DERIVATIVES OF 5α-ANDROSTAN-3α- AND 3β-OL WITH ACRYLATE SIDE CHAIN*

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Hydroxy derivatives *I*, *II*, *III*, *XVII* and *XX* were oxidized to give the respective aldehydes *IV*, *V*, *VI*, *XVIII* and *XXI* which were further converted by Wittig–Horner reaction into unsaturated methyl and ethyl esters. Removal of the acetal protecting group in position 3 afforded methyl esters *X*, *XXIV* and *XXXVI* and ethyl esters *XIV*, *XXV* and *XXXVII*. Compounds *XXIV*, *XXV*, *XXXVI* and *XXXVII* were converted into the corresponding hemisuccinates *XXVIII*, *XXIX*, *XL* and *XLI* and β-D-glucosides *XXXII*, *XXXIII*, *XLIV* and *XLV*.

An unsaturated ester functionality bonded in the position 17β of the steroid skeleton may interact with the bonding sites of the enzyme Na^+, K^+-ATPase (EC 3.6.1.3), similarly as the α,β-unsaturated lactone ring in natural cardiotonically active steroids[1]. In this context many compounds of this type, i.e. esters of (20*E*)-3-hydroxy--20-pregnene-21-carboxylic acid, have been synthesized. Most of them have been prepared by reaction of the 17β-formyl derivatives with Wittig–Horner reagent as suggested by Thomas and coworkers[2].

Recently, we have described[3] the preparation of 17β-hydroxymethyl derivatives *I*–*III* in which the 3β-hydroxyl is protected as tetrahydro-2*H*-pyran-2-yl (THP), 1-ethoxyethyl (EE) or 1-methoxyethyl (ME) ether. Since the synthesis of compounds *I*, *II* and *III* from the readily accessible etienic acid (3β-hydroxy-5-androstene-17β--carboxylic acid) proceeds without isolation of intermediates in high yields (91%, 69% and 85%, respectively) we decided to utilize them for the preparation of unsaturated esters *X* and *XIV*. In the first step, the alcohols *I*–*III* were converted into the corresponding aldehydes *IV*–*VI*. Alcohol *I* was oxidized with pyridinium chlorochromate in the presence of anhydrous sodium acetate[4]. Alcohols *II* and *III* that contain more acid-labile protecting groups[3] EE and ME were converted into the corresponding aldehydes *V* and *VI* by treatment with chromium trioxide–pyridine complex in dichloromethane in the presence of anhydrous magnesium sulfate[5].

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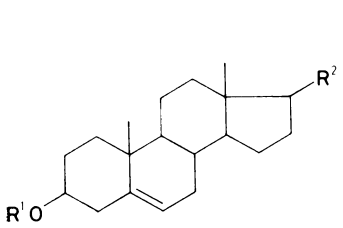
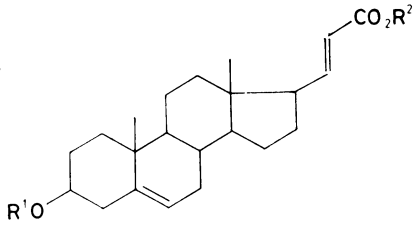
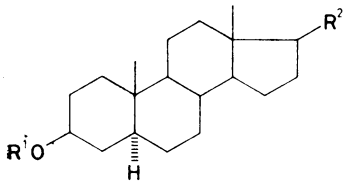


I, R^1= THP ; R^2= CH_2OH
II, R^1= EE ; R^2= CH_2OH
III, R^1= ME ; R^2= CH_2OH
IV, R^1= THP ; R^2= CHO
V, R^1= EE ; R^2= CHO
VI, R^1= ME ; R^2= CHO

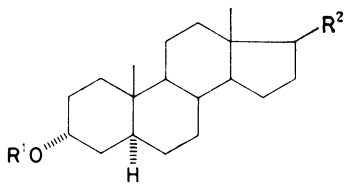


VII, R^1= THP ; R^2= CH_3
VIII, R^1= EE ; R^2= CH_3
IX, R^1= ME ; R^2= CH_3
X, R^1= H ; R^2= CH_3
XI, R^1= THP ; R^2= CH_2CH_3
XII, R^1= EE ; R^2= CH_2CH_3
XIII, R^1= ME ; R^2= CH_2CH_3
XIV, R^1= H ; R^2= CH_2CH_3

Reaction of aldehydes *IV*–*VI* with the Wittig–Horner reagent (prepared from trialkyl phosphoacetate and sodium hydride) led to α,β-unsaturated methyl esters *VII*–*IX* and ethyl esters *XI*–*XIII*. *p*-Toluenesulfonic acid monohydrate-catalyzed deprotection afforded the 3-hydroxy derivatives *X* and *XIV*. The overall yields (from *I*–*III*) were 58–74% and did not depend much on the protecting group or the ester type. Our previously described[6] preparation of the methyl ester *X*, using an acetyl group for protection of the 3-hydroxyl, had an overall yield of only 27% (from etienic acid). The yield of the above-described preparation of methyl ester *X* via the THP-protected derivative is more than double (66%).



XV, R^1= H ; R^2= COOH
XVI, R^1= H ; R^2= $COOCH_3$
XVII, R^1= THP ; R^2= CH_2OH
XVIII, R^1= THP ; R^2= CHO

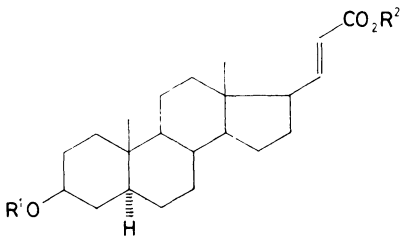


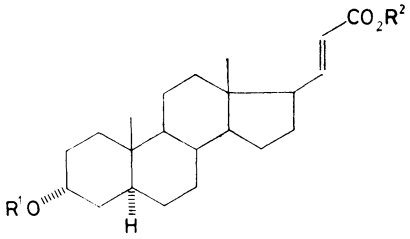
XIX, R^1= H ; R^2= $COOCH_3$
XX, R^1= THP ; R^2= CH_2OH
XXI, R^1= THP ; R^2= CHO

EE = 1-ethoxyethyl ; ME = 1-methoxyethyl ; THP = tetrahydro-2*H*-pyran-2-yl

The starting compound for the synthesis of esters *XXIV* and *XXV*, i.e. alcohol *XVII*, was prepared analogously as the alcohol *I* (cf. ref.[3]). Reaction of acid *XV* with

dihydropyran in the presence of *p*-toluenesulfonic acid monohydrate, followed by reduction with sodium bis(2-methoxyethoxy)aluminium hydride, afforded the alcohol *XVII* in 88% yield. The esters *XXIV* and *XXV* were prepared via aldehyde *XVIII* using the above-mentioned reaction sequence. The methyl ester *XXIV* has already been described[7], however, the reported melting point differs much from the value found by us (see Experimental). Starting compound for preparation of derivatives with axial hydroxy group in position 3 (i.e. 3α-OH) was the methyl ester *XVI*, containing an equatorial hydroxyl (3β-OH). The configuration of the hydroxyl was inverted using the described procedure[8] consisting in reaction of the 3β-hydroxy derivative with N,N'-dicyclohexylcarbodiimide, catalyzed by copper(I) chloride, followed by solvolysis of the obtained isourea with formic acid and selective hydrolysis of the 3-formate group. The 3α-hydroxy derivative *XIX* was obtained in 75% yield. The configuration of the hydroxyl in position 3 is confirmed by an H-3β signal that appears as a multiplet at 4·04 ppm (W = 12 Hz); these values are characteristic of an axial hydroxyl on a cyclohexane ring. Reaction of methyl ester *XIX* with dihydropyran under catalysis with *p*-toluenesulfonic acid monohydrate and subsequent reduction with sodium bis(2-methoxyethoxy)aluminium hydride gave





