.97 (*s*, CH_3(19)); 2.04 (*s*, AcO); 2.34 (*m*, H_α–C(6)); 2.51 (*m*, H_β–C(7)); 2.58 (*dd*, $J = 11, 4$, H–C(9)); 2.74 (*t*, $J = 9.5$, H–C(14)); 2.82 (*m*, H_α–C(7)); 2.98 (*m*, H_β–C(6)); 3.94 (*dt*, $J = 11, 5.5$, H–C(4)); 4.36 (*td*, $J = 11, 4$, H–C(4)); 4.86 (*t*, $J = 9.5$, H–C(17)). ^{13}C-NMR: 208.9 (*s*, C(8)); 172.6 (*s*, C(5)); 170.7 (*s*, CH_3COO); 77.9 (*d*, C(17)); 63.0 (*d*, C(9)); 62.7 (*t*, C(4)); 61.0 (*s*, C(10)); 55.3 (*d*, C(14)); 45.7 (*s*, C(13)); 38.4 (*t*, C(7)); 36.9 (*t*, C(6)); 34.1 (*t*, C(1)); 28.5 (*t*, C(12)); 28.2 (*t*, C(16)); 26.5 (*t*, C(3)); 23.1 (*t*, C(15)); 22.6 (*t*, C(11)); 21.1 (*q*, CH_3COO); 21.0 (*t*, C(2)); 16.7 (*q*, C(19)); 14.5 (*q*, C(18)). Anal. calc. for $C_{21}H_{32}O_6$ (380.487): C 66.29, H 8.48; found: C 66.47, H 8.45.

Elution with Et_2O gave (9*S*,10*S*)-isomer **8a** (78 mg, 22.2%; see **6a**). Oil. $[\alpha]_D^{20} = -49.8$ ($c = 0.99$, $CHCl_3$). IR (film): 3500–2500*w*, 2960*m*, 2935*m*, 1735*s*, 1710*s*, 1375*m*, 1245*s*. ^{1}H-NMR: 0.81 (*s*, CH_3(18)); 0.83 (*t*, $J = 8$, CH_3(4)); 1.18 (*s*, CH_3(19)); 1.98 (*s*, AcO); 2.53–2.67 (*m*, CH_2(6), CH_2(7), H–C(14)); 2.70 (*t*, $J = 9$, H–C(9)); 4.83 (*t*, $J = 7$, H–C(17)). ^{13}C-NMR: 208.5 (*s*, C(8)); 176.5 (*s*, C(5)); 170.2 (*s*, CH_3COO); 78.7 (*d*, C(17)); 63.1 (*d*, C(9)); 60.9 (*s*, C(10)); 55.4 (*d*, C(14)); 46.5 (*s*, C(13)); 38.1 (*t*, C(6)); 38.0 (*t*, C(7)); 35.6 (*t*, C(1)); 27.4 (*t*, C(12)); 27.2 (*t*, C(2)); 27.0 (*t*, C(16)); 23.2 (*t*, C(3)); 22.6 (*t*, C(1)); 22.4 (*t*, C(15)); 20.7 (*q*, CH_3COO); 16.1 (*q*, C(18)); 16.1 (*q*, C(18)); 15.2 (*q*, C(19)); 13.6 (*q*, C(4)). Anal. calc. for $C_{21}H_{34}O_6$ (382.503): C 65.94, H 8.96; found: C 65.74, H 9.13.

