SYNTHESIS OF 17β-STEROIDAL 4-(2-BUTENOLIDES)*

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Derivatives of 5-androsten-3β-ol with 2-butenolide ring in position 17β were prepared by addition of lithium salt of protected propargyl alcohol to 17β-carbaldehyde *IV*, hydrogenation of the formed isomeric acetylenes over P-2 nickel and oxidative cyclization of the obtained olefinic 20,24-diols *IX* and *X*. Stereochemistry of the desired lactones *XII* and *XIII* was determined by CD spectroscopy. The 17β-(2-furyl) derivative *XI* was formed as the cyclization side-product. The 3β-hydroxyl was protected by a methoxymethyl group which allowed a selective removal of tetrahydropyranyl group during the synthesis.

Within the framework of our approach[1,2] to steroidal derivatives with a butenolide ring attached to the $C_{(17)}$ atom it was necessary to apply this reaction sequence also to 5-androstene derivatives with a hydroxyl on the $C_{(3)}$ carbon atom. The crucial problem appeared to be the choice of a suitable protecting group. Since the removal of 2-methoxyethoxymethyl group (MEM) from hydroxyl on $C_{(3)}$ in Westphalen-type derivatives[2] as well as in cholesterol gave low yields, we decided to use another protecting group. We chose the methoxymethyl protecting group which can be removed quantitatively from cholesterol in an acid medium. We found conditions under which it was possible in the presence of this group to remove selectively a tetrahydropyranyl group, a condition, necessary for the application of the previously used[1,2] synthetic way to the butenolide ring. Use of the methoxymethyl group for protection of steroidal derivatives has been recently described in an independent study[3].

Our synthesis started from the methyl ester of etienic acid (*I*), obtained by methylation of the acid with dimethyl sulfate[4]. The protecting group was introduced by reaction with chloromethyl methyl ether in dichloromethane in the presence of N,N-dimethylaniline as a base. In the second step, the ester group of the methoxymethyl derivative *II* was reduced with lithium aluminium hydride in ether, affording the alcohol *III* in practically quantitative yield. Its oxidation with pyridinium chlorochromate in dichloromethane gave the versatile intermediate, 3β-methoxymethoxy-21-nor-5-pregnen-20-al (*IV*), which was immediately used in the next step. Its

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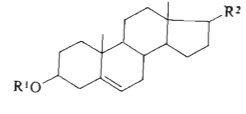
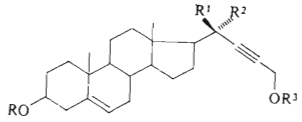
^{1}H NMR spectrum exhibits a doublet at $\delta = 9{\cdot}76$ due to an aldehyde proton whereas the methoxymethoxy group is represented by singlets at $\delta = 4{\cdot}67$ and $\delta = 3{\cdot}35$.

The first step in the synthesis of the butenolide grouping was addition of lithium salt of 1-(2-tetrahydropyranyloxy)-2-propyne to the carbonyl group in aldehyde *IV*. The resulting mixture of the (20*S*)-isomer *V* and the (20*R*)-isomer *VI* was separated by column chromatography on silica gel saturated with ammonia, affording 52% of the more mobile isomer *V* and 23% of the isomer *VI*. The ^{1}H NMR spectra of both isomers display characteristic signals of the protecting groups: tetrahydropyranyl ($\delta = 4{\cdot}82$ bs, $3{\cdot}65$ bm) and methoxymethyl ($\delta = 4{\cdot}68$ s, $3{\cdot}37$ s). Configuration at $C_{(20)}$ was determined by comparison of chemical shifts of ^{1}H NMR signals due to the angular methyl groups[1] in *IV* and *V*; this assignment is in accord with both the polarity of the molecules and the reaction mixture composition (the predominant isomer should arise by attack from the less hindered side of the aldehyde *IV*), similarly as found in analogous cases[1,2]. The assigned configuration agrees also with that of the final lactones *XII* and *XIII* which was proved by CD spectroscopy.