XXII, R^1 = THP ; R^2 = CH_3
XXIII, R^1 = THP ; R^2 = CH_2CH_3
XXIV, R^1 = H ; R^2 = CH_3
XXV, R^1 = H ; R^2 = CH_2CH_3
XXVI, R^1 = X ; R^2 = CH_3
XXVII, R^1 = X ; R^2 = CH_2CH_3
XXVIII, R^1 = Y ; R^2 = CH_3
XXIX, R^1 = Y ; R^2 = CH_2CH_3
XXX, R^1 = Ac_4-β-D-Glc ; R^2 = CH_3
XXXI, R^1 = Ac_4-β-D-Glc ; R^2 = CH_2CH_3
XXXII, R^1 = β-D-Glc ; R^2 = CH_3
XXXIII, R^1 = β-D-Glc ; R^2 = CH_2CH_3

XXXIV, R^1 = THP ; R^2 = CH_3
XXXV, R^1 = THP ; R^2 = CH_2CH_3
XXXVI, R^1 = H ; R^2 = CH_3
XXXVII, R^1 = H ; R^2 = CH_2CH_3
XXXVIII, R^1 = X ; R^2 = CH_3
XXXIX, R^1 = X ; R^2 = CH_2CH_3
XL, R^1 = Y ; R^2 = CH_3
XLI, R^1 = Y ; R^2 = CH_2CH_3
XLII, R^1 = Ac_4-β-D-Glc ; R^2 = CH_3
XLIII, R^1 = Ac_4-β-D-Glc ; R^2 = CH_2CH_3
XLIV, R^1 = β-D-Glc ; R^2 = CH_3
XLV, R^1 = β-D-Glc ; R^2 = CH_2CH_3

X = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$; Y = $OCCH_2CH_2COOH$
THP = tetrahydro-2*H*-pyran-2-yl
Ac_4-β-D-Glc = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl
β-D-Glc = β-D-glucopyranosyl

alcohol *XX* in 96% yield. Esters *XXXVI* and *XXXVII* were prepared via aldehyde *XXI* using the above-described procedure.

The α,β-unsaturated esters *XXIV*, *XXV*, *XXXVI* and *XXXVII* were converted[9] into the corresponding hemisuccinates *XXVIII*, *XXIX*, *XL* and *XLI*. Hemisuccinates derived from esters *X* and *XIV* have already been prepared previously[10,11]. The esters *XXIV*, *XXV*, *XXXVI* and *XXXVII* were also transformed into the β-D--glucosides *XXXII*, *XXXIII*, *XLIV* and *XLV*, respectively, by the silver silicate promoted[12] glycosidation with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. Without further purification, the obtained crude acetylated glucosides were hydrolyzed to give the free β-D-glucosides whose structure was confirmed by acetylation to the corresponding tetracetates *XXX*, *XXXI*, *XLII* and *XLIII*. The ^{1}H NMR signals of the sugar moiety correspond to signals found for β-D-glucosides derived from the esters *X* and *XIV*, prepared previously[6,11].

EXPERIMENTAL

Melting points were determined on a micromelting point apparatus Boetius (G.D.R.). Optical rotations were measured at 25°C on a Perkin–Elmer 141 MC polarimeter. Infrared spectra were recorded on a Perkin–Elmer PE 580 spectrometer (wavenumbers in cm^{-1}). ^{1}H NMR spectra were taken on a TESLA BS-497 (FT mode, 100 MHz) and on a Varian XL-200 (FT mode, 200 MHz) instruments at 23°C in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. All parameters were obtained by first order analysis. Column chromatography was performed on silica gel (according to Pitra, 60—120 μm) or on neutral alumina (Reanal, activity II), thin-layer chromatography on silica gel G according to Stahl (ICN Biochemicals). Prior to evaporation, solutions in organic solvents were dried over anhydrous sodium sulfate. Solvents were evaporated in vacuo (about 2 kPa). Analytical samples were dried over phosphorus pentoxide at 40°C/26 Pa for 12 h. The identity of samples prepared by different routes was checked by comparison of their IR and ^{1}H NMR spectra, thin-layer chromatography and mixture melting point determination.

3β-(2-Tetrahydropyranyloxy)-21-nor-5α-pregnan-20-ol (*XVII*)

p-Toluenesulfonic acid monohydrate (38 mg, 0·2 mmol) and dihydropyran (4·56 ml, 50 mmol) were added to a suspension of acid *XV* (ref.[13]; 4·81 g, 15 mmol) in benzene (90 ml). After stirring for 5 h at room temperature the mixture was mixed with 3·5M sodium bis(2-methoxyethoxy)-dihydroaluminium hydride in benzene (19 ml) and refluxed under argon for 5 h. After cooling to room temperature the excess hydride was decomposed by addition of moist ether and water and the mixture was partitioned between ethyl acetate (400 ml) and water (150 ml). The aqueous phase was extracted with ethyl acetate and the combined organic portions were washed with saturated solution of sodium chloride (3×). The solvent was evaporated and the residue chromatographed on a column of alumina (500 g). Light petroleum – benzene – ether (45 : 45 : 10) eluted nonpolar impurities; the same solvents in the ratio 40 : 40 : 20 eluted the product *XVII* (5·16 g, 88%), m.p. 155—161°C (ether); $[\alpha]_D$ +52° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 625, 3 560 (OH); 1 131, 1 114, 1 076, 1 024 (C–O). ^{1}H NMR spectrum (100 MHz): 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 0·81 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{25}H_{42}O_3$ (390·6) calculated: 76·87% C, 10·84% H; found: 77·14% C, 11·06% H.

Methyl 3α-Hydroxy-5α-androstane-17β-carboxylate (*XIX*)

N,N'-Dicyclohexylcarbodiimide (6·20 g, 30 mmol) and copper (I) chloride (70 mg, 0·7 mmol) were added to a solution of methyl ester *XVI* (ref.[13]; 8·36 g, 25 mmol) in dioxane (30 ml). The mixture was warmed to 50°C for 45 h, diluted with a mixture of benzene and ether (1 : 1, 300 ml) and filtered through a column of alumina (80 g). The column was washed with ether, the organic phases were combined and the solvents were evaporated in vacuo. The residue (13·9 g) was mixed with dioxane (40 ml) and formic acid (3·4 ml, 90 mmol), the mixture was heated to 100°C for 45 h and diluted with ether (100 ml). The separated N,N'-dicyclohexylurea was filtered off, the filtrate was diluted with ether (250 ml), washed with a potassium hydrogen carbonate solution (3×) and water. After evaporation of the solvent, the residue was dissolved in a mixture of benzene (140 ml) and methanol (140 ml) and set aside with a solution of potassium hydroxide (2·81 g, 50 mmol) in a mixture of water (18 ml) and methanol (18 ml). After standing at room temperature for 1 h, the mixture was neutralized with acetic acid (2·8 ml) and the solvents were evaporated in vacuo. The residue was dissolved in ether, the ethereal solution washed with water, the solvent evaporated and the residue chromatographed on a column of silica gel (500 g). Light petroleum – benzene – ether (50 : 45 : 5) washed out nonpolar impurities and the same solvents in the ratio 45 : 45 : 10 eluted the title methyl ester *XIX* (6·27 g; 75%), m.p. 187—188°C (ether); $[\alpha]_D$ +47° (*c* 0·4, chloroform). Reported[14] m.p. 178—181°C; $[\alpha]_D$ +52·6°. IR spectrum (chloroform): 3 615, 3 505 (OH); 1 724 (COOR). ^{1}H NMR spectrum (100 MHz): 4·04 m, 1 H (H-3, W = 12); 3·66 s, 3 H ($COOCH_3$); 0·79 s, 3 H (3 × H-19); 0·64 s, 3 H (3 × H-18).

