PREPARATION OF 21-METHOXYCARBONYL-21-METHYLENE--5-PREGNEN-3β-OL DERIVATIVES*

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Received March 20th, 1987

Reaction of 3β-methoxymethoxy-21-nor-5-pregnen-20-ol *p*-toluenesulfonate (*II*) with sodium dimethyl malonate afforded dimethyl 3β-methoxymethoxy-5-pregnene-21,21-dicarboxylate (*III*). Partial hydrolysis of *III*, followed by reaction with formaldehyde and diethylamine, gave methyl 3β-methoxymethoxy-21-methylene-5-pregnene-21-carboxylate (*XVI*) which was further transformed into hemisuccinate *XIX*.

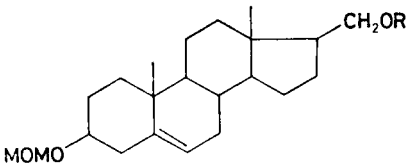
Derivatives of 21-methoxycarbonyl-21-methylenepregnane are analogues of cardenolids[1] in which the α,β-unsaturated lactone ring is replaced by an α,β-unsaturated ester moiety. Their described syntheses[2,3] use 21-methoxycarbonylpregnan-21--carboxylic acid derivatives as the key intermediates. They are synthesized from 17β-formylandrostane derivatives which are converted into derivatives of methyl (20*E*)-20-pregnene-21-carboxylate, using the Wittig–Horner reaction. The desired product is then obtained by hydrogenation of the double bond followed by carboxylation of lithium salt of the formed saturated ester. The side chain carbon atoms are thus added stepwise; the first two in the Wittig–Horner reaction and then the third one from carbon dioxide. Our present work studies the possible preparation of model 21-methoxycarbonyl-21-methylene-5-pregnene derivatives by combining the one--carbon side chain in position 17β with the malonate synthon.

As starting compound we chose the easily accessible[4] alcohol *I* whose tosylate *II* reacted with sodium salt of dimethyl malonate in boiling dioxane to give diester *III* in 47% yield. The structure of the compound *III* was confirmed by its IR spectrum, containing two bands of geminal ester carbonyl groups (1 756 cm^{-1} and 1 740 cm^{-1}). Its ^1H NMR spectrum exhibits, besides signals due to the steroid skeleton and the methoxymethyl protecting group, a singlet at δ 3·71 due to two methyl ester groups; the H-21 proton signal is obscured by the H-3 signal.

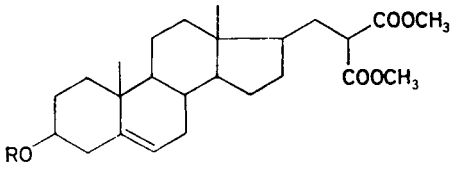
Removal of the protecting group in position 3 converted the compound *III* into

* Part CCCXXXIV in the series On Steroids; Part CCCXXXIII: Collect. Czech. Chem. Commun. *52*, 2521 (1987).

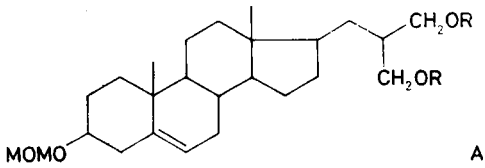
the hydroxy derivative *IV*. Its IR spectrum again displays two characteristic geminal ester carbonyl groups (1 750 cm^{-1} and 1 732 cm^{-1}) and also the molecular ion 418



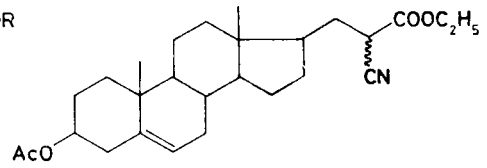
I, R = H
II, R = Tos



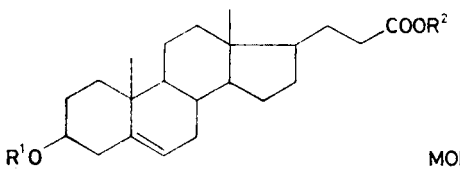
III, R = MOM
IV, R = H
V, R = $CONHCOCCl_3$