I, $R^1 = H$, $R^2 = COOCH_3$
II, $R^1 = R$, $R^2 = COOCH_3$
III, $R^1 = R$, $R^2 = CH_2OH$
IV, $R^1 = R$, $R^2 = CHO$

V, $R^1 = H$, $R^2 = OH$, $R^3 = THP$
VI, $R^1 = OH$, $R^2 = R^3 = THP$
VII, $R^1 = R^3 = H$, $R^2 = OH$
VIII, $R^1 = OH$, $R^2 = R^3 = H$

$R = CH_2OCH_3$

The tetrahydropyranyl protecting group was selectively removed from the primary hydroxyl at $C_{(24)}$ in compounds *V* and *VI* by treatment with *p*-toluenesulfonic acid in aqueous methanol. The acetylenic diols *VII* ((20*S*)-isomer) and *VIII* ((20*R*)-isomer) were obtained in 85% and 81% yield, respectively.

The triple bond in derivatives *VII* and *VIII* was partially reduced over P-2 nickel in the presence of 1,2-diaminoethane[5]. The obtained olefins *IX* and *X* were assigned the (22*Z*)-configuration on the basis of analogy with similar reductions of 21-nor-5α-cholane derivatives[1]; this configuration follows also from the further reaction path since the isomeric (*E*)-olefin would not have afforded any cyclization product.

The olefins *IX* and *X* underwent oxidative cyclization with silver carbonate on Celite[6] upon reflux in benzene for 1 h. In both cases this procedure afforded a mixture of two compounds which were separated on silica gel. In both cases the more mobile fraction consisted of the side-product, the furyl derivative *XI*. Its structure follows from the ^{1}H NMR spectrum which exhibits a marked ABX system, formed by the

protons H-3′, H-4′ and H-5′ with the respective shifts δ = 5·89, 6·17 and 7·21, and coupling constants $J_{3',4'}$ = 3·2, $J_{4',5'}$ = 1·8 and $J_{3',5'}$ = 0·8 Hz. These values are comparable with those for 2-substituted furans (*e.g.* for 2-methylfuran[7] the respective shifts are 5·90, 6·19 and 7·20 and $J_{3,4}$ = 3·12, $J_{4,5}$ = 2·0 and $J_{3,5}$ = 1·03 Hz). The presence of a furan ring is indicated also by bands at 1 591 and 1 505 cm^{-1} in the aromatic region of the IR spectrum (*cf.* bands at 1 602 and 1 508 cm^{-1} for 2-methylfuran[8]). The lactones represented the more polar fractions: in the (20*R*)-series the olefin *IX* afforded the lactone *XII* (36% of *XII* besides 50% of the furan *XI*), in the (20*S*)-series the olefin *X* cyclized to the lactone *XIII* (56% of *XIII* besides 22% of *XI*). The structure of both lactones was studied by ^{1}H NMR, IR and CD spectra and the selected parameters are summarized in Table I, which, for comparison, contains also the corresponding data for the lactones *XIV* and *XV* (ref.[1]). The CD spectra enabled an assignment of configuration at $C_{(20)}$ based on correlation[9] of the sign of Cotton effect due to the $\pi - \pi^*$ transition with orientation of γ-substituents on the lactone ring. The mutual orientation of hydrogen and the steroid moiety in *XII* corresponds to a positive, whereas in *XIII* to a negative, sign of the Cotton effect in the region 205–235 nm which is in accord with the observed values (Table I). Lactones of this type were already synthesized as 3β-acetates by other routes[4,10] which, however, led only to non-separable mixture of isomers at $C_{(20)}$.

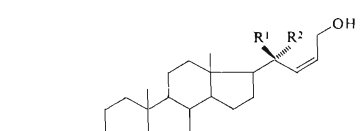
The hydroxyl at $C_{(3)}$ in derivatives *XII* and *XIII* was deblocked with hydrochloric acid in methanol at 40°C to give the hydroxy derivatives *XVI* and *XVII*. Biological activity of these compounds, together with activity of their glucosides and hemisuccinates, is being studied and the results will be published elsewhere.