3α-(2-Tetrahydropyranyloxy)-21-nor-5α-pregnan-20-ol (*XX*)

The title alcohol *XX* was prepared from the methyl ester *XIX* (5·02 g, 15 mmol) in the same manner as described for the preparation of alcohol *XVII* from acid *XV*. Yield 5·63 g (96%) of amorphous alcohol *XX*; $[\alpha]_D$ +11° (*c* 1·6, chloroform). IR spectrum (chloroform): 3 625, 3 455 (OH); 1 132, 1 075, 1 028, 1 006 (C–O). ^{1}H NMR spectrum (100 MHz): 4·62 bs, 1 H (H-2' of tetrahydropyranyloxy group); 3·68 m, 1 H (H-3); 0·81 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{25}H_{42}O_3$ (390·6) calculated: 76·87% C, 10·84% H; found: 76·97% C, 10·55% H.

General Procedure for Preparation of Aldehydes *IV*, *XVIII* and *XXI*

Anhydrous sodium acetate (656 mg, 8 mmol) and pyridinium chlorochromate (3.45 g, 16 mmol) were added to a solution of the alcohol (5 mmol) in dichloromethane (40 ml). After stirring for 2 h at room temperature in an argon atmosphere, the reaction mixture was diluted with ether (80 ml), filtered through a column of alumina (50 g) and the product was washed out with ether. The combined filtrates were concentrated in vacuo and the the residue was freed from pyridine by coevaporation with toluene in vacuo. The obtained aldehyde was used without further purification.

3β-(2-*Tetrahydropyranyloxy*)-21-*nor*-5-*pregnen*-20-*al* (IV). Alcohol *I* (ref.[3]; 1·94 g) was converted into the aldehyde *IV* (1·81 g; 94%). ^{1}H NMR spectrum (100 MHz): 9·77 d, 1 H (H-20, J(17,20) = 1·5); 5·35 bd, 1 H (H-6, J = 4·5); 4·71 bs, 1 H (H-2' of tetrahydropyranyloxy group); 1·02 s, 3 H (3 × H-19); 0·76 s, 3 H (3 × H-18).

3β-(2-*Tetrahydropyranyloxy*)-21-*nor*-5α-*pregnan*-20-*al* (XVIII). The title aldehyde *XVIII* (1·84 g; 95%) was obtained from alcohol *XVII* (1·95 g). ^{1}H NMR spectrum (100 MHz): 9·76 d, 1 H (H-20, J(17,20) = 1·5); 4·70 bs, 1 H (H-2' of tetrahydropyranyloxy group); 0·82 s, 3 H (3 × H-19); 0·74 s, 3 H (3 × H-18).

3α-(2-*Tetrahydropyranyloxy*)-21-*nor*-5α-*pregnan*-20-*al* (XXI). Alcohol *XX* (1·95 g) was converted into the title aldehyde *XXI* (1·86 g; 96%). ^{1}H NMR spectrum (100 MHz): 9·76 d, 1 H (H-20, J(17,20) = 1·5); 4·63 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 3·88 m, 1 H (H-3); 0·79 s, 3 H (3 × H-19); 0·74 s, 3 H (3 × H-18).

3β-(1-Ethoxyethoxy)-21-nor-5-pregnen-20-al (*V*)

Pyridine (4·05 ml, 50 mmol) was added dropwise at 0°C in an argon atmosphere to a stirred suspension of chromium(VI) oxide (2·5 g, 25 mmol) and anhydrous magnesium sulfate (2·1 g) in dichloromethane (70 ml). After stirring for 30 min at 0°C, a solution of alcohol II (ref.[3]; 1·88 g, 5 mmol) in dichloromethane (20 ml) was added. The reaction mixture was stirred under argon at 0°C for 30 min and then at room temperature for 2 h, diluted with ether (150 ml) and filtered through a column of alumina (100 g) which was then washed with ether. The combined filtrates were concentrated in vacuo and pyridine was removed from the residue by coevaporation with toluene in vacuo. Yield 1·76 g (94%) of aldehyde *V* which was used without further purification. ^{1}H NMR spectrum (100 MHz): 9·78 d, 1 H (H-20, J(17,20) = 1·6); 5·34 bd, 1 H (H-6, J = 4·5); 4·71 q, 1 H (O–CH–O, J = 6); 3·54 m, 3 H (OCH_2CH_3 and H-3); 1·31 d, 3 H (O–CH(CH_3)–O, J = 6); 1·20 t, 3 H (OCH_2CH_3, J = 7); 1·02 s, 3 H (3× H-19); 0·77 s, 3 H (3 × H-18).

3β-(1-Methoxyethoxy)-21-nor-5-pregnen-20-al (*VI*)

The title compound was prepared from alcohol *III* (ref.[3]; 1·81 g, 5 mmol) as described for the preparation of aldehyde *V* from alcohol II (see the preceding experiment). Yield 1·75 g (97%) of aldehyde *VI* which was used without further purification. ^{1}H NMR spectrum (100 MHz): 9·78 d, 1 H (H-20, J(17,20) = 2); 5·35 bd, 1 H (H-6, J = 4·5); 4·74 q, 1 H (O–CH–O, J = 5·5); 3·41 m, 1 H (H-3, W = 36); 3·31 s, 3 H (OCH_3); 1·30 d, 3 H (O–CH(CH_3)–O, J = 5·5); 1·03 s, 3 H (3 × H-19); 0·78 s, 3 H (3 × H-18).

General Procedure for Preparation of Methyl Esters *VII*—*IX*, *XXII* and *XXXIV*

Trimethyl phosphonoacetate (2·28 ml, 20 mmol) was added during 10 min under argon to an ice-cooled suspension of sodium hydride (480 mg, 20 mmol) in 1,2-dimethoxyethane (45 ml). The mixture was stirred at room temperature for 20 min and then a solution of the aldehyde (4 mmol) in 1,2-dimethoxyethane (20 ml) was added. After stirring at room temperature for 3 h in an argon atmosphere, the solvent was evaporated in vacuo and the residue partitioned between ether and water. The aqueous phase was extracted with ether, the combined organic phases were washed with water (3×), the solvent was evaporated and the residue was chromatographed on a column of alumina (150 g). Light petroleum–ether (96 : 4) washed out nonpolar impurities and light petroleum–ether (92 : 8) eluted the product.

Methyl (20*E*)-3β-(2-*tetrahydropyranyloxy*)-5,20-*pregnadiene*-21-*carboxylate* (VII). Aldehyde *IV* (1·55 g) was converted into the methyl ester *VII* (1·41 g; 79%), m.p. 148—151°C (hexane – ether); $[\alpha]_D$ +7° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 1 726, 1 654 (C=C—COOR); 1 137, 1 035, 1 025 (C—O). ^{1}H NMR spectrum (100 MHz): 6·97 dd, 1 H (H-20, J(17, 20) = 7·8; J(20, 21) = 16·0); 5·78 dd, 1 H (H-21, J(17, 21) = 1·5; J(20, 21) = 16·0); 5·35 bd, 1 H (H-6, J = 4·5); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 3·70 s, 3 H ($COOCH_3$); 1·01 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{28}H_{42}O_4$ (442·6) calculated: 75·98% C, 9·55% H; found: 76·23% C, 9·83% H.