5. *Hydrogenation of (9S,10S,E)-Isomer* **4b**. As described in *Exper. 2*, **4b** (909 mg; see **3b**) in AcOEt (100 ml) was hydrogenated (PtO_2 (100 mg)) and the product mixture chromatographed (silica gel (35 g), benzene/AcOEt 97:3): (9*S*,10*S*)-isomer **7b** (460 mg, 50.4%; see **5b**). M.p. 78°. $[\alpha]_D^{20} = +49.2$ ($c = 1.00$, $CHCl_3$). IR (KBr): 2920*s*, 1725*s*, 1700*s*, 1460*m*, 1370*m*, 1210*m*, 1172*s*, 1115*m*. ^{1}H-NMR: 0.87 (*s*, CH_3(18)); 0.88 (*d*, CH_3(26), CH_3(27)); 0.91 (*d*, CH_3(21)); 1.25 (*s*, CH_3(19)); 2.30 (*m*, H_α–C(6)); 2.46 (*m*, H_β–C(7)); 2.69 (*dd*, $J = 9, 3.5$, H–C(9)); 2.71 (*t*, $J = 8$, H–C(14)); 2.79 (*m*, H_α–C(7)); 2.96 (*m*, H_β–C(6)); 3.89 (*dt*, $J = 10, 6$, H–C(4)); 4.49 (*td*, $J = 9.5, 3$, H–C(4)). ^{13}C-NMR: 209.8 (*s*, C(8)); 172.5 (*s*, C(5)); 62.6 (*d*, C(9)); 61.4 (*t*, C(4)); 60.7 (*s*, C(10)); 57.4 (*d*, C(17)); 48.9 (*d*, C(14)); 45.6 (*s*, C(13)); 38.9 (*t*, C(24)); 37.5 (*t*, C(7)); 36.2 (*t*, C(6)); 35.1 (*t*, C(22)); 32.8 (*d*, C(20)); 32.3 (*t*, C(1)); 28.1 (*t*, (16)); 27.7 (*t*, C(12)); 27.5 (*d*, C(25)); 25.2 (*t*, C(11)); 23.7 (*t*, C(23)); 23.3 (*t*, C(3)); 22.2 (*q*, C(26)); 22.2 (*q*, C(27)); 22.0 (*t*, C(15)); 20.1 (*t*, C(2)); 18.5 (*q*, C(21)); 16.3 (*q*, C(18)); 15.6 (*q*, C(19)). Anal. calc. for $C_{27}H_{46}O_4$ (434.665): C 74.61, H 10.67; found: C 74.76, H 10.48.

Elution with AcOEt afforded (9*S*,10*S*)-isomer **8b** (213 mg, 23.2%; see **6b**). Oil. $[\alpha]_D^{20} = -16.3$ ($c = 0.965$, $CHCl_3$). IR (film): 2500–3500*w*, 2960*s*, 1738*m*, 1710*s*, 1470*m*, 1385*m*. ^{1}H-NMR: 0.81 (*s*, CH_3(18)); 0.87 (*d*, CH_3(26), CH_3(27)); 0.90 (*t*, $J = 6.5$, CH_3(4)); 0.94 (*d*, CH_3(21)); 1.27 (*s*, CH_3(19)); 2.57–2.73 (*m*, CH_2(6), CH_2(7), H–C(14)); 2.85 (*t*, $J = 8.5$, H–C(9)). ^{13}C-NMR: 210.7 (*s*, C(8)); 177.9 (*s*, C(5)); 63.9 (*d*, C(9)); 61.6 (*s*, C(10)); 57.9 (*d*, C(17)); 51.1 (*d*, C(14)); 47.9 (*s*, C(13)); 39.6 (*t*, C(24)); 39.0 (*t*, C(7)); 38.6 (*t*, C(6)); 35.7 (*t*, C(22)); 35.6 (*t*, C(1)); 33.6 (*d*, C(20)); 28.1 (*d*, C(25)); 27.9 (*t*, C(16)); 27.6 (*t*, C(12)); 26.7 (*t*, C(11)); 24.8 (*t*, C(2)); 24.6 (*t*, C(15)); 23.6 (*t*, C(23)); 22.9 (*t*, C(3)); 22.9 (*q*, C(27)); 22.7 (*q*, C(26)); 19.5 (*q*, C(21)); 17.8 (*q*, C(19)); 16.8 (*q*, C(18)); 14.2 (*q*, C(4)). Anal. calc. for $C_{27}H_{48}O_4$ (436.681): C 74.26, H 11.08; found: C 74.08, H 10.89.