EXPERIMENTAL

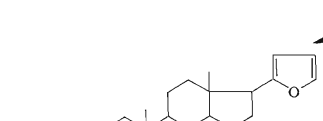
Melting points were determined on a Boetius block, optical rotations on a VDRNA (Opton, Germany) or on a Perkin–Elmer 141 MC polarimeters in chloroform at 23–25°C. IR spectra were taken on UR-20 (Zeiss, Jena) or PE-580 (Perkin–Elmer) spectrophotometers; wavenumbers are given in cm^{-1}. ^{1}H NMR spectra were determined on a Tesla BS-467 (60 MHz) instrument in deuteriochloroform; chemical shifts are given in ppm (δ-scale) with tetramethylsilane as internal standard, coupling constants (J) and band widths (W) are given in Hz. All parameters were obtained by first-order analysis. Mass spectra were measured on an AEI 901 spectrometer, CD spectra on a Dichrographe II (Roussel-Jouan) instrument. Preparative chromatography was carried out on silica gel columns (according to Pitra, 60–120 μm, from Service Laboratories of this Institute), thin-layer chromatography (TLC) was performed on silica gel G according to Stahl (Woelm). Spots were detected by spraying with sulfuric acid followed by heating. Solutions in non-polar solvents were dried over sodium sulfate; all solutions were taken down on a rotatory evaporator at bath temperature 40–50°C and pressure 2–2·5 kPa. Analytical samples were dried over phosphorus pentoxide at 25 Pa.

Methyl 3β-Methoxymethoxy-5-androstene-17β-carboxylate (*II*)

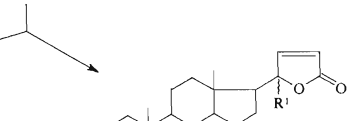
N,*N*-Dimethylaniline (10·5 ml; 82·8 mmol) and chloromethyl methyl ether (6·3 ml; 82·9 mmol) were added to a solution of the hydroxy derivative *I* (ref.[4], 18·5 g; 55·7 mmol) in dichloromethane



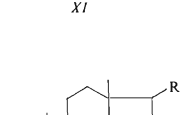
IX, $R^1 = H$, $R^2 = OH$
X, $R^1 = OH$, $R^2 = H$

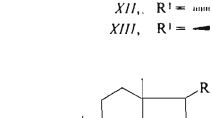


XI



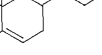
XII, R^1 = dashed H
XIII, R^1 = wedge H



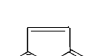


XIV, R =

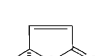
XVI, R =



XV, R =



XVII, R =



(250 ml). The mixture was set aside for 48 h at room temperature, the reaction being monitored by TLC in benzene–ether (8 : 2). The mixture was poured into water (250 ml), the organic layer washed successively with 5% hydrochloric acid, water, saturated potassium hydrogen carbonate solution and again with water, and taken down. Crystallization of the residue from ether–light petroleum afforded 16·5 g (79%) of the methoxymethoxy derivative *II*; m.p. 130–133°C, $[\alpha]_D$ −18° (*c* 0·44). ^{1}H NMR spectrum: 5·35 bd (1 H, $C_{(6)}$—H, J = 4), 4·67 s (2 H, O—CH_2—O), 3·64 s (3 H, CH_3OCO), 3·34 s (3 H, CH_3—O), 3·0–3·7 bm (1 H, $C_{(3)}$—H), 1·00 s (3 H, $C_{(19)}$—H), 0·66 s (3 H, $C_{(18)}$—H). For $C_{23}H_{36}O_4$ (376·5) calculated: 73·37% C, 9·64% H; found: 75·58% C, 9·45% H.