Methyl (20*E*)-3β-(1-*ethoxyethoxy*)-5,20-*pregnadiene*-21-*carboxylate* (VIII). Aldehyde *V* (1·50 g) was converted into the methyl ester *VIII* (1·19 g; 69%), m.p. 110–114°C (hexane–ether); $[\alpha]_D$ −29° (*c* 1·6, chloroform). IR spectrum (tetrachloromethane): 1 720, 1 652 (C=C—COOR); 1 132, 1 101, 1 045 (C–O). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, *J*(17, 20) = 7·8; *J*(20, 21) = 16·2); 5·78 dd, 1 H (H-21, *J*(17, 21) = 1·1; *J*(20, 21) = 16·2); 5·34 bd, 1 H (H-6, *J* = 4·5); 4·77 q, 1 H (O–CH–O, *J* = 5·5); 3·72 s, 3 H ($COOCH_3$); 3·50 q and 3·61 q, 2 H (OCH_2CH_3, *J* = 7·2); 3·39 m, 1 H (H-3); 1·30 d, 3 H (O–CH(CH_3)–O, *J* = 5·5); 1·19 t, 3 H (OCH_2CH_3, *J* = 7·2); 1·01 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{27}H_{42}O_4$ (430·6) calculated: 75·31% C, 9·83% H; found: 75·55% C, 10·03% H.

Methyl (20*E*)-3β-(1-*methoxyethoxy*)-5,20-*pregnadiene*-21-*carboxylate* (IX). Aldehyde *VI* (1·44 g) was converted into the methyl ester *IX* (1·03 g; 62%), m.p. 141–143°C (hexane–ether); $[\alpha]_D$ −29° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 726, 1 654 (C=C—COOR); 1 146, 1 133, 1 101, 1 045 (C–O). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, *J*(17, 20) = = 7·5; *J*(20, 21) = 16·0); 5·79 dd, 1 H (H-21, *J*(17, 21) = 1·5; *J*(20, 21) = 16·0); 5·35 bd, 1 H (H-6, *J* = 4·5); 4·74 q, 1 H (O–CH–O, *J* = 5·9); 3·73 s, 3 H ($COOCH_3$); 3·31 s, 3 H (OCH_3); 1·30 d, 3 H (O–CH(CH_3)–O, *J* = 5·9); 1·01 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{26}H_{40}O_4$ (416·6) calculated: 74·96% C, 9·68% H; found: 75·11% C, 9·55% H.

Methyl (20*E*)-3β-(2-*tetrahydropyranyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXII). Aldehyde *XVIII* (1·55 g) was converted into the title methyl ester *XXII* (1·26 g; 71%), m.p. 114–117°C (ether); $[\alpha]_D$ +39° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 727, 1 654 (*C*=*C*–COOR). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, *J*(17, 20) = 7·6; *J*(20, 21) = = 15·6); 5·77 dd, 1 H (H-21, *J*(20, 21) = 15·6; *J*(17, 21) = 1·0); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 3·72 s, 3 H ($COOCH_3$); 0·81 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{28}H_{44}O_4$ (444·7) calculated: 75·63% C, 9 97% H; found: 76·35% C, 9·91% H.

Methyl (20*E*)-3α-(2-*tetrahydropyranyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXIV). Aldehyde *XXI* (1·55 g) was converted into the title methyl ester *XXXIV* (1·19 g; 69%), m.p. 102–105°C (hexane–ether); $[\alpha]_D$ +37° (*c* 0·1, chloroform). IR spectrum (tetrachloromethane): 1 726, 1 654 (C=C– COOR); 1 035, 1 024, 1 007 (C–O). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, *J*(17,20) = 7·5; *J*(20, 21) = 15·7); 5·77 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20, 21) = 15·7); 4·61 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 3·87 m, 1 H (H-3, *W* = 14); 3·72 s, 3 H ($COOCH_3$); 0·78 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{28}H_{44}O_4$ (444·7) calculated: 75·63% C, 9·97% H; found: 75·33% C, 10·30% H.

General Procedure for Preparation of Ethyl Esters *XI*–*XIII*, *XXIII* and *XXXV*

Triethyl phosphonoacetate (3·97 ml, 20 mmol) was added under argon during 10 min to a stirred ice-cooled suspension of sodium hydride (480 mg, 20 mmol) in 1,2-dimethoxyethane (15 ml). The mixture was stirred at room temperature for 20 min and then a solution of the aldehyde (4 mmol) in 1,2-dimethoxyethane (15 ml) was added. After stirring in an atmosphere of argon at room temperature for 3 h, the solvent was evaporated in vacuo and the residue partitioned between ether and water. The aqueous phase was extracted with ether, the combined organic phases were washed with water (3×) and the residue was chromatographed on a column of alumina (150 g). After washing out nonpolar impurities with light petroleum–ether (96 : 4), the product was eluted with light petroleum–ether (92 : 8).

Ethyl (20*E*)-3β-(2-*tetrahydropyranyloxy*)-5,20-*pregnadiene*-21-*carboxylate* (XI). Aldehyde *IV* (1·55 g) was converted into the ethyl ester *XI* (1·28,g; 69%), m.p. 120–123°C (hexane–ether); $[\alpha]_D$ −31° (*c* 0·4) chloroform). IR spectrum (tetrachloromethane): 1 720, 1 652 (C=C—COOR).

^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, J(17, 20) = 7·8; J(20, 21) = 16·0); 5·76 dd, 1 H (H-21, J(17, 21) = 1·0; J(20, 21) = 16·0); 5·35 bd, 1 H (H-6, J = 4·5); 4·71 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 4·18 q, 2 H (COOC**H**$_2$CH$_3$, J = 7·0); 1·27 t, 3 H (COOCH$_2$C**H**$_3$, J = 7·0); 1·00 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{29}H_{44}O_4$ (456·7) calculated: 76·27% C, 9·71% H; found: 76·31% C, 9·56% H.

Ethyl (20*E*)-3β-(1-*ethoxyethoxy*)-5,20-*pregnadiene*-21-*carboxylate* (XII). Aldehyde *V* (1·50 g) was converted into the ethyl ester *XII* (1·36 g; 75%), m.p. 94—99°C (hexane–ether); $[\alpha]_D$ −29° (*c* 1·8, chloroform). IR spectrum (tetrachloromethane): 1 720, 1 652 (*C*=C—COOR); 1 176, 1 132, 1 100, 1 048 (C–O). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, J(17, 20) = 7·5; J(20, 21) = 15·8); 5·78 dd, 1 H (H-21, J(20, 21) = 15·8; J(17,21) = 1·1); 5·34 bd, 1 H (H-6, J = 4·5); 4·77 q, 1 H (O–CH–O, J = 5·5); 4·19 q, 2 H (COOC**H**$_2$CH$_3$, J = 7·0); 3·51 q and 3·61 q, 2 H (OC**H**$_2$CH$_3$, J = 7·2); 3·50 m, 1 H (H-3); 1·31 d, 3 H (O–CH(C**H**$_3$)–O, J = 5·5); 1·29 t, 3 H (COOCH$_2$C**H**$_3$, J = 7·0); 1·20 t, 3 H (OCH$_2$C**H**$_3$, J = 7·2); 1·01 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{28}H_{44}O_4$ (444·7) calculated: 75·63% C, 9·97% H; found: 75·89% C, 10·21% H.