6. *Alkaline Hydrolysis of* **5a**. To a soln. of **5a** (122 mg) in MeOH (10 ml), 5% KOH/MeOH (0.5 ml) was added. The mixture was left at r.t. for 30 min, neutralized with AcOH, and evaporated to give an oil which was acetylated with Ac_2O (5 ml) in pyridine (5 ml) at r.t. overnight. After treatment with MeOH to destroy excess of Ac_2O, the mixture was evaporated and the oily residue chromatographed on silica gel (10 g). Benzene/Et_2O 9:1 eluted *(methyl 9R,10S)-9,10-diacetoxy-4,10-epoxy-8-oxo-4,5:5,10:8,9-trisecoandrostan-5-oate* (= *methyl (9R,10S)-9,17-diacetoxy-4,10-epoxy-8-oxo-4,5-secoandroklastan-5-oate;* **10a**; 17 mg, 11.7%). Oil. $[\alpha]_D^{20} = -21.5$ ($c = 0.97$, $CHCl_3$). IR (film): 2920*m*, 1725*s*, 1705*s*, 1430*m*, 1360*m*, 1235*s*, 1030*m*. ^{1}H-NMR: 0.87 (*s*, CH_3(18)); 1.15 (*s*, CH_3(19)); 2.04, 2.08 (2*s*, AcO–C(9), AcO–C(17)); 2.56, 2.72 (2*m*, CH_2(6), CH_2(7), H–C(14)); 3.62 (*m*, CH_2(4)); 3.67 (*s*, CH_3OOC(5)); 4.86 (*t*, $J = 7.5$, H–C(17)); 4.99 (*dd*, $J = 10, 2$, H–C(9)). ^{13}C-NMR: 209.1 (*s*, C(8)); 173.1 (*s*, C(5)); 171.0 (*s*, CH_3COO); 170.6 (*s*, CH_3COO); 79.5 (*d*, C(9)); 77.2 (*d*, C(17)); 74.1 (*s*, C(10)); 61.1 (*t*, C(4)); 56.1 (*d*, C(14)); 51.7 (*q*, CH_3OOC); 47.1 (*s*, C(13)); 38.8 (*t*, C(7)); 36.4 (*t*, C(6)); 32.0 (*t*, C(1)); 28.0 (*t*, C(16)); 27.7 (*t*, C(3)); 25.6 (*t*, C(12)); 23.2 (*t*, C(11)); 23.1 (*t*, C(15)); 21.1 (*q*, CH_3COO); 21.0 (*q*, CH_3COO); 18.8 (*t*, C(2)); 18.3 (*q*, C(19)); 15.5 (*q*, C(18)). Anal. calc. for $C_{24}H_{38}O_8$ (454.568): C 63.41, H 8.43; found: C 63.29, H 8.43.

Elution with benzene/Et_2O 85:15 afforded *methyl (9R,10R)-4,17β-diacetoxy-9,10-epoxy-8-oxo-4,5:5,10:8,9-trisecoandrostan-5-oate* (= *methyl (9R,10R)-4,17β-diacetoxy-9,10-epoxy-8-oxo-4,5-secoandroklastan-5-oate*; **9a**; 83 mg, 56.9%). Oil. $[\alpha]_D^{20} = -9.8$ ($c = 1.00$, $CHCl_3$). IR (film): 2920*m*, 1725*s*, 1705*s*, 1430*m*, 1360*m*, 1235*s*, 1030*m*. ^{1}H-NMR: 0.89 (*s*, CH_3(18)); 1.25 (*s*, CH_3(19)); 2.04, 2.05 (2*s*, AcO–C(4), AcO–C(17)); 2.58, 2.71 (2*m*, CH_2(6),

CH_2(7), H–C(14)); 2.73 (*t*, *J* = 8, H–C(9)); 3.67 (*s*, CH_3OOC(5)); 4.05 (*t*, *J* = 7, CH_2(4)); 4.88 (*t*, *J* = 8, H–C(17)). ^{13}C-NMR: 209.0 (*s*, C(8)); 173.1 (*s*, C(5)); 171.2 (*s*, CH_3COO); 170.6 (*s*, CH_3COO); 79.5 (*d*, C(17)); 64.3 (*t*, C(4)); 63.3 (*d*, C(9)); 60.8 (*s*, C(10)); 56.3 (*d*, C(14)); 51.8 (*q*, CH_3OOC); 46.9 (*s*, C(13)); 38.7 (*t*, C(7)); 38.2 (*t*, C(6)); 36.4 (*t*, C(1)); 29.7 (*t*, C(12)); 28.6 (*t*, C(2)); 27.7 (*t*, C(16)); 23.8 (*t*, C(11)); 23.4 (*t*, C(15)); 21.6 (*q*, CH_3COO); 21.1 (*q*, CH_3COO); 21.0 (*t*, C(3)); 16.5 (*q*, C(19)); 15.4 (*q*, C(18)). Anal. calc. for $C_{24}H_{38}O_8$: C 63.41, H 8.43; found: C 63.22, H 8.42.