3β-Methoxymethoxy-21-nor-5-pregnen-20-ol (*III*)

Lithium aluminium hydride (9 g) was added to a solution of the methyl ester *II* (16 g; 42·5 mmol) in ether (900 ml). After refluxing and stirring for 4 h, the mixture was decomposed with water and dilute hydrochloric acid. The product was taken up in ether, the extract washed successively with 5% hydrochloric acid, water, potassium hydrogen carbonate and water, dried and filtered through a short column of silica gel (30 g). After evaporation of the solvent, the residue was crystallized from ether–light petroleum mixture, affording 14·1 g (95%) of the alcohol *III*; m.p. 116–118°C; $[\alpha]_D$ −60° (*c* 0·47). ^{1}H NMR spectrum: 5·34 bd (1 H, $C_{(6)}$—H, J = 4), 4·67 s (2 H, O—CH_2—O), 3·60 m (2 H, $C_{(20)}$—H), 3·35 s (3 H, CH_3—O), 1·00 s (3 H, $C_{(19)}$—H), 0·64 (3 H, $C_{(18)}$—H). For $C_{22}H_{36}O_3$ (348·5) calculated: 75·82% C, 10·41% H; found: 75·72% C, 10·25% H.

3β-Methoxymethoxy-21-nor-5-pregnen-20-al (*IV*)

Pyridinium chlorochromate (5 g; 23·2 mmol) was added to a stirred solution of the alcohol *III* (5 g; 14·4 mmol) in dichloromethane (100 ml). After stirring for 2 h at room temperature, the mixture was passed through a column, containing layers of Celite (20 g) and alumina (20 g). The column was then washed with dichloromethane and the filtrate taken down. The crude aldehyde *IV* was used without purification in the next step. An analytical sample was crystallized from light petroleum; m.p. 75–100°C (decomposition); $[\alpha]_D$ −7° (*c* 1·2). ^{1}H NMR spectrum: 9·76 d (1 H, $C_{(20)}$—H, J = 1·5), 5·34 bd (1 H, $C_{(6)}$—H, J = 4), 4·67 s (2 H, O—CH_2—O), 3·35 s (3 H, CH_3—O), 3·0–3·8 bm (1 H, $C_{(3)}$—H), 1·01 s (3 H, $C_{(19)}$—H), 0·76 s (3 H, $C_{(18)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·47% C, 9·97% H.

(20*S*)-3β-Methoxymethoxy-24-(2-tetrahydropyranyloxy)-21-norchol-5-en-22-yn-20-ol (*V*) and Its (20*R*)-Isomer *VI*

A solution of 1-butyllithium in hexane (17·9 ml, c = 1·6 mol l^{-1}) was added dropwise to a stirred and cooled (−78°) solution of 1-(2-tetrahydropyranyloxy)-2-propyne (ref.[1]; 4·83 g; 34·5 mmol) in tetrahydrofuran (34 ml). The mixture was stirred at −20°C for 1 h, cooled again to −78°C and a solution of the above-prepared aldehyde *IV* (from 5 g, *i.e.* 14·4 mol, of alcohol *III*) in tetra-

TABLE I

IR and CD spectral data for the butenolide derivatives

Compound (configuration)	IR bands cm^{-1}	$[M]_D$	$\Delta[M]_D$[a]	$\Delta\varepsilon/\lambda_{max}$[b]
XII (20*R*)	1 760, 1 789	− 44°	+397°	+13·2/215
XIII (20*S*)	1 763, 1 792	−441°		− 7·6/210
XIV (20*R*)[c]	1 760, 1 788	+253°	+426°	+18·6/210
XV (20*S*)[c]	1 763, 1 793	−173°		− 8·8/210

[a] $\Delta[M]_D$ is the difference between rotations of the (20*R*)- and (20*S*)-epimers: $[M]_D^R - [M]_D^S$; [b] CD spectra measured in dioxane, λ_{max} in nm; [c] taken from the literature[1].