Ethyl (20*E*)-3β-(1-*methoxyethoxy*)-5,20-*pregnadiene*-21-*carboxylate* (XIII). Aldehyde *VI* (1·44 g) was converted into the ethyl ester *XIII* (1·36 g; 79%), m.p. 119—121°C (hexane–ether); $[\alpha]_D$ −17° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 720, 1 653 (C=C—COOR); 1 145, 1 134, 1 100, 1 046 (C–O). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, J(17, 20) = 8·0 J(20,21) = 16·0); 5·78 dd, 1 H (H-21, J(20, 21) = 16·0; J(17, 21) = 1·0); 5·36 bd, 1 H (H-6; J = 4·5); 4·73 q, 1 H (O–CH–O, J = 6·0); 4·20 q, 2 H (COOC**H**$_2$CH$_3$, J = 8·0); 3·31 s, 3 H (OCH$_3$); 1·32 d, 3 H (O–CH(C**H**$_3$)–O, J = 6·0); 1·30 t, 3 H (COOCH$_2$C**H**$_3$, J = 8·0); 1·02 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{27}H_{42}O_4$ (430·6) calculated: 75·31% C, 9·83% H; found: 75·45% C, 9·87% H.

Ethyl (20*E*)-3β-(2-*tetrahydropyranyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXIII). Aldehyde *XVIII* (1·55 g) was converted into the ethyl ester *XXIII* (1·58 g; 86%), m.p. 119—122°C (hexane); $[\alpha]_D$ +9° (*c* 0·4, chloroform). IR spectrum (tetrachloromethane): 1 718, 1 657 (C=C—COOR); 1 140, 1 025 (C–O). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, J(17, 20) = 7·8; J(20, 21) = 15·9); 5·76 dd, 1 H (H-21, J(17, 21) = 1·0; J(20, 21) = 15·9); 4·74 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 4·18 q, 2 H (COOC**H**$_2$CH$_3$, J = 7·0); 1·28 t, 3 H (COOCH$_2$C**H**$_3$, J = 7·0); 0·81 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{29}H_{46}O_4$ (458·7) calculated: 75·94% C, 10·11% H; found: 76·22% C, 10·20% H.

Ethyl (20*E*)-3α-(2-*tetrahydropyranyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXV). Aldehyde *XXI* (1·55 g) was converted into the ethyl ester *XXXV* (1·19 g; 65%), m.p. 81—84°C (hexane); $[\alpha]_D$ +32° (*c* 1·3, chloroform). IR spectrum (tetrachloromethane): 1 718, 1 650 (C=C—COOR); 1 140, 1 034, 1 022, 1 006 (C–O). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, J(17, 20) = = 7·8; J(20, 21) = 16·0); 5·76 dd, 1 H (H-21, J(17, 21) = 1·1; J(20,21) = 16·0); 4·62 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 4·18 q, 2 H (COOC**H**$_2$CH$_3$, J = 7·1); 3·88 m, 1 H (H-3); 1·28 t, 3 H (COOCH$_2$C**H**$_3$, J = 7·1); 0·78 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{29}H_{46}O_4$ (458·7) calculated: 75·94% C, 10·11% H; found: 75·73% C, 10·30% H.

General Procedure for Preparation of Hydroxy Derivatives *X*, *XIV*, *XXIV*, *XXV*, *XXXVI* and *XXXVII*

p-Toluenesulfonic acid monohydrate (875 mg, 4·6 mmol) was added to a solution of the protected ester (2 mmol) in a mixture of benzene (15 ml) and methanol (30 ml; in the case of methylesters) or ethanol (40 ml; in the case of ethyl esters). The mixture was warmed to 45°C for 6 h (THP-

derivatives) or 2 h (EE- and ME-derivatives), the solvents were evaporated in vacuo, the residue was partitioned between ether and water and the aqueous phase was extracted with ether. The organic phases were combined and washed successively with water, saturated aqueous potassium hydrogen carbonate solution and water. After evaporation of the solvent, the residue was chromatographed on a column of silica gel (50 g) unless stated otherwise. Nonpolar impurities were washed out with light petroleum–benzene–ether (50 : 45 : 5) and the product was then eluted with light petroleum–benzene–ether (40 : 40 : 20).

Methyl (20*E*)-3β-*hydroxy*-5,20-*pregnadiene*-21-*carboxylate* (X).

a) Reaction of the THP-derivative *VII* (881 mg), followed by chromatography in benzene–ether (80 : 20), afforded the hydroxy derivative *X* (697 mg; 97%), m.p. 148–150°C, identical with an authentic sample[6].

b) The EE-derivative *VIII* (861 mg) afforded the title hydroxy derivative *X* (681 mg; 95%), m.p. 148–150°C, identical with the compound prepared by procedure *a*).

c) The ME-derivative *IX* (833 mg) afforded, after crystallization from ether–light petroleum, the hydroxy derivative *X* (694 mg; 97%), m.p. 148–150°C, identical with the sample prepared according to procedure *a*).

Ethyl (20*E*)-3β-*hydroxy*-5,20-*pregnadiene*-21-*carboxylate* (XIV).

a) The THP-derivative *XI* (909 mg) afforded the hydroxy derivative *XIV* (670 mg; 94%), m.p. 132–134°C (ether–hexane); $[\alpha]_D$ −41° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 607, 3 460 (OH); 1 718, 1 650 (C=C—COOR). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, $J(17, 20) = 7{\cdot}7$; $J(20,21) = 15{\cdot}8$); 5·75 dd, 1 H (H-21, $J(17, 21) = 1{\cdot}0$; $J(20, 21) = 15{\cdot}8$); 5·35 bd, 1 H (H-6, $J = 4{\cdot}5$); 4·17 q, 2 H ($COOCH_2CH_3$, $J = 7{\cdot}3$); 3·51 m, 1 H (H-3, $W = 36$); 1·29 t, 3 H ($COOCH_2CH_3$, $J = 7{\cdot}3$); 1·02 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{24}H_{36}O_3$ (372·6) calculated: 77·38% C, 9·74% H; found: 77·12% C, 9·85% H.

b) The EE-derivative *XII* (889 mg) afforded the hydroxy derivative *XIV* (722 mg; 97%), m.p. 132–134°C (ether–hexane), identical with the product prepared by procedure *a*).

c) The ME-derivative *XIII* (861 mg) afforded, after crystallization from light petroleum–ether, the hydroxy derivative *XIV* (725 mg; 97%), m.p. 133–134°C, identical with the product prepared by procedure *a*).

Methyl (20*E*)-3β-*hydroxy*-5α-*pregn*-20-*ene*-21-*carboxylate* (XXIV). The methyl ester *XXII* (889 mg) afforded the hydroxy derivative *XXIV* (706 mg; 98%), m.p. 132–134°C (hexane); $[\alpha]_D$ +29° (*c* 0·3, chloroform). Reported[7] m.p. 87°C. IR spectrum (chloroform): 3 610, 3 460 (OH); 1 711, 1 651 (C=C—COOR). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, $J(17, 20) = 7{\cdot}6$; $J(20, 21) = 15{\cdot}6$); 5·77 dd, 1 H (H-21, $J(17, 21) = 1{\cdot}1$; $J(20, 21) = 15{\cdot}6$); 3·72 s, 3 H ($COOCH_3$); 0·81 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{23}H_{36}O_3$ (360·5) calculated: 76·62% C, 10·06% H; found: 76·87% C, 9·85% H.