7. *Alkaline Hydrolysis of* **5b**. As described in *Exper. 6*, **5b** (280 mg) in MeOH (20 ml) and 5% KOH/MeOH (1 ml) gave after acetylation (Ac_2O/pyridine 1:1 (10 ml)) and chromatography (short column of silica gel (2 g), benzene/Et_2O 95:5), *methyl (9R,10R)-4-acetoxy-9,10-epoxy-8-oxo-4,5:5,10:8,9-trisecocholestan-5-oate* (= *methyl (9R,10R)-4-acetoxy-9,10-epoxy-8-oxo-4,5-secocholeklastan-5-oate*; **9b**; 310 mg, 94.6%). Oil. $[\alpha]_D^{20} = +1.3$ (*c* = 1.00, $CHCl_3$). IR (film): 2920*s*, 1740*s*, 1710*s*, 1465*m*, 1438*m*, 1385*m*, 1365*m*, 1240*s*. ^{1}H-NMR: 0.83 (*s*, CH_3(18)); 0.86 (*d*, CH_3(26), CH_3(27)); 0.96 (*d*, CH_3(21)); 1.28 (*s*, CH_3(19)); 2.06 (*s*, AcO–C(4)); 2.55 (2*m*, CH_2(6), CH_2(7), H–C(14)); 2.77 (*t*, *J* = 9.6, H–C(9)); 3.68 (*s*, CH_3OOC(5)); 4.07 (*t*, *J* = 6.5, CH_2(4)). ^{13}C-NMR: 210.0 (*s*, C(8)); 172.7 (*s*, C(5)); 170.6 (*s*, CH_3COO); 63.7 (*t*, C(4)); 63.0 (*d*, C(9)); 60.2 (*s*, C(10)); 57.4 (*d*, C(17)); 51.1 (*q*, CH_3OOC); 50.4 (*d*, C(14)); 47.2 (*s*, C(13)); 38.9 (*t*, C(24)); 38.2 (*t*, C(7)); 37.7 (*t*, C(6)); 35.0 (*t*, C(22)); 35.0 (*t*, C(1)); 32.9 (*d*, C(20)); 28.1 (*t*, C(16)); 27.4 (*d*, C(25)); 27.1 (*t*, C(12)); 25.9 (*t*, C(11)); 24.2 (*t*, C(2)); 23.9 (*t*, C(3)); 22.8 (*t*, C(23)); 22.2 (*q*, C(27)); 22.0 (*q*, C(26)); 21.1 (*t*, C(15)); 20.4 (*q*, CH_3COO); 18.9 (*q*, C(21)); 16.8 (*q*, C(18)); 16.0 (*q*, C(18)). Anal. calc. for $C_{30}H_{52}O_6$ (508.746): C 70.83, H 10.30; found: C 70.80, H 10.04.

8. *Alkaline Hydrolysis of* **7a**. As described in *Exper. 6*, **7a** (147 mg) in MeOH (10 ml) and 5% KOH/MeOH (0.5 ml) gave after acetylation (Ac_2O/pyridine 1:1 (10 ml)) and chromatography (silica gel (10 g), benzene/Et_2O 85:15), (9*S*,10*R*)-isomer **12a** (3 mg, 1.7%; see **10a**). Oil. IR (film): 2940*m*, 1735*s*, 1710*s*, 1438*m*, 1372*m*, 1240*s*, 1040*m*. ^{1}H-NMR: 0.85 (*s*, CH_3(18)); 1.15 (*s*, CH_3(19)); 2.04, 2.08 (2*s*, AcO–C(9), AcO–C(17)); *ca.* 2.70 (*m*, CH_2(6), CH_2(7), H–C(14)); 3.65 (*m*, CH_2(4)); 3.70 (*s*, CH_3OOC(5)); 4.85 (*t*, *J* = 7, H–C(17)); 5.00 (*dd*, *J* = 10, 4, H–C(9)).