hydrofuran (35 ml) was added dropwise during 10 min. The stirred mixture was allowed to warm to room temperature in the course of 1 h and stirring was continued for further 2 h at this temperature. After pouring into saturated ammonium sulfate solution, the solution was extracted with ether, the ethereal solution dried and taken down and the residue chromatographed on a column of silica gel, pretreated for 3 days with ammonia (500 g). Elution with light petroleum–ether (10 : 1–4 : 1) afforded as the first fraction 3·7 g (52%) of the (20*S*)-isomer *V*; m.p. 107–109°C (ether), $[\alpha]_D$ −58° (*c* 0·41). IR spectrum (tetrachloromethane): 3 620 (OH), 3 030, 1 668 (C=C), 1 108, 1 041, 1 029 (—O—). ^{1}H NMR spectrum: 5·36 bm (1 H, $C_{(6)}$—H, $W = 12$), 4·82 bs (1 H, $C_{(2')}$—H), 4·68 s (2 H, O—CH_2—O), 4·28 s (2 H, $C_{(24)}$—H), 3·65 bm (2 H, $C_{(6')}$—H, $W = 30$), 3·37 s (3 H, CH_3—O), 0·99 s (3 H, $C_{(19)}$—H), 0·73 s (3 H, $C_{(18)}$—H). The second more polar fraction was 1·6 g (23%) of amorphous (20*R*)-isomer *VI*, $[\alpha]_D$ −23° (*c* 1·85). IR spectrum (tetrachloromethane): 3 615 (OH), 3 035, 1 667 (C=C), 1 107, 1 050, 1 040, 1 028 (—O—). ^{1}H NMR spectrum: 5·37 bm (1 H, $C_{(6)}$—H, $W = 10$), 4·82 bs (1 H, $C_{(2')}$—H), 4·69 s (2 H, O—CH_2—O), 4·32 s (2 H, $C_{(24)}$—H), 3·68 (2 H, $C_{(6')}$—H, $W = 30$), 3·37 s (3 H, CH_3—O), 1·01 s (3 H, $C_{(19)}$—H). 0·72 s (3 H, $C_{(18)}$—H. For $C_{30}H_{46}O_5$ (486·7) calculated: 74·04% C, 9·53% H; for *V* found: 74·12% C, 9·39% H; for *VI* found: 74·21% C, 9·70% H.

(20*S*)-3β-Methoxymethoxy-21-norchol-5-en-22-yne-20,24-diol (*VII*)

A solution of *p*-toluenesulfonic acid monohydrate (420 mg; 2·2 mmol) in water (7 ml) was added to a solution of the tetrahydropyranyl derivative *V* (3·7 g; 7·6 mmol) in methanol (140 ml) and the mixture was stirred at room temperature for 4 h. The reaction was monitored by TLC in ether–chloroform (4 : 1). The solution was taken down, the residue dissolved in chloroform and washed with potassium hydrogen carbonate solution and water. After drying and removal of the solvent, 2·9 g (95%) of the diol *VII* was obtained; m.p. 179–182°C (dec.) (acetone–benzene). $[\alpha]_D$ −78° (*c* 0·38). IR spectrum (chloroform): 3 605 (OH), 1 668 (C=C), 1 146, 1 102, 1 040 (—O—). ^{1}H NMR spectrum: 5·36 m (1 H, $C_{(6)}$—H, $W = 12$), 4·69 s (2 H, O—CH_2—O), 4·24 bm (1 H, $C_{(20)}$—H, $W = 20$), 4·23 s (2 H, $C_{(24)}$—H), 3·37 s (3 H, CH_3—O), 1·00 s (3 H, $C_{(19)}$—H), 0·73 s (3 H, $C_{(18)}$—H). For $C_{25}H_{38}O_4$ (402·6) calculated: 74·59% C, 9·51% H; found: 74·80% C, 9·59% H.