Ethyl (20*E*)-3β-*hydroxy*-5α-*pregn*-20-*ene*-21-*carboxylate* (XXV). The ethyl ester *XXIII* (917 mg) afforded the hydroxy derivative *XXV* (719 mg; 96%), m.p. 133–135°C (ether–hexane); $[\alpha]_D$ +29° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 610, 3 490 (OH); 1 706, 1 648 (C=C—COOR). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, $J(17, 20) = 7{\cdot}6$; $J(20, 21) = 15{\cdot}7$); 5·75 dd, 1 H (H-21, $J(17, 21) = 1{\cdot}0$; $J(20, 21) = 15{\cdot}7$); 4·18 q, 2 H ($COOCH_2CH_3$, $J = 7{\cdot}4$); 3·59 m, 1 H (H-3, $W = 40$); 1·29 t, 3 H ($COOCH_2CH_3$, $J = 7{\cdot}4$); 0·82 s, 3 H (3 × H-19); 0·64 s, 3 H (3 × H-18). For $C_{24}H_{38}O_3$ (374·6) calculated: 76·96% C, 10·23% H; found: 76·98% C, 10·15% H.

Methyl (20*E*)-3α-*hydroxy*-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXVI). The methyl ester *XXXIV*

(889 mg) afforded the hydroxy derivative *XXXVI* (663 mg; 92%), m.p. 153–155°C (ether–hexane); $[\alpha]_D$ +29° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 615, 3 490 (OH); 1 707, 1 650 (C=C—COOR). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, *J*(17, 20) = 7·7; *J*(20, 21) = 15·6); 5·77 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20, 21) = 15·6); 4·04 m, 1 H (H-3, *W* = 12); 3·72 s, 3 H ($COOCH_3$); 0·78 s, 3 H (3 × H-19); 0·64 s, 3 H (3 × H-18). For $C_{23}H_{36}O_3$ (360·5) calculated: 76·62% C, 10·06% H; found: 76·77% C, 10·23% H.

Ethyl (20*E*)-3α-*hydroxy*-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXVII). The ethyl ester *XXXV* (917 mg) afforded the hydroxy derivative *XXXVII* (719 mg; 96%), m.p. 137–139°C (ether–hexane); $[\alpha]_D$ +31° (*c* 1·5, chloroform). IR spectrum (chloroform): 3 615, 3 480 (OH); 1 706, 1 649 (C=C—COOR). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, *J*(17, 20) = 7·8; *J*(20, 21) = 16·0); 5·76 dd, 1 H (H-21, *J*(17, 21) = 1·2; *J*(20, 21) = 16·0); 4·22 q, 2 H ($COOCH_2CH_3$, *J* = 7·3); 4·03 m, 1 H (H-3); 1·28 t, 3 H ($COOCH_2CH_3$, *J* = 7·3); 0·78 s, 3 H (3 × H-19); 0·64 s, 3 H (3 × H-18). For $C_{24}H_{38}O_3$ (374·6) calculated: 76·96% C, 10·23% H; found: 77·25% C, 10·45% H.

General Procedure for Preparation of Hemisuccinate *XXVIII*, *XXIX*, *XL* and *XLI*

2-(Trimethylsilyl)ethyl hydrogen butanedioate[9] (415 mg, 1·9 mmol) and 4-dimethylaminopyridine (7 mg, 60 μmol) were added to a solution of the hydroxy derivative (1 mmol) in tetrahydrofuran (4·5 ml). After addition of 0·5M solution of N,N′-dicyclohexylcarbodiimide in benzene (2·5 ml), the reaction mixture was stirred at room temperature for 6 h, diluted with light petroleum (10 ml) and set aside for 10 min. The separated N,N′-dicyclohexylurea was filtered off, washed with light petroleum and the filtrate was evaporated in vacuo. The residue was chromatographed on a column of silica gel (35 g) in light petroleum–benzene–ether (50 : 49 : 1). After washing out nonpolar impurities, the chromatography was continued with light petroleum–benzene–ether (50 : 48 : 2). The eluted succinate was characterized only by the IR spectrum and dissolved in tetrahydrofuran (10 ml). To this solution was added 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (2 ml). After stirring at room temperature for 8 h, the reaction mixture was diluted with benzene (200 ml) and washed with 10% sulfuric acid (2×) and water (3×). The solvent was evaporated and the residue crystallized from hexane–dichloromethane at −78°C to give the desired hemisuccinate.

(20*E*)-21-*Methoxycarbonyl*-5α-*pregn*-20-*en*-3β-*yl hydrogen butanedioate* (XXVIII). The hydroxy derivative *XXIV* (360 mg) afforded the succinate *XXVI* (540 mg). IR spectrum (tetrachloromethane): 1 731, 1 653 (C=C—COOR); 1 253, 860, 839 (Si–C). The succinate *XXVI* was further converted into the hemisuccinate *XXVIII* (250 mg; 54%), m.p. 129–132°C; $[\alpha]_D$ +15° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 500–2 500, 1 717 (COOH); 1 717, 1 651 (C=C—COOR); 1 717 (COOR). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, *J*(17, 20) = 7·5; *J*(20,21) = 16·0); 5·77 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20, 21) = 16·0); 3·72 s, 3 H ($COOCH_3$); 2·62 s, 4 H ($OOCCH_2CH_2COO$); 0·82 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{27}H_{40}O_6$ (460·6) calculated: 70·41% C, 8·75% H; found: 70·67% C, 9·03% H.

(20*E*)-21-*Ethoxycarbonyl*-5α-*pregn*-20-*en*-3β-*yl hydrogen butanedioate* (XXIX). The hydroxy derivative *XXV* (374 mg) afforded the succinate *XXVII* (557 mg). IR spectrum (tetrachloromethane): 1 732, 1 162 (COOR); 1 715, 1 650 (C=C—COOR); 1 252, 861, 839 (Si–C). The succinate *XXVII* was then converted into the hemisuccinate *XXIX* (275 mg; 58%), m.p. 110–113°C; $[\alpha]_D$ +20° (*c* 0·4, chloroform). IR spectrum (chloroform): 3 500–2 500, 1 715 (COOH); 1 715, 1 650 (C=C—COOR); 1 715 (COOR). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, *J*(17, 20) = 7·7; *J*(20, 21) = 16·0); 5·77 dd, 1 H (H-21, *J*(17, 21) = 0·6; *J*(20, 21) = 16·0); 4·18 q, 2 H ($COOCH_2CH_3$, *J* = 7·0); 2·62 s, 4 H ($OOCCH_2CH_2COO$); 1·28 t, 3 H

($COOCH_2CH_3$, J = 7·0); 0·82 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{28}H_{42}O_6$ (474·6) calculated: 70·86% C, 8·92% H; found: 71·01% C, 8·93% H.