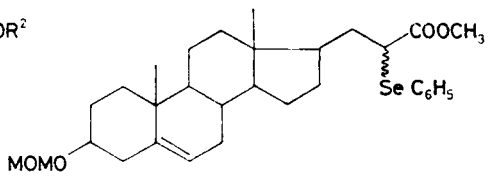
VI, R = H
VII, R = Ac



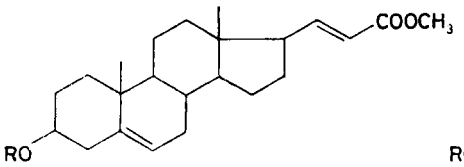
VIII



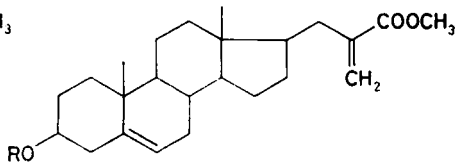
IX, $R^1 = R^2 = H$
X, $R^1 = Ac$; $R^2 = H$
XI, $R^1 = H$; $R^2 = CH_3$
XII, $R^1 = MOM$; $R^2 = CH_3$



XIII



XIV, R = MOM
XV, R = H



XVI, R = MOM
XVII, R = H
XVIII, R = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
XIX, R = $OCCH_2CH_2COOH$

Tos = *p*-toluenesulfonyl, MOM = CH_2OCH_3

in the mass spectrum agrees with the suggested structure. The H-21 signal in the ^{1}H NMR spectrum is obscured by the H-3 signal, however, on *in situ* acylation with trichloroacetyl isocyanate[5] (carbamate *V*) the H-3 signal is shifted downfield (δ 4·71) and the H-21 signal can be identified as a doublet of doublets (δ 3·35, $J = 6$; $J' = 7$). For further characterization we reduced both the ester groups in *III* with sodium bis(2-methoxyethoxy)aluminium hydride to obtain the diol *VI* which was further converted into the diacetate *VII*.

In order to verify its structure by chemical correlation, the dimethyl ester *III* was subjected to demethoxycarbonylation[6] by treatment with sodium cyanide in dimethyl sulfoxide. The obtained methyl ester *XII* was identical with the product obtained from the known[7] ester-nitrile *VIII* by hydrolysis combined with decarboxylation, conversion of the arising hydroxy acid *IX* into the methyl ester *XI* and protection of the 3-hydroxyl group with methoxymethyl group. In turn, the methyl ester *XII* was transformed into the dimethyl ester *III* by treatment with lithium diisopropylamide and reaction of the resulting lithium salt with methyl chloroformate[8]. Another structural proof was obtained by reaction of the above-mentioned lithium salt of methyl ester *XII* with diphenyl diselenide[9] and subsequent oxidative elimination[10] of the formed phenylselenyl derivative *XIII*. Structure of the obtained unsaturated ester *XIV* follows from the infrared spectrum (bands due to α,β-unsaturated ester 1 726 and 1 654 cm^{-1}) and from its ^{1}H NMR spectrum which contains signals of the H-20 proton (doublet of doublets δ 6·95) and of the H-21 proton (doublet δ 5·76). Also the observed coupling constants $J(20, 21) = 15{\cdot}8$ Hz and $J(17, 20) = 7{\cdot}2$ Hz agree with the values found previously for analogous derivatives[11]. Removal of the methoxymethyl group in position 3 converted the derivative *XIV* into the known[12] *XV*.

Partial hydrolysis of *III* with potassium hydroxide in methanol–benzene[13] afforded the monomethyl ester which on reaction with formaldehyde and diethylamine[2] furnished the α-methylene derivative *XVI*. The structure of the latter is confirmed by the exo-methylene signals at δ 6·09 and δ 5·52 and a singlet of the methyl ester group at δ 3·73 in its ^{1}H NMR spectrum. The chemical shifts and shape of the signals agree with those published[2] for analogous steroid derivatives. The methoxymethyl protecting group in position 3 was removed with hydrochloric acid in methanol–benzene and the obtained hydroxy derivative *XVII* was converted into the hemisuccinate *XIX* by an indirect method[14] *via* the intermediate *XVIII*. Structure of the compound *XIX* is confirmed by α,β-unsaturated ester (1 717, 1 630 cm^{-1}) and carboxyl (3 500–2 500, 1 717 cm^{-1}) bands in the infrared spectrum; the ^{1}H NMR spectrum exhibits signals of two exomethylene protons at δ 6·10 and δ 5·53, a methyl ester singlet at δ 3·75 and a narrow multiplet of the four succinate protons at δ 2·64.

Our synthesis of compound *XVI* from the alcohol *I* (reaction sequence $I \rightarrow II \rightarrow \rightarrow III \rightarrow XVI$) gives the desired product in 21% overall yield, about the same as

in the previously described syntheses[2,3] starting from 17β-formylandrostane derivatives. The advantage of the employed reaction sequence is in avoiding intermediates with carbonyl group in position 20 whose enolisability can limit the original synthesis.

EXPERIMENTAL

Melting points were determined on a melting-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 580 spectrometer (wavenumbers in cm^{-1}). ^1H NMR spectra were taken on Tesla BS-467 (60 MHz, CW mode) or Tesla BS-497 (100 MHz, FT mode) instruments at 23°C, in deuteriochloroform (*XIII* in tetrachloromethane) with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and bandwidths (W) in Hz. All values were obtained by first-order analysis. Mass spectra were taken on an AEI 901 spectrometer. Column chromatography was performed on silica gel (according to Pitra, 60 to 120 μm) or on neutral alumina (Reanal, activity II), thin-layer chromatography on silica gel G according to Stahl (Woelm). 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/25 Pa for 12 h. Identity of samples prepared by different routes was checked by comparison of their IR and ^1H NMR spectra, thin-layer chromatography and mixture melting point determinations.

3β-Methoxymethoxy-21-nor-5-pregnen-20-ol *p*-Toluenesulfonate (*II*)

p-Toluenesulfonyl chloride (4·9 g; 26 mmol) was added during 20 min to an ice-cooled solution of *I* (4·5 g; 13 mmol; ref.[4]) in pyridine. After stirring overnight at room temperature, the mixture was poured on ice. The precipitated product was collected, washed with water and dissolved in ether. The ethereal solution was washed successively with dilute (1 : 4) hydrochloric acid, water, saturated potassium hydrogen carbonate solution and water. Crystallization of the residue from light petroleum–acetone afforded 4·3 g (66%) of *II*, m.p. 121–123°C, $[\alpha]_D$ −31° (*c* 0·3, chloroform). IR spectrum (chloroform): 1 600 (aromatic system); 1 370, 1 188, 1 178 (—SO_2—); 1 150, 1 107, 1 048 (CH_3OCH_2O). ^1H NMR spectrum: 7·87 m, 2 H (arom. H); 7·26 m, 2 H (arom. H); 5·33 bd, 1 H (H-6, J = 4·5); 4·63 s, 2 H (OCH_2O); 3·75 bd, 2 H (H-20, J = 6); 3·33 s, 3 H (OCH_3); 2·43 s, 3 H (arom. CH_3); 0·98 s, 3 H (3 × H-19); 0·57 s, 3 H (3 × H-18). For $C_{29}H_{42}O_5S$ (502·7) calculated: 69·29% C, 8·42% H, 6·38% S; found: 69·22% C, 8·39% H, 6·39% S.

Dimethyl 3β-Methoxymethoxy-5-pregnen-21,21-dicarboxylate (*III*)

A) Dimethyl malonate (4 ml; 35 mmol) was added during 20 min to a suspension of sodium hydride (840 mg; 35 mmol) in dioxane (60 ml) in an argon atmosphere. After heating to 70°C for 20 min, a solution of tosylate *II* (5·03 g; 10 mmol) in dioxane (20 ml) was added. The stirred mixture was heated to 100°C for 20 h, the solvent was evaporated *in vacuo* and the residue was partitioned between ether and water. The aqueous layer was extracted with ether, the combined organic phases were washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and water. The solvent was evaporated and the residue was chromatographed on a column of silica gel (250 g). Elution with light petroleum–acetone (98 : 2) afforded 2·18 g (47%) of *III*, m.p. 105–107°C (hexane–ether), $[\alpha]_D$ −35° (*c* 0·4, chloroform). IR spectrum (tetrachloromethane): 1 756, 1 740 ($CH(COOR)_2$); 1 152, 1 108, 1 048 (CH_3OCH_2O); 3 033, 1 680 (C=C—H).

^{1}H NMR spectrum: 5·36 bd, 1 H (H-6, J = 5); 4·61 s, 2 H (OCH_2O); 3·71 s, 6 H (2 × $COOCH_3$); 3·35 s, 3 H (OCH_3); 1·01 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). Mass spectrum (m/z): 400 $(M - 62)^+$. For $C_{27}H_{42}O_6$ (462·6) calculated: 70·10% C, 9·15% H; found: 70·13% C, 9·39% H.

B) A solution of 1-butyllithium in hexane (1·9 ml, c 1·6 mol l^{-1}) was added at −78°C under argon to diisopropylamine (0·3 g; 3 mmol) in tetrahydrofuran (5 ml). After stirring at −78°C for 30 min, ester *XII* (780 mg; 1·9 mmol) in tetrahydrofuran (4 ml) was added and the mixture was stirred for 40 min at −78°C. Methyl chloroformate (0·23 ml; 3 mmol) was added, the stirring at −78°C was continued for 3 h and the mixture was decomposed with saturated aqueous solution of ammonium chloride. The product was extracted with ether, the ethereal phase was washed with saturated ammonium chloride solution, dried and taken down. Crystallization of the residue from light petroleum gave 650 mg (73%) of *III*, identical with the product prepared ad *A*).

Dimethyl 3β-Hydroxy-5-pregnen-21,21-dicarboxylate (*IV*)

A mixture of *III* (750 mg; 1·6 mmol), methanol (25 ml), benzene (25 ml), and concentrated hydrochloric acid (0·3 ml) was heated to 40°C for 7 h. The solvent was evaporated *in vacuo*, the residue was dissolved in ether and the ethereal phase was washed with potassium hydrogen carbonate solution and water. After drying and evaporation of the solvent, the residue was crystallized from light petroleum–ether to give 483 mg (71%) of *IV*, m.p. 87–90°C, $[\alpha]_D$ −33·5° (c 0·2, chloroform). IR spectrum (chloroform): 1 750, 1 732 (COOR); 3 612, 3 450 (OH). ^{1}H NMR spectrum: 5·41 bd, 1 H (H-6, J = 4·5); 3·71 s, 6 H (2 × $COOCH_3$), 3·70–3·15 bm, 2 H (H-21 and H-3); 1·00 s, 3 H (3 × H-19); 0·61 s, 3 H (3 × H-18). ^{1}H NMR spectrum (after addition of trichloroacetyl isocyanate): 8·35 s, 1 H ($Cl_3CCONHCO$); 5·40 bd, 1 H (H-6, J = 4·5); 4·71 m, 1 H (H-3, W = 35); 3·72 s, 6 H (2 × $COOCH_3$); 3·35 dd, 1 H (H-21, J = 6, J' = 7); 1·03 s, 3 H (3 × H-19); 0·64 s, 3 H (3 × H-18). Mass spectrum (m/z): 418 M^+, 400 $(M - H_2O)^+$. For $C_{25}H_{38}O_5$ (418·6) calculated: 71·74% C, 9·15% H; found: 71·62% C, 9·01% H.

3β-Methoxymethoxy-21,21-bis(hydroxymethyl)-5-pregnene (*VI*)

A solution of sodium bis(2-methoxyethoxy)aluminium hydride in benzene (1·5 ml; c 3·5 mol l^{-1}) was added to a solution of *III* (400 mg; 0·86 mmol) in tetrahydrofuran (35 ml). After refluxing for 2 h under argon, the mixture was decomposed with water and dilute (1 : 4) hydrochloric acid and extracted with ether. The combined organic extracts were washed successively with dilute hydrochloric acid, water, potassium hydrogen carbonate solution, and again with water. The solvent was evaporated and the residue chromatographed on a column of silica gel (35 g) in chloroform–acetone (9 : 1), affording 237 mg (67%) of *VI*, m.p. 171–173°C (hexane–ether–chloroform), $[\alpha]_D$ −35° (c 0·2, chloroform). IR spectrum (chloroform): 3 626, 3 470 (OH); 1 150, 1 105, 1 037 (CH_3OCH_2O); 1 668 (C=C). ^{1}H NMR spectrum: 5·33 s, 1 H (H-6, J = 4·5); 4·66 s, 2 H (OCH_2O); 3·68 m, 4 H (2 × OCH_2-21); 3·35 s, 3 H (OCH_3); 1·02 s, 3 H (3 × H-19); 0·60 s, 3 H (3 × H-18). Mass spectrum (m/z): 344 $(M - 62)^+$. For $C_{25}H_{42}O_4$ (406·6) calculated: 73·85% C, 10·41% H; found: 74·01% C, 10·28% H.

3β-Methoxymethoxy-21,21-bis(acetoxymethyl)-5-pregnene (*VII*)

A mixture of *VI* (210 mg; 0·5 mmol), pyridine (2 ml), and acetic anhydride (0·5 ml) was allowed to stand for 24 h at room temperature and then poured on ice. The product was taken up in ethyl acetate, the organic layer was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate and water. Chromatography on a silica gel column (30 g) in benzene–acetone (98 : 2), followed by crystallization from acetone–methanol, afforded 127 mg (91%) of *VII*, m.p.

54—55°C; $[\alpha]_D$ —33° (*c* 0·2, chloroform). IR spectrum (chloroform): 1 743, 1 226 ($OOCCH_3$); 1 150, 1 106, 1 048, 917 (CH_3OCH_2O), 1 669 (C=C). ^{1}H NMR spectrum: 5·35 bd, 1 H (H-6, J = 4·5); 4·68 s, 2 H (OCH_2O); 4·05 s, 4 H (2 × $AcOCH_2$-21); 3·35 s, 3 H (OCH_3); 2·03 s, 6 H (2 × $OOCCH_3$); 1·00 s, 3 H (3 × H-19); 0·58 s, 3 H (3 × H-18). Mass spectrum (*m/z*): 428 $(M - 62)^+$. For $C_{29}H_{46}O_6$ (490·7) calculated: 70·99% C, 9·45% H; found: 71·04% C, 9·65% H.

3β-Acetoxy-5-pregnene-21-carboxylic Acid (*X*)

A mixture of *VIII* (2 g; 4·5 mmol, ref.[7]), potassium hydroxide (4·6 g), and ethylene glycol (100 ml) was refluxed for 33 h, cooled, poured into water (1 l) and acidified with hydrochloric acid. The product was taken up in ethyl acetate, the extract was washed with water, decolorized with charcoal and the solvent was evaporated. The residue was crystallized from methanol to give 1·12 g (68%) of the acid *IX*. IR spectrum (chloroform): 3 500—2 500 br, 1 706 (COOH); 3 380 (OH). A mixture of *IX* (600 mg; 1·65 mmol), pyridine (3·7 ml), and acetic anhydride (2·5 ml) was set aside at room temperature overnight. Water (2·5 ml) was added and the mixture was refluxed for 1 h. After standing for 24 h at + 5°C, the product was collected on filter, washed with water and dried in a desiccator over phosphorus pentoxide at 26 Pa; yield 584 mg (63% from *VIII*) of *X*, m.p. 194—196·5°C, $[\alpha]_D$ —49° (*c* 0·1, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 712 (COOH); 1 730, 1 258 ($OOCCH_3$). ^{1}H NMR spectrum: 5·36 bd, 1 H (H-6, J = 4·5); 4·57 m, 1 H (H-3, W = 36); 1·99 s, 3 H ($OOCCH_3$); 1·00 s, 3 H (3 × H-19); 0·58 s, 3 H (3 × H-18). Mass spectrum (*m/z*): 328 $(M - 60)^+$. For $C_{24}H_{36}O_4$ (388·6) calculated: 74·19% C, 9·34% H; found: 74·30% C, 9·27% H.

Methyl 3β-Hydroxy-5-pregnene-21-carboxylate (*XI*)

A mixture of *IX* (520 mg; 1·4 mmol; see the preceding experiment), anhydrous potassium carbonate (800 mg; 5·8 mmol), dimethyl sulfate (0·37 ml; 3·9 mmol), and acetone (8·4 ml) was refluxed with stirring for 5 h, cooled and diluted with a mixture of ether and dichloromethane (1 : 1; 200 ml). The solution was filtered through a column of alumina (30 g), the column was washed with the same solvent mixture and the solvents were evaporated *in vacuo*. Crystallization of the residue from acetone gave 400 mg (83%) of *XI*, m.p. 140—143°C; $[\alpha]_D$ —63° (*c* 0·1, chloroform). IR spectrum (chloroform): 3 610, 3 490 (OH); 1 728 (COOR). ^{1}H NMR spectrum: 5·33 bd, 1 H (H-6, J = 4·5); 3·63 s, 3 H ($COOCH_3$); 0·98 s, 3 H (3 × H-19); 0·59 s, 3 H (3 × H-18). Mass spectrum (*m/z*): 360 $(M)^+$. For $C_{23}H_{36}O_3$ (360·5) calculated: 76·62% C, 10·06% H; found: 76·75% C, 9·76% H.

Methyl 3β-Methoxymethoxy-5-pregnene-21-carboxylate (*XII*)

A) N,N-Dimethylaniline (1·7 ml; 13 mmol) and chloromethyl methyl ether (1 ml; 13 mmol) were added to a solution of *XI* (3·0 g; 8 mmol) in dichloromethane (40 ml). After standing at room temperature for 48 h, the mixture was poured in water, the product was taken up in ether and the extract was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate, and water. The solvent was evaporated and the residue chromatographed on a silica gel column (200 g) in benzene–ether (98 : 2); yield 2·68 g (87%) of *XII*, m.p. 115—116°C; $[\alpha]_D$ —42° (*c* 0·2, chloroform). IR spectrum (chloroform): 1 730 (COOR); 1 150, 1 106, 1 044, 913 (CH_3OCH_2O). ^{1}H NMR spectrum: 5·35 bd, 1 H, (H-6, J = 4·5); 4·68 s, 2 H (OCH_2O); 3·63 s, 3 H ($COOCH_3$); 3·33 s, 3 H (OCH_3); 1·00 s, 3 H (3 × H-19); 0·60 s, 3 H (3 × H-18). Mass spectrum (*m/z*): 342 $(M - C_2H_6O_2)^+$. For $C_{25}H_{40}O_4$ (404·6) calculated: 74·22% C, 9·97% H; found: 74·49% C, 9·74% H.

B) A mixture of *III* (250 mg; 0·54 mmol), sodium cyanide (50 mg; 1 mmol), and dimethyl sulfoxide (3 ml) was heated in an argon atmosphere for 6 h. After cooling, the mixture was partitioned between ether and water, the aqueous layer was extracted with ether and the combined organic phases were washed with water and taken down. The residue was chromatographed on a column of silica gel (15 g) in light petroleum–acetone (95 : 5), affording 125 mg (57%) of *XII*, identical with the product obtained under *A*).

Methyl (20*E*)-3β-Methoxymethoxy-5,20-pregnadiene-21-carboxylate (*XIV*)

A solution of 1-butyllithium in hexane (0·93 ml; *c* 1·6 mol l^{-1}) was added at −78°C under argon to a solution of diisopropylamine (152 mg; 1·5 mmol) in tetrahydrofuran (3 ml). After stirring for 30 min at −78°C, methyl ester *XII* (405 mg; 1 mmol) in tetrahydrofuran (2 ml) was added, followed, after stirring for 40 min at −78°C, by diphenyl diselenide (468 mg; 1·5 mmol) in tetrahydrofuran (4 ml). The mixture was stirred for 1 h at −78°C for 30 min at 0°C and then poured into saturated aqueous solution of ammonium sulfate. The product was extracted with ethyl acetate, the extract was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution, and water. The solvent was evaporated and the residue chromatographed on a column of silica gel (40 g). Light petroleum–benzene (1 : 1) eluted the unreacted diphenyl diselenide, light petroleum–benzene–ethyl acetate (50 : 49 : 1) washed out 412 mg (74%) of the oily *XIII*. ^{1}H NMR spectrum (tetrachloromethane): 7·53 m and 7·27 m, 5 H (C_6H_5Se); 5·28 m, 1 H (H-6); 4·54 s, 2 H (OCH_2O); 3·57 s, 3 H ($COOCH_3$); 3·26 s, 3 H (OCH_3); 1·00 s, 3 H (3 × H-19); 0·58 s, 3 H (3 × H-18). Acetic acid (0·15 ml) and 30% hydrogen peroxide (0·3 ml) were added at 0°C to a solution of *XIII* (388 mg; 0·69 mmol) in tetrahydrofuran (3 ml) and, after stirring for 30 min at room temperature, the mixture was poured into a solution of potassium hydrogen carbonate. The product was taken up in ether, the ethereal extract was washed with saturated aqueous sodium sulfite and with water and the solvent was evaporated. The residue was chromatographed on a silica gel column (40 g) in light petroleum–benzene–ether (50 : 48 : 2), affording 224 mg (59% based on *XII*) of *XIV*, m.p. 145–147°C (hexane); $[\alpha]_D$ −33° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 1 726, 1 654 (C=C—COOR); 1 148, 1 106, 1 041, 917 (CH_3OCH_2O). ^{1}H NMR spectrum: 6·95 dd, 1 H (H-20, *J*(17, 20) = 7·2, *J*(20, 21) = = 15·8); 5·76 d, 1 H (H-21, *J*(20, 21) = 15·8); 5·34 bd, 1 H (H-6, *J* = 4·5); 4·68 s, 2 H (OCH_2O); 3·71 s, 3 H ($COOCH_3$); 3·35 s, 3 H (OCH_3); 1·00 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{25}H_{38}O_4$ (402·6) calculated: 74·59% C, 9·51% H; found: 74·77% C, 9·45% H.

Methyl (20*E*)-3β-Hydroxy-5,20-pregnadiene-21-carboxylate (*XV*)

Concentrated hydrochloric acid (30 µl) was added to a solution of *XIV* (114 mg; 0·28 mmol) in benzene (3 ml) and methanol (3 ml). After warming to 42°C for 11 h, the solvents were evaporated *in vacuo*, the residue was dissolved in benzene–ether (1 : 1), the solution filtered through a silica gel column (3 g) and taken down *in vacuo*. Crystallization from light petroleum–ether afforded 79 mg (78%) of *XV*, m.p. 146–148°C; $[\alpha]_D$ −59° (*c* 0·2, chloroform), identical with an authentic sample[12].

Methyl 3β-Methoxymethoxy-21-methylene-5-pregnene-21-carboxylate (*XVI*)

A solution of potassium hydroxide (73 mg; 1·3 mmol) in water (0·1 ml) was added to a solution of *III* (463 mg; 1 mmol) in a mixture of methanol (5 ml) and benzene (5 ml). After heating to 42°C for 7 h, the solvents were evaporated *in vacuo* and the residue was partitioned between dilute sulfuric acid (1 : 4, cooled to 0°C) and ether. The aqueous phase was extracted with ether

and the combined organic phases were washed with water. Evaporation of the solvents *in vacuo* afforded 480 mg of product which was immediately used in the next reaction. The product was mixed with methanol (1 ml), 37% aqueous formaldehyde (10 ml), and diethylamine (2·5 ml). After refluxing for 1 h with stirring, the mixture was poured into dilute (1 : 4) hydrochloric acid, the product was extracted with ether and the extract washed with dilute hydrochloric acid, water, solution of potassium hydrogen carbonate, and water, The evaporation residue was chromatographed on a column of silica gel (26 g) in light petroleum–benzene–ether (50 : 48 : 2) to give 281 mg (67%) of *XVI*, m.p. 97—98°C (hexane–ether); $[\alpha]_D$ −57° (*c* 1·5, chloroform). IR spectrum (tetrachloromethane): 1 723, 1 630 (C=C—COOR); 1 668 (C=C); 1 148, 1 105, 1 042, 916 (CH_3OCH_2O). ^{1}H NMR spectrum (100 MHz): 6·09 d, 1 H and 5·52 d, 1 H (C=CH_2, J = 1·5); 5·35 bd, 1 H (H-6, J = 4·5); 4·68 s, 2 H (OCH_2O); 3·73 s, 3 H ($COOCH_3$); 3·36 s, 3 H (OCH_3); 1·02 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{26}H_{40}O_4$ (416·6) calculated: 74·96% C, 9·68% H; found: 75·22% C, 9·55% H.

Methyl 3β-Hydroxy-21-methylene-5-pregnene-21-carboxylate (*XVII*)

Concentrated hydrochloric acid (70 µl) was added to a solution of *XVI* (265 mg; 0·64 mmol) in benzene (7 ml) and methanol (3 ml). The mixture was heated to 45°C for 8 h, the solvents were evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (20 g) in light petroleum–benzene–ether (45 : 45 : 10) to give 206 mg (87%) of *XVII*, m.p. 155—157°C (ether); $[\alpha]_D$ −69° (*c* 1·0, chloroform). IR spectrum (chloroform): 3 608, 3 465 (OH); 1 715, 1 630 (C=C—COOR); 1 668 (C=C). ^{1}H NMR spectrum (100 MHz): 6·09 d, 1 H and 5·53 d, 1 H (C=CH_2, J = 1·4); 5·35 bd, 1 H (H-6, J = 4·5); 3·74 s, 3 H ($COOCH_3$); 3·52 m, 1 H (H-3, W = 36); 1·02 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{24}H_{36}O_3$ (372·6) calculated: 77·38% C, 9·74% H; found: 77·24% C, 10·03% H.

21-Methoxycarbonyl-21-methylene-5-pregnen-3β-yl Hydrogen Butanedioate (*XIX*)

A solution of N,N′-dicyclohexylcarbodiimide (103 mg; 0·50 mmol) in benzene (3 ml), followed by 4-dimethylaminopyridine (3 mg), was added to a solution of *XVII* (170 mg; 0·45 mmol) and 2-(trimethylsilyl)ethyl hydrogen butanedioate[14] (186 mg; 0·85 mmol) in a mixture of tetrahydrofuran (5 ml) and benzene (2 ml). After stirring at room temperature for 24 h, the reaction mixture was diluted with light petroleum (10 ml), the precipitated N,N′-dicyclohexylurea was filtered off and the filtrate was taken down *in vacuo*. Chromatography on a column of silica gel (20 g) in light petroleum–benzene–ether (50 : 48 : 2) afforded 206 mg (79%) of oily *XVIII*. IR spectrum (tetrachloromethane): 1 735 (COOR); 1 735, 1 630 (C=C—COOR); 1 252, 860, 839 ($Si(CH_3)_3$). A solution of *XVIII* (165 mg; 0·29 mmol) in tetrahydrofuran (4 ml) was stirred with solution of tetrabutylammonium fluoride in tetrahydrofuran (0·6 ml, *c* 1 mol l^{-1}). After stirring at room temperature for 5 h, the mixture was diluted with benzene (150 ml), washed with dilute sulfuric acid (1 : 4) and water, and taken down. Crystallization from light petroleum–dichloromethane yielded 108 mg (63% based on *XVII*) of *XIX*, m.p. 144—146°C; $[\alpha]_D$ −51° (*c* 1·2, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 717 (COOH); 1 717, 1 630 (C=C—COOR). ^{1}H NMR spectrum (100 MHz): 6·10 d, 1 H and 5·53 d, 1 H (C=CH_2, J = 1·3); 5·38 bd, 1 H (H-6, J = 4); 4·63 m, 1 H (H-3, W = 36); 3·75 s, 3 H ($COOCH_3$); 2·64 m, 4 H ($OOCCH_2CH_2COO$); 1·03 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{28}H_{40}O_6$ (472·6) calculated: 71·16% C, 8·53% H; found: 71·31% C, 8·66% H.

We thank Mrs Z. Ledvinová for optical rotation determinations and Dr A. Trka for taking mass spectra. Our thanks are also due to Dr S. Vašíčková for measurement and interpretation of the

IR spectra, and to Mrs J. Jelínková and Mrs M. Snopková for the ^{1}H NMR *spectral measurements. The elemental analyses were carried out in the Analytical Laboratory of our Institute (Dr V. Pechanec, Head).*

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Translated by M. Tichý.