(20*R*)-3β-Methoxymethoxy-21-norchol-5-en-22-yne-20,24-diol (*VIII*)

The derivative *VI* (1·5 g; 3·1 mmol) was hydrolyzed analogously as described for *V*. The diol *VIII* was obtained in an 81% yield (1 g), m.p. 154–155°C, $[\alpha]_D$ −58° (*c* 0·30). IR spectrum (chloroform): 3 605 (OH), 1 667 (C=C), 1 148, 1 102, 1 038, 1 011 (—O—). ^{1}H NMR spectrum: 5·37 m (1 H, $C_{(6)}$—H, $W = 10$), 4·53 s (2 H, O—CH_2—O), 4·30 s (2 H, $C_{(24)}$—H), 4·23 bm (1 H, $C_{(20)}$—H, $W = 20$), 3·35 s (3 H, CH_3—O), 1·00 s (3 H, $C_{(19)}$—H), 0·72 s (3 H, $C_{(18)}$—H). For $C_{25}H_{38}O_4$ (402·6) calculated: 74·59% C, 9·51% H; found: 74·72% C, 9·40% H.

(20*R*,22*Z*)-3β-Methoxymethoxy-21-nor-5,22-choladiene-20,24-diol (*IX*)

Sodium borohydride (400 mg) was dissolved with shaking in a mixture of ethanol (9·5 ml) and 2M-NaOH (0·5 ml). Part of this solution (2·3 ml) was added dropwise to a stirred solution of nickel(II) acetate tetrahydrate (545 mg) in ethanol (65 ml) and the mixture was hydrogenated for 30 s. 1,2-Diaminoethane (0·3 ml), followed by a solution of the diol *VII* (2·7 g; 6·71 mmol) in ethanol (200 ml), was added. The mixture was hydrogenated at room temperature for 1 h, and passed through a short column of silica gel (30 g) which was then washed with chloroform. The combined eluates were dried and taken down and the residue crystallized from benzene (15 ml),

affording 1·7 g (66%) of the diol *IX*; m.p. 163–165° (ethanol), $[\alpha]_D$ −73° (*c* 1·07). IR spectrum (chloroform): 3 477, 3 617 (OH), 1 667 (C=C), 1 147, 1 102, 1 034, 1 008 (—O—). ^{1}H NMR spectrum: 5·62 m (2 H, $C_{(22)}$—H, $C_{(23)}$—H), 5·33 m (1 H, $C_{(6)}$—H), 4·67 s (2 H, O—CH_2—O), 4·29 bm (1 H, $C_{(20)}$—H, W = 25), 4·22 bt (2 H, $C_{(24)}$—H, J = 5), 3·35 s (3 H, CH_3—O) 1·01 s (3 H, $C_{(19)}$—H), 0·79 s (3 H, $C_{(18)}$—H). For $C_{25}H_{40}O_4$ (404·6) calculated; 74·22% C 9·97% H; found: 74·08% C, 10·12% H.

(20*S*,22*Z*)-3β-Methoxymethoxy-21-nor-5,22-choladiene-20,24-diol (*X*)

Diol *VIII* (870 mg; 2·16 mmol) was hydrogenated in the same manner as described for *VII*, affording 740 mg (85%) of the diol *X*, m.p. 187–189°C, $[\alpha]_D$ −9° (*c* 0·16). IR spectrum (chloroform): 3 610 (OH), 1 668 (C=C), 1 148, 1 104, 1 040, 1 004 (—O—). ^{1}H NMR spectrum: 5·64 m (2 H, $C_{(22)}$—H, $C_{(23)}$—H), 5·33 m (1 H, $C_{(6)}$—H), 4·68 s (2 H, O—CH_2—O), 4·25 m (3 H, $C_{(20)}$—H, $C_{(24)}$—H), 3·35 s (3 H, CH_3—O), 0·98 s (3 H, $C_{(19)}$—H), 0·63 s (3 H, $C_{(18)}$—H). For $C_{25}H_{40}O_4$ (404·6) calculated: 74·22% C, 9·97% H; found: 74·37% C, 9·74% H.

17β-(2-Furyl)-3β-methoxymethoxy-5-androstene (*XI*) and
(20*R*)-3β-Methoxymethoxy-21-nor-5,22-choladiene-24→20-olide (*XII*)

A stirred suspension of silver carbonate on Celite (ref.[6]; 20 g) in benzene (100 ml) was refluxed using an azeotropic separator. After removal of 10 ml of a turbid condensate, a solution of the diol *IX* (1·5 g; 3·7 mmol) in benzene (50 ml) was added and 10 ml of the condensate was again separated. After refluxing for 1 h (monitoring by TLC in benzene–ether 8 : 2), the mixture was cooled and filtered through a short column of silica gel (20 g) which was then washed with ether. The filtrate was taken down and the residue chromatographed on a column of silica gel (100 g) in benzene–ether (50 : 1–20 : 1). The first fraction consisted of the furyl derivative *XI* (710 mg; 50%), m.p. 107–108°C (ether); $[\alpha]_D$ −40° (*c* 0·36). IR spectrum (tetrachloromethane): 1 668 (C=C), 1 591, 1 505 (furan), 1 149, 1 108, 1 041 (—O—). ^{1}H NMR spectrum (tetrachloromethane): 7·21 dd (1 H, $C_{(5')}$—H, $J_{3',5'}$ = 0·8, $J_{4',5'}$ = 1·8), 6·17 dd (1 H, $C_{(4')}$—H, $J_{3',4'}$ = 3·2, $J_{4',5'}$ = 1·8), 5·89 bd ($C_{(3')}$—H, J = 3), 5·28 bd (1 H, $C_{(6)}$—H, J = 3·7), 4·66 s (2 H, O—CH_2—O), 3·33 s (3 H, CH_3—O), 0·97 s (3 H, $C_{(19)}$—H), 0·46 s (3 H, $C_{(18)}$—H). Mass spectrum (*m*/*z*): 384 (M^+), 322 (M−$C_2H_6O_2$), 228 (M−C_6H_6O), 94 (C_6H_6O). For $C_{25}H_{36}O_3$ (384·6) calculated: 78·08% C, 9·44% H; found: 78·20% C, 9·43% H. The lactone *XII* was eluted as the second fraction (530 mg, 36%); m.p. 191–193°C (dec.) (benzene); $[\alpha]_D$ −11° (*c* 0·35). IR spectrum (tetrachloromethane): 1 789, 1 760 (butenolide). ^{1}H NMR spectrum: 7·44 dd (1 H, $C_{(22)}$—H, $J_{20,22}$ = 1·4, $J_{22,23}$ = 5·7), 6·08 dd (1 H, $C_{(23)}$—H, $J_{20,23}$ = 1·9, $J_{22,23}$ = 5·7), 5·34 bd (1 H, $C_{(6)}$—H, J = 4), 4·92 bd (1 H, $C_{(20)}$—H, J = 8), 4·67 s (2 H, O—CH_2—O), 3·35 s (3 H, CH_3—O), 1·03 s (3 H, $C_{(19)}$—H), 0·85 s (3 H, $C_{(18)}$—H). CD spectrum (dioxane): 215 nm, $\Delta\varepsilon$ +13·16. For $C_{25}H_{36}O_4$ (400·6) calculated: 74·96% C, 9·06% H; found: 74·69% C, 8·95% H.

17β-(2-Furyl)-3β-methoxymethoxy-5-androstene (*XI*) and
(20*S*)-3β-Methoxy-21-nor-5,22-choladiene-24→20-olide (*XIII*)

The diol *X* (0·8 g; 1·98 mmol) was oxidized in the same manner as described for *XII*. In addition to the furyl derivative *XI* (170 mg; 22%), identical with the sample obtained in the (20*R*)-series, chromatographic separation afforded 440 mg (56%) of the lactone *XIII*, m.p. 162–163°C; $[\alpha]_D$ −110° (*c* 0·25). IR spectrum (tetrachloromethane): 1 792, 1 763 (butenolide), 1 149, 1 106, 1 044 (—O—). ^{1}H NMR spectrum: 7·53 dd (1 H, $C_{(22)}$—H, $J_{20,22}$ = 1·5, $J_{22,23}$ = 5·8), 6·10 dd (1 H, $C_{(23)}$—H, $J_{20,23}$ = 2·0, $J_{22,23}$ = 5·8), 5·38 m (1 H, $C_{(6)}$—H, W = 12), 5·02 m (1 H, $C_{(20)}$—H, W = 12), 4·69 s (2 H, O—CH_2—O), 3·37 s (3 H, CH_3—O), 1·03 s (3 H, $C_{(19)}$—H),

0·83 s (3 H, $C_{(18)}$—H). CD spectrum (dioxane): 210 nm, $\Delta\varepsilon$ −7·62. For $C_{25}H_{36}O_4$ (400·6) calculated: 74·96% C, 9·06% H; found: 74·99% C, 9·00% H.

(20*R*)-3β-Hydroxy-21-nor-5,22-choladien-24→20-olide (*XVI*)

A stirred mixture of methanol (20 ml), conc. hydrochloric acid (0·2 ml) and a solution of the lactone *XII* (520 mg; 1·3 mmol) in benzene (20 ml) was heated to 40°C for 8 h. The reaction was followed by TLC in ether–chloroform (4 : 1). The solution was taken down, the residue coevaporated with ethanol (50 ml), dissolved in chloroform and the solution washed with saturated potassium hydrogen carbonate solution and water. After drying, the solvent was evaporated and the residue crystallized from ethanol, affording 380 mg (82%) of the lactone *XVI*, m.p. 215–219°C (dec.); $[\alpha]_D$ −19° (*c* 0·22). IR spectrum (chloroform): 3 604, 3 490 (OH), 1 751, 1 790 (butenolide). ^{1}H NMR spectrum: 7·47 dd (1 H, $C_{(22)}$—H, $J_{20,22}$ = 1·4, $J_{22,23}$ = 5·8), 6·07 dd (1 H, $C_{(23)}$—H, $J_{20,23}$ = 1·9, $J_{22,23}$ = 5·8), 5·33 bd (1 H, $C_{(6)}$—H, J = 4), 4·92 bd (1 H, $C_{(20)}$—H, J = 8), 3·48 m (1 H, $C_{(3)}$—H, W = 30), 1·02 s (3 H, $C_{(19)}$—H), 0·84 s (3 H, $C_{(18)}$—H). For $C_{23}H_{32}O_3$ (356·5) calculated: 77·49% C, 9·05% H; found: 77·55% C, 8·86% H.

(20*S*)-3β-Hydroxy-21-nor-5,22-choladien-24→20-olide (*XVII*)

The protected lactone *XIII* (0·4 g; 1 mmol) was hydrolyzed in the same manner as described for *XII*. Crystallization from ethanol afforded 180 mg (50%) of the desired product, m.p. 185 to 199°C (dec.); $[\alpha]_D$ −126° (*c* 0·15). IR spectrum (chloroform): 3 607 (OH), 1 798, 1 750 (butenolide), 1 669 (C=C). ^{1}H NMR spectrum: 7·53 dd (1 H, $C_{(22)}$—H, $J_{20,22}$ = 1·5, $J_{22,23}$ = 5·8), 6·09 dd (1 H, $C_{(23)}$—H, $J_{20,23}$ = 1·6, $J_{22,23}$ = 5·8), 5·35 m (1 H, $C_{(6)}$—H, W = 12), 5·01 m (1 H, $C_{(20)}$—H, W = 12), 3·48 bm (1 H, $C_{(3)}$—H, W = 30), 1·01 s (3 H, $C_{(19)}$—H), 0·81 s (3 H, $C_{(18)}$—H). For $C_{23}H_{32}O_3$ (356·5) calculated: 77·49% C, 9·05% H; found: 77·33% C, 9·06% H.

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