(20*E*)-21-*Methoxycarbonyl*-5α-*pregn*-20-*en*-3α-*yl hydrogen butanedioate* (XL). The hydroxy derivative *XXXVI* (360 mg) afforded the succinate *XXXVIII* (521 mg). IR spectrum (tetrachloromethane): 1 731, 1 653 (C=C—COOR); 1 731 (COOR); 1 253, 860, 839 (Si–C). The succinate *XXXVIII* was then further converted into the hemisuccinate *XL* (270 mg; 59%), m.p. 122—125°C; $[\alpha]_D$ +40° (*c* 0·1, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 717 (COOH); 1 717, 1 652 (C=C—COOR); 1 717 (COOR). ^{1}H NMR spectrum (100 MHz): 6·96 dd, 1 H (H-20, J(17, 20) = 7·8; J(20,21) = 15·8); 5·77 dd, 1 H (H-21, J(17, 21) = 1·0; J(20,21) = 15·8); 5·06 m, 1 H (H-3, W = 14); 3·73 s, 3 H ($COOCH_3$); 2·66 s, 4 H ($OOCCH_2CH_2COO$); 0·79 s, 3 H (3 × × H-19); 0·65 s, 3 H (3 × H-18). For $C_{27}H_{40}O_6$ (460·6) calculated: 70·41% C, 8·75% H; found: 70·67% C, 8·89% H.

(20*E*)-21-*Ethoxycarbonyl*-5α-*pregn*-20-*en*-3α-*yl hydrogen butanedioate* (XLI). The hydroxy derivative *XXXVII* (374 mg) afforded the succinate *XXXIX* (542 mg). IR spectrum (tetrachloromethane): 1 732 (COOR); 1 732, 1 652 (C=C—COOR); 1 253, 861, 840 (Si–C). The succinate; *XXXIX* was further converted into the hemisuccinate *XLI* (318 mg; 67%), m.p. 118—120°C $[\alpha]_D$ +50° (*c* 0·1, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 717 (COOH); 1 717 (C=C—COOR); 1 717 (COOR). ^{1}H NMR spectrum (100 MHz): 6·95 dd, 1 H (H-20, J(17, 20) = = 7·8; J(20, 21) = 15·8); 5·77 dd, 1 H (H-21, J(17, 21) = 1·0; J(20,21) = 15·8); 5·05 m, 1 H (H-3, W = 14); 4·19 q, 2 H ($COOCH_2CH_3$, J = 7·3); 2·66 bs, 4 H ($OOCCH_2CH_2COO$); 1·28 t, 3 H ($COOCH_2CH_3$, J = 7·3); 0·79 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{28}H_{42}O_6$ (474·6) calculated: 70·86% C, 8·92% H; found: 71·01% C, 8·93% H.

General Procedure for Preparation of Glucosides *XXXII*, *XXXIII*, *XLIV*, and *XLV*

A dry mixture of the hydroxy derivative (1 mmol), silver silicate[12] (1·4 g) and ground molecular sieve 4A (2 g) was stirred in vacuo (10 Pa) for 4 h. The flask was then filled with argon under slight overpressure (about 5 kPa) and 1,2-dichloroethane (20 ml) was injected through a septum. The mixture was stirred at room temperature for 20 min and a solution of 2,3,4,6-tetra-O-acetyl--α-D-glucopyranosyl bromide (500 mg, 1·2 mmol) in 1,2-dichloroethane (3 ml) was added (through septum). After stirring at room temperature for 20 h, the catalyst was removed by filtration through a column of silica gel layered with Celite. The column was washed with chloroform–ether (4 : 1) and the combined filtrates were washed with 5% aqueous sodium hydrogen carbonate and water. The solvents were evaporated and the residue was dissolved in methanol (30 ml, in case of the methyl esters *XXIV* and *XXXVI*) or in ethanol (30 ml, in case of the ethyl esters *XXV* and *XXXVII*). After addition of 20 drops of 5% solution of the corresponding sodium alkoxide, the mixture was stirred at room temperature for 3 h, neutralized with dry ice (about 300 mg) and the solvent was evaporated in vacuo. The residue was chromatographed on a column of Silpearl (40 g) in chloroform–methanol (9 : 1, for compounds *XXXII* and *XLIV*) or in chloroform–ethanol (9 : 1, for compounds *XXXIII* and *XLV*). The product was further purified by crystallization.

Methyl (20*E*)-3β-(β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXII). The hydroxy derivative *XXIV* (360 mg) afforded, after crystallization from chloroform–methanol, the glucoside *XXXII* (340 mg; 65%), m.p. 232—234°C; $[\alpha]_D$ +12° (*c* 2·2, chloroform). IR spectrum (KBr): 3 430 (OH); 1 729, 1 656 (C=C—COOR); 1 158, 1 075, 1 015 (C–O). For $C_{29}H_{46}O_8$ (522·7) calculated: 66·64% C, 8·87% H; found: 66·87% C, 9·05% H.

Ethyl (20*E*)-3β-(β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXIII). The hydroxy derivative *XXV* (374 mg) afforded, after crystallization from ether–ethanol, the glucoside

XXXIII (260 mg; 49%), m.p. 223–226°C; $[\alpha]_D$ −5° (*c* 2·1, chloroform). IR spectrum (KBr): 3 420 (OH); 1 719, 1 653 (C=C—COOR). For $C_{30}H_{48}O_8$ (536·7) calculated: 67·14% C, 9·01% H; 66·89% C, 8·76% H.

Methyl (20*E*)-3α-(β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XLIV). The hydroxy derivative *XXXVI* (360 mg) afforded, after crystallization from ether, the glucoside *XLIV* (317 mg; 61%), m.p. 162–163°C; $[\alpha]_D$ +26° (*c* 4·0, chloroform). IR spectrum (KBr): 3 440, 3 370 (OH); 1 729, 1 653 (C=C—COOR); 1 148, 1 077, 1 043 (C–O). For $C_{29}H_{46}O_8$ (522·7) calculated: 66·64% C, 8·87% H; found: 66·92% C, 9·09% H.

Ethyl (20*E*)-3α-(β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XLV). The hydroxy derivative *XXXVII* (374 mg) afforded, after crystallization from ether, the glucoside *XLV* (280 mg; 52%), m.p. 112–113°C; $[\alpha]_D$ +23° (*c* 2·5, chloroform). IR spectrum (KBr): 3 420 (OH); 1 721, 1 649 (C=C—COOR); 1 094, 1 077, 1 037 (C–O). For $C_{30}H_{48}O_8$ (536·7) calculated: 67·14% C, 9·01% H; found: 67·32% C, 8·76% H.

General Procedure for Preparation of Tetracetates *XXX*, *XXXI*, *XLII* and *XLIII*

A solution of the glucoside (0·2 mmol) in a mixture of pyridine (1 ml) and acetic anhydride (1 ml) was allowed to stand overnight at room temperature. The mixture was coevaporated with toluene (3×), the residue was dissolved in ether, filtered through Celite and the solvent was evaporated in vacuo. The product was further purified by crystallization.