Benzene/Et_2O 4:1 eluted (9*S*,10*S*)-isomer **11a** (120 mg, 68.3%; see **9a**). Oil. $[\alpha]_D^{20} = -34.9$ (*c* = 0.92, $CHCl_3$). IR (film): 2940*m*, 1780*w*, 1735*s*, 1710*s*, 1438*m*, 1372*m*, 1240*s*, 1040*m*. ^{1}H-NMR: 0.88 (*s*, CH_3(18)); 1.25 (*s*, CH_3(19)); 2.04, 2.06 (2*s*, AcO–C(4), AcO–C(17)); 2.58, 2.73 (2*m*, CH_2(6), CH_2(7), H–C(9), H–C(14)); 3.68 (*s*, CH_3OOC(5)); 4.06 (*t*, *J* = 7, CH_2(4)); 4.90 (*t*, *J* = 8, H–C(17)). ^{13}C-NMR: 208.9 (*s*, C(8)); 173.1 (*s*, C(5)); 171.2 (*s*, CH_3COO); 170.6 (*s*, CH_3COO); 79.1 (*d*, C(17)); 64.3 (*t*, C(4)); 63.3 (*d*, C(9)); 60.8 (*s*, C(10)); 55.8 (*d*, C(14)); 51.8 (*q*, CH_3OOC); 46.8 (*s*, C(13)); 38.7 (*t*, C(7)); 38.2 (*t*, C(6)); 35.9 (*t*, C(1)); 28.6 (*t*, C(12)); 27.8 (*t*, C(16)); 27.6 (*t*, C(2)); 23.6 (*t*, C(11)); 23.1 (*t*, C(15)); 21.6 (*t*, C(3)); 21.1 (*q*, CH_3COO); 21.1 (*q*, CH_3COO); 16.5 (*q*, C(19)); 15.6 (*q*, C(18)). Anal. calc. for $C_{24}H_{38}O_8$ (454.568): C 63.41, H 8.43; found: C 63.68, H 8.63.

9. *Alkaline Hydrolysis of* **7b**. As described in *Exper. 6*, **7b** (300 mg) in MeOH (20 ml) and 5% KOH/MeOH (1 ml) gave after acetylation (Ac_2O/pyridine 1:1 (10 ml)) and chromatography (silica gel (10 g), benzene/Et_2O 85:15), (9*S*,10*S*)-isomer **11b** (252 mg, 71.8%; see **9b**). Oil. $[\alpha]_D^{20} = -19.1$ (*c* = 1.05, $CHCl_3$). IR (film): 2920*s*, 1740*s*, 1710*s*, 1470*m*, 1435*m*, 1385*m*, 1365*m*, 1240*s*. ^{1}H-NMR: 0.82 (*s*, CH_3(18)); 0.87 (*d*, CH_3(26), CH_3(27)); 0.94 (*d*, CH_3(21)); 1.28 (*s*, CH_3(19)); 2.06 (*s*, AcO–C(4)); 2.56, 2.72 (2*m*, CH_2(6), CH_2(7), H–C(14)); 2.86 (*t*, *J* = 8, H–C(9)); 3.68 (*s*, CH_3OOC(5)); 4.06 (*t*, *J* = 6, CH_2(4)). ^{13}C-NMR: 210.0 (*s*, C(8)); 172.7 (*s*, C(5)); 170.6 (*s*, CH_3COO); 63.7 (*t*, C(4)); 63.0 (*d*, C(9)); 60.3 (*s*, C(10)); 57.2 (*d*, C(17)); 51.1 (*q*, CH_3OOC); 50.4 (*d*, C(14)); 47.2 (*s*, C(13)); 38.9 (*t*, C(24)); 38.5 (*t*, C(7)); 37.7 (*t*, C(6)); 35.0 (*t*, C(1)); 35.0 (*t*, C(22)); 32.9 (*d*, C(20)); 28.1 (*t*, C(16)); 27.5 (*d*, C(25)); 27.2 (*t*, C(12)); 26.0 (*t*, C(11)); 24.1 (*t*, C(2)); 23.9 (*t*, C(15)); 22.9 (*t*, C(23)); 22.2 (*q*, C(27)); 22.0 (*q*, C(26)); 21.1 (*t*, C(3)); 20.5 (*q*, CH_3COO); 18.9 (*q*, C(21)); 17.1 (*q*, C(19)); 16.1 (*q*, C(18)). Anal. calc. for $C_{30}H_{52}O_6$ (508.746): C 70.83, H 10.30; found: C 70.69, H 10.44.

REFERENCES

[1] Lj. Lorenc, L. Bondarenko, M. Lj. Mihailović, *Tetrahedron Lett.* **1985,** *26,* 389.

[2] Lj. Lorenc, L. Bondarenko, V. Pavlović, H. Fuhrer, G. Rihs, J. Kalvoda, M. Lj. Mihailović, *Helv. Chim. Acta* **1989,** *72,* 608.

[3] M. Balci, *Chem. Rev.* **1984,** *81,* 91.

[4] B. Tinant, J. P. Declercq, Lj. Lorenc, M. Lj. Mihailović, to be published.

[5] P. Rylander, 'Catalytic Hydrogenation in Organic Syntheses', Academic Press, New York, 1979, pp. 46–48, and refs. cit. therein.

[6] A. Prelle, E. Winterfeldt, *Heterocycles* **1989,** *28,* 33.