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Studies on Topical Antiinflammatory Corticosteroids. I. Syntheses and Vasoconstrictive Activities of 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17-Ester and 17,21-Diester Derivatives

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Seven 17-ester and thirty-eight 17,21-diester compounds (**3** and **4**) of 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (6α-methylprednisolone, **1**) were synthesized and thirty-eight selected compounds were tested for vasoconstrictive activity in humans. Except for $\mathbf{4g}_1$ and $\mathbf{4g}_2$, they were more active than the mother compound (**1**). In particular, the activities of ten compounds (**3b**—**g**, $\mathbf{4b}_{9,10}$, $\mathbf{4c}_{2,3}$, and $\mathbf{4c}_6$) were equal to or greater than that of 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV). The activities of 21-methoxyacetate compounds ($\mathbf{4b}_9$, $\mathbf{4c}_6$ and $\mathbf{4d}_5$) were potent. The structure–activity relationship is discussed.

Keywords——corticosteroid; 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione; 17α-acyloxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione; 17α,21-diacyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione; 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-cyclic ortho ester; esterification; vasoconstrictive activity; structure–activity relationship

The introduction of corticosteroids as topical antiinflammatory agents represents a new advance in dermatological therapy. Various potent topical halogenated corticosteroids are now widely used for the therapy of dermatological disorders.[1] However, systemic side effects such as hypothalamic-pituitary-adrenal axis depression have recently been observed during long-term topical application therapy with such corticosteroids.[2] Hence, corticosteroids for prolonged use should be systemically weak (*e.g.*, showing slow absorption and/or rapid metabolism).

In order to develop such active corticosteroids without appreciable systemic side effects, we have directed our attention to the introduction of certain ester groups into a corticosteroid skeleton without any halogen atom. This paper reports the synthesis, vasoconstrictive activities in human skin and structure–activity relationship of 17-ester and 17,21-diester derivatives (**3** and **4**) of 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (6α-methylprednisolone, **1**).[3]

Results and Discussion

Synthesis of 17-Ester Derivatives (3) of 6α-Methylprednisolone (1)

Seven 17-ester compounds (**3**) of **1** were synthesized by the route shown in Chart 1. 6α-

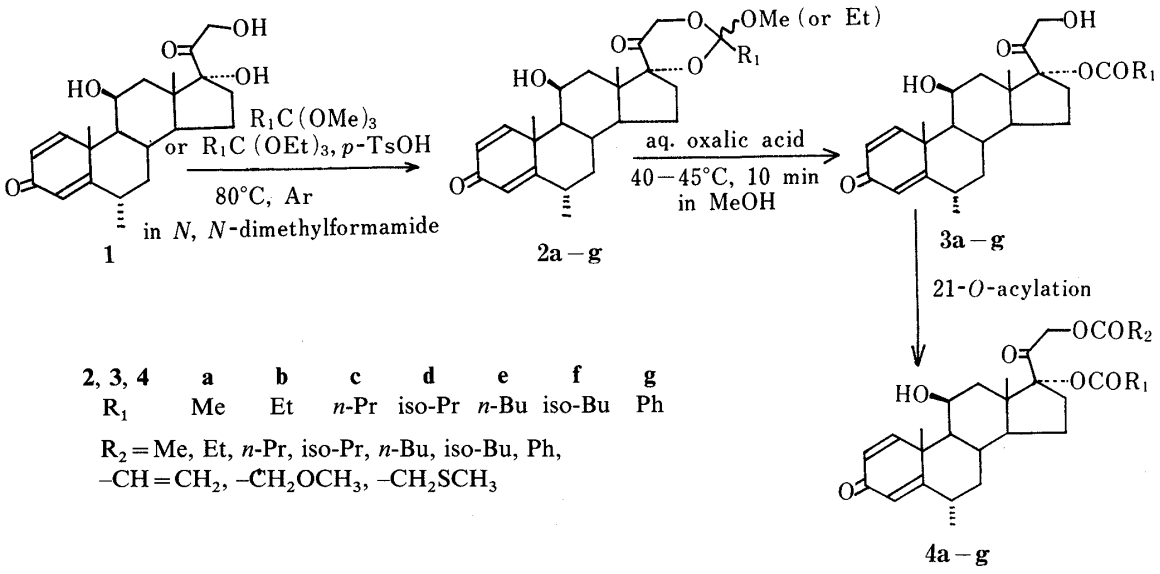

Chart 1

TABLE I. Yields, Physical Properties and Elementary Analyses of 6α-Methylprednisolone 17-Ester Derivatives (**3a—g**)

Compd. 3	Yield[a] (%)	mp (°C) (lit.[b])	*Rf* value[c]	Formula	Analysis (%) Found (Calcd)	
					C	H
3a	69.8	200—202 (198—201)	0.50	$C_{24}H_{32}O_6$	69.27 (69.21)	7.81 (7.74)
3b	78.3	209—212 (214)	0.52	$C_{25}H_{34}O_6$	69.85 (69.74)	8.03 (7.96)
3c	74.8	Amorphous	0.52	$C_{26}H_{36}O_6$	70.48 (70.25)	7.99 (8.16)
3d	77.3	Amorphous	0.52	$C_{26}H_{36}O_6$	70.15 (70.25)	8.33 (8.16)
3e	90.2	Amorphous	0.53	$C_{27}H_{38}O_6$	70.91 (70.71)	8.24 (8.35)
3f	69.5	Amorphous (164)	0.53	$C_{27}H_{38}O_6$	70.58 (70.71)	8.31 (8.35)
3g	80.8	227—229 (230)	0.53	$C_{29}H_{34}O_6$	72.68 (72.78)	7.40 (7.16)

a) Isolated yield of homogeneous sample (TLC analysis). *b*) Schering A.-G., Japan Kokai Tokkyo Koho 8374698 (1983) [*Chem. Abstr.*, **99**, 38713*s* (1983)]. *c*) Benzene : EtOH = 7 : 1. Silica gel (Merck, Art. 5715).

Methylprednisolone 17,21-cyclic ortho esters (**2**) were prepared by the procedure reported previously.[4] Their acid-catalyzed hydrolysis[5] with oxalic acid followed by silica-gel preparative thin-layer chromatography (PTLC, $CH_2Cl_2 : Et_2O = 3 : 1$) gave the 17-esters (**3**) in good yields. The yields and physical properties of the compounds (**3**) are summarized in Table I.

Synthesis of 17,21-Diester Derivatives (4) of 6α-Methylprednisolone (1)

Thirty-eight 17,21-diester compounds (**4**) were obtained by acylation of the 17-ester compounds (**3**) with the corresponding carboxylic acid halides or carboxylic anhydrides in the presence of triethylamine, or the corresponding carboxylic acid and *N,N'*-dicyclohexylcarbodiimide (DCC) followed by silica-gel column chromatography (CH_2Cl_2) or PTLC

TABLE II. Yields, Physical Properties and Elementary Analyses of 6α-Methylprednisolone 17,21-Diester Derivatives (**4a—g**)

Compd. **4**	R_1	R_2	Method[a]	Yield[b] (%)	mp (°C) (lit.[c])	*Rf* value[d]	Formula	Analysis (%) Found (Calcd) C	H
4a$_1$	Me	Me	B	55.8	221—224 (216)	0.37	$C_{26}H_{34}O_7$	67.91 (68.10)	7.21 (7.47)
4a$_2$	Me	Et	B	59.2	162—164	0.38	$C_{27}H_{36}O_7$	68.52 (68.62)	7.93 (7.68)
4a$_3$	Me	*n*-Pr	B	73.7[e]	157—159	0.40	$C_{28}H_{38}O_7$	69.23 (69.12)	7.83 (7.87)
4a$_4$	Me	iso-Pr	B	57.6	177—179	0.40	$C_{28}H_{38}O_7$	69.06 (69.12)	8.03 (7.87)
4a$_5$	Me	*n*-Bu	A	54.0	148—150	0.42	$C_{29}H_{40}O_7$	69.60 (69.57)	8.15 (8.05)
4a$_6$	Me	iso-Bu	A	50.0	127—130	0.41	$C_{29}H_{40}O_7$	69.46 (69.57)	8.10 (8.05)
4a$_7$	Me	Ph	A	63.5	136—139	0.41	$C_{31}H_{36}O_7$	71.72 (71.52)	7.26 (6.97)
4b$_1$	Et	Me	B	56.9	129—131 (138)	0.38	$C_{27}H_{36}O_7$	68.42 (68.62)	7.42 (7.68)
4b$_2$	Et	Et	B	91.1[e]	114—116 (126)	0.40	$C_{28}H_{38}O_7$	69.08 (69.12)	7.87 (7.87)
4b$_3$	Et	*n*-Pr	B	54.4	113—115	0.40	$C_{29}H_{40}O_7$	69.59 (69.57)	7.82 (8.05)
4b$_4$	Et	iso-Pr	B	53.2	144—146	0.41	$C_{29}H_{40}O_7$	69.63 (69.57)	8.16 (8.05)
4b$_5$	Et	*n*-Bu	A	67.3	142—143	0.43	$C_{30}H_{42}O_7$	69.79 (70.01)	8.07 (8.23)
4b$_6$	Et	iso-Bu	A	50.4	125—126	0.42	$C_{30}H_{42}O_7$	69.86 (70.01)	8.35 (8.23)
4b$_7$	Et	Ph	A	66.0	Amorphous	0.43	$C_{32}H_{38}O_7$	71.63 (71.89)	7.26 (7.16)
4b$_8$	Et	$-CH=CH_2$	A	60.2	112—114	0.39	$C_{28}H_{36}O_7$	69.43 (69.40)	7.47 (7.49)
4b$_9$	Et	$-CH_2OCH_3$	C	47.0	Amorphous		$C_{28}H_{38}O_8$	66.67 (66.91)	7.51 (7.62)
4b$_{10}$	Et	$-CH_2SCH_3$	C	64.9	126—128		$C_{28}H_{38}O_7S$	64.68 (64.84)	7.66 (7.38)
4c$_1$	*n*-Pr	Me	B	78.9	159—161 (158)	0.38	$C_{28}H_{38}O_7$	69.31 (69.12)	8.04 (7.87)
4c$_2$	*n*-Pr	Et	B	88.8[e]	121—123 (126)	0.41	$C_{29}H_{40}O_7$	69.47 (69.57)	8.19 (8.05)
4c$_3$	*n*-Pr	*n*-Pr	B	95.4[e]	142—144	0.42	$C_{30}H_{42}O_7$	70.18 (70.01)	8.43 (8.23)
4c$_4$	*n*-Pr	iso-Pr	B	89.2[e]	155—157	0.43	$C_{30}H_{42}O_7$	70.03 (70.01)	8.42 (8.23)
4c$_5$	*n*-Pr	$-CH=CH_2$	C	63.1	130—132		$C_{29}H_{38}O_7$	70.13 (69.86)	7.54 (7.68)
4c$_6$	*n*-Pr	$-CH_2OCH_3$	C	58.9	112—113		$C_{29}H_{40}O_8$	67.66 (67.42)	7.85 (7.80)
4c$_7$	*n*-Pr	$-CH_2SCH_3$	C	68.7	173—174		$C_{29}H_{40}O_7S$	65.52 (65.39)	7.73 (7.57)
4d$_1$	iso-Pr	Me	B	81.0[e]	142—144	0.39	$C_{28}H_{38}O_7$	68.91 (69.12)	8.00 (7.87)
4d$_2$	iso-Pr	Et	B	88.7[e]	127—131	0.41	$C_{29}H_{40}O_7$	69.29 (69.57)	7.86 (8.05)
4d$_3$	iso-Pr	*n*-Pr	B	81.6[e]	121—124	0.43	$C_{30}H_{42}O_7$	69.95 (70.01)	8.14 (8.23)
4d$_4$	iso-Pr	iso-Pr	B	66.4	165—167	0.43	$C_{30}H_{42}O_7$	70.26 (70.01)	8.18 (8.23)
4d$_5$	iso-Pr	$-CH_2OCH_3$	C	77.4[e]	119—121		$C_{29}H_{40}O_8$	67.22 (67.42)	7.41 (7.39)
4d$_6$	iso-Pr	$-CH_2SCH_3$	C	58.3	136—138		$C_{29}H_{40}O_7S$	65.19 (65.39)	7.84 (7.57)
4e$_1$	*n*-Bu	Me	B	82.5[e]	175—177	0.40	$C_{29}H_{40}O_7$	69.43 (69.57)	8.15 (8.05)
4e$_2$	*n*-Bu	Et	B	83.3[e]	183—184	0.42	$C_{30}H_{42}O_7$	70.05 (70.01)	8.49 (8.23)
4e$_3$	*n*-Bu	*n*-Bu	A	69.7	212—213	0.45	$C_{32}H_{46}O_7$	70.81 (70.82)	8.63 (8.54)
4f$_1$	iso-Bu	Me	B	93.7[e]	179—181 (172)	0.39	$C_{29}H_{40}O_7$	69.33 (69.57)	8.14 (8.05)
4f$_2$	iso-Bu	Et	B	80.1[e]	164—165	0.43	$C_{30}H_{42}O_7$	70.28 (70.01)	8.22 (8.23)
4g$_1$	Ph	Me	B	87.8[e]	269—270 (258)	0.42	$C_{31}H_{36}O_7$	71.57 (71.52)	7.19 (6.97)
4g$_2$	Ph	Et	B	73.8[e]	246—248 (241)	0.44	$C_{32}H_{38}O_7$	72.12 (71.89)	7.32 (7.16)
4g$_3$	Ph	Ph	A	61.3	Amorphous	0.46	$C_{36}H_{38}O_7$	74.41 (74.21)	6.73 (6.57)

a) A; R_2COCl/Et_3N in CH_2Cl_2: B; $(R_2CO)_2O/Et_3N$ in CH_2Cl_2: C; R_2COOH/DCC in CH_2Cl_2. *b*) Isolated and overall yield from **2** unless otherwise stated. *c*) Schering A.-G., Japan Kokai Tokkyo Koho 8374698 (1983) [*Chem. Abstr.*, **99**, 38713*s* (1983)]. *d*) Benzene : EtOH = 10 : 1. Silica gel (Merck, Art. 5715). *e*) From isolated **3**.