Methyl (20*E*)-3β-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXX). The glucoside *XXXII* (105 mg) was converted into the acetate *XXX* which was crystallized from ether; yield 130 mg (94%), m.p. 176–177°C; $[\alpha]_D$ +8° (*c* 2·0, chloroform). IR spectrum (tetrachloromethane): 1 762, 1 750 shoulder, 1 220, 1 041 (CH_3COO); 1 727, 1 653 (C=C—COOR). ^{1}H NMR spectrum (200 MHz): 6·94 dd, 1 H (H-20, J(17, 20) = 8·0; J(20, 21) = 15·7); 5·77 dd, 1 H (H-21, J(17, 21) = 1·1; J(20, 21) = 15·7); 5·20 t, 1 H (H-3′, J(3′, 2′) = 9·4; J(3′, 4′) = 9·2); 5·06 t, 1 H (H-4′, J(4′, 3′) = 9·2; J(4′, 5′) = 9·8); 4·94 dd, 1 H (H-2′, J(2′, 1′) = 7·9; J(2′, 3′) = 9·4); 4·59 d, 1 H (H-1′, J(1′, 2′) = 7·9); 4·26 dd, 1 H (H-6a′, J(6a′, 6b′) = 12·3; J(6a′, 5′) = 4·8); 4·11 dd, 1 H (H-6b′, J(6b′, 6a′) = 12·3; J(6b′, 5′) = 2·6); 3·72 s, 3 H ($COOCH_3$); 3·68 ddd, 1 H (H-5′, J(5′, 4′) = 9·8; J(5′, 6a′) = 4·8; J(5′, 6b′) = 2·6); 3·55 m, 1 H (H-3, W = 32); 2·08 s, 3 H (CH_3COO); 2·04 s, 3 H (CH_3COO); 2·02 s, 3 H (CH_3COO); 2·00 s, 3 H (CH_3COO); 0·79 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{37}H_{54}O_{12}$ (690·8) calculated: 64·33% C, 7·88% H; found: 64·55% C, 8·07% H.

Ethyl (20*E*)-3β-(2,3,4,6-*tetra*-0-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XXXI). The glucoside *XXXIII* (107 mg) was converted into the acetate *XXXI*, m.p. 167–168°C (ether), yield 132 mg (94%); $[\alpha]_D$ +7° (*c* 2·0, chloroform). IR spectrum (tetrachloromethane): 1 761, 1 750 shoulder, 1 219, 1 041 (CH_3COO); 1 719, 1 652 (C=C—COOR). ^{1}H NMR spectrum (200 MHz): 6·93 dd, 1 H (H-20, J(17, 20) = 7·9; J(20, 21) = 15·7); 5·76 dd, 1 H (H-21, J(17, 21) = 1·1; J(20, 21) = 15·7); 5·20 t, 1 H (H-3′, J(3′, 2′) = 9·3; J(3′, 4′) = 9·4); 5·06 t, 1 H (H-4′, J(4′, 3′) = 9·4; J(4′, 5′) = 9·5); 4·94 dd, 1 H (H-2′, J(2′, 1′) = 7·9; J(2′, 3′) = 9·3); 4·59 d, 1 H (H-1′, J(1′, 2′) = 7·9); 4·26 dd, 1 H (H-6a′, J(6a′, 6b′) = 12·2; J(6a′, 5′) = 4·8); 4·18 q, 2 H ($COOCH_2CH_3$), J = 7·1); 4·11 dd, 1 H (H-6b′, J(6b′, 6a′) = 12·2; J(6b′, 5′) = 2·6); 3·68 ddd, 1 H (H-5′, J(5′, 4′) = 9·5; J(5′, 6a′) = 4·8; J(5′, 6b′) = 2·6); 3·55 m, 1 H (H-3, W = 32); 2·08 s, 3 H (CH_3COO); 2·04 s, 3 H (CH_3COO); 2·02 s, 3 H (CH_3COO); 2·00 s, 3 H (CH_3COO); 1·29 t, 3 H ($COOCH_2CH_3$, J = 7·1); 0·79 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{38}H_{56}O_{12}$ (704·9) calculated: 64·75% C, 8·01% H; found: 65·03% C, 7·78% H.

Methyl (20*E*)-3α-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XLII). The glucoside *XLIV* (105 mg) was converted into the acetate *XLII*, which was crystallized from chloroform–ether; m.p. 185–187°C, yield 130 mg (94%); $[\alpha]_D$ +3° (*c* 3·0, chloroform). IR spectrum (tetrachloromethane): 1 760, 1 220, 1 041 (CH_3COO); 1 276, 1 653 (C=C—COOR). ^{1}H NMR spectrum (200 MHz): 6·94 dd, 1 H (H-20, *J*(17, 20) = 8·0; *J*(20, 21) = 15·7); 5·77 dd, 1 H (H-21, *J*(17,21) = 1·1; *J*(20,21) = 15·7); 5·21 t, 1 H (H-3′, *J*(3′, 2′) = 9·6; *J*(3′, 4′) = 9·3); 5·07 t, 1 H (H-4′, *J*(4′, 3′) = 9·3; *J*(4′, 5′) = 9·6); 5·00 d, 1 H (H-2′, *J*(2′, 1′) = 7·9; *J*(2′, 3′) = = 9·6); 4·54 d, 1 H (H-1′, *J*(1′, 2′) = 7·9); 4·24 dd, 1 H (H-6a′, *J*(6a′, 6b′) = 12·1; *J*(6a′, 5′) = = 4·9); 4·11 dd, 1 H (H-6b′, *J*(6b′, 6a′) = 12·1; *J*(6b′, 5′) = 2·6); 3·91 m, 1 H (H-3); 3·72 s, 3 H ($COOCH_3$); 3·66 ddd, 1 H (H-5′, *J*(5′, 4′) = 9·6; *J*(5′, 6a′) = 4·9; *J*(5′, 6b′) = 2·6); 2·07 s, 3 H (CH_3COO); 2·04 s, 3 H (CH_3COO); 2·02 s, 3 H (CH_3COO); 2·01 s, 3 H (CH_3COO); 0·77 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{37}H_{54}O_{12}$ (690·8) calculated: 64·33% C, 7·88% H; found: 64·61% C, 7·66% H.

Ethyl (20*E*)-3α-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carboxylate* (XLIII). The glucoside *XLV* (107 mg) was converted into the acetate *LXIII*, which was purified by crystallization from ether; yield 136 mg (97%); m.p. 179–182°C, $[\alpha]_D$ +12° (*c* 4·1, chloroform). IR spectrum (tetrachloromethane): 1 761, 1 220, 1 041 (CH_3COO); 1 718, 1 650 (C=C—COOR). ^{1}H NMR spectrum (200 MHz): 6·93 dd, 1 H (H-20, *J*(17, 20) = 8·1; *J*(20, 21) = 15·7); 5·77 dd, 1 H (H-21, *J*(17,21) = 1·1; *J*(20, 21) = 15·7); 5·22 t, 1 H (H-3′, *J*(3′, 2′) = 9·4; *J*(3′, 4′) = 9·4); 5·07 t, 1 H (H-4′, *J*(4′, 3′) = 9·4; *J*(4′, 5′) = 9·6); 5·00 dd, 1 H (H-2′, *J*(2′, 1′) = 7·8; *J*(2′, 3′) = = 9·4); 4·54 d, 1 H (H-1′, *J*(1′, 2′) = 7·8); 4·24 dd, 1 H (H-6a′, *J*(6a′, 6b′) = 12·2; *J*(6a′, 5′) = = 4·8); 4·18 q, 2 H ($COOCH_2CH_3$, *J* = 7·1); 4·11 dd, 1 H (H-6b′, *J*(6b′, 6a′) = 12·2; *J*(6b′, 5′)= = 2·5); 3·67 ddd, 1 H (H-5′, *J*(5′, 4′) = 9·6; *J*(5′, 6a′) = 4·8, *J*(5′, 6b′) = 2·5); 3·91 m, 1 H (H-3, *W* = 13); 2·07 s, 3 H (CH_3COO); 2·04 s, 3 H (CH_3COO); 2·02 s, 3 H (CH_3COO); 2·01 s 3 H (CH_3COO); 1·28 t, 3 H ($COOCH_2CH_3$, *J* = 7·1); 0·77 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × × H-18). For $C_{38}H_{56}O_{12}$ (704·9) calculated: 64·75% C, 8·01% H; found: 65·00% C, 8·26% H.

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