($CH_2Cl_2 : Et_2O = 4—5 : 1$), in good yields (Chart 1). The yields and physical properties are listed in Table II.

Vasoconstrictive Activities in Human Skin

Thirty-eight selected compounds (**3** and **4**) were tested for vasoconstrictive activities in humans.[6] This test correlates well with the clinical efficacy of topical antiinflammatory corticosteroids.[6] The test was divided into experiments 1—4. Preparations of 0.01 w/w% vaseline ointment of these compounds were applied to the flexor aspects of both forearms of

TABLE III. Vasoconstrictive Activities of 6α-Methylprednisolone 17-Ester and 17,21-Diester Derivatives (**3** and **4**)

Compd. **3** and **4**	Vasoconstrictive activity[a]		Compd. **3** and **4**	Vasoconstrictive activity[a]	
	After 2 h	After 6 h		After 2 h	After 6 h
Experiment 1[b]			Experiment 3[b]		
3a	1.20[g]	0.85[g]	$\mathbf{4a}_1$	2.25[h]	1.10[g,h]
3b	2.60[h]	2.20[h]	$\mathbf{4a}_3$	2.15[g,h]	0.75[g]
3c	2.90[h]	2.55[h]	$\mathbf{4a}_4$	1.80[g,h]	0.40[g]
3e	2.15[h]	1.85[h]	$\mathbf{4a}_7$	2.25[h]	1.20[g,h]
$\mathbf{4c}_6$	2.70[h]	2.10[h]	$\mathbf{4b}_1$	2.80[h]	1.60[g,h]
$\mathbf{4e}_1$	2.20[h]	1.45[g,h]	$\mathbf{4b}_2$	2.70[h]	1.30[g,h]
$\mathbf{4f}_1$	2.40[h]	1.90[g,h]	$\mathbf{4b}_3$	2.55[h]	1.30[g,h]
$\mathbf{4g}_1$	0.40[g]	0.45[g]	$\mathbf{4b}_4$	2.40[h]	1.35[g,h]
Control			$\mathbf{4b}_8$	1.75[g,h]	0.75[g]
HC[c]	0.55[g]	0.25[g]	$\mathbf{4c}_1$	2.60[h]	1.85[h]
MP[d]	0.65[g]	0.50[g]	$\mathbf{4c}_4$	2.50[h]	1.30[g,h]
BV[e]	2.60	2.35	$\mathbf{4d}_1$	2.85[h]	1.55[g,h]
Experiment 2[b]			$\mathbf{4d}_3$	2.10[h]	1.55[g,h]
3d	2.90[h]	2.60[g,h]	Control		
3f	2.75[h]	2.25[h]	HC[c]	0.90[g]	0.25[g]
3g	2.65[h]	2.35[h]	MP[d]	0.60[g]	0.45[g]
$\mathbf{4a}_2$	2.30[h]	1.45[g,h]	BV[e]	2.70	2.20
$\mathbf{4b}_7$	2.45[h]	1.85[h]	Experiment 4[f]		
$\mathbf{4c}_2$	2.85[h]	2.40[h]	$\mathbf{4b}_9$	2.64[h]	1.86[h]
$\mathbf{4c}_3$	2.60[h]	2.40[h]	$\mathbf{4b}_{10}$	2.36[h]	1.93[h]
$\mathbf{4d}_2$	2.25[h]	1.55[h]	$\mathbf{4d}_5$	2.29[h]	1.64[h]
$\mathbf{4d}_4$	1.70[g,h]	1.30[g]	$\mathbf{4d}_6$	1.43	1.14
$\mathbf{4e}_2$	1.95[h]	1.50[h]	Control		
$\mathbf{4e}_3$	0.65[g]	0.60[g]	HC[c]	1.29[g]	0.57[g]
$\mathbf{4f}_2$	1.85[g]	1.70[h]	MP[d]	0.71[g]	0.29[g]
$\mathbf{4g}_2$	0.55[g]	0.80[g]	BV[e]	2.21	2.00
Control					
HC[c]	0.55[g]	0.80[g]			
MP[d]	0.50[g]	0.70[g]			
BV[e]	2.50	2.15			

a) Shown as mean value. The degrees of blanching were expressed as follows: 0, no blanching (normal skin); 1, slight; 2, moderate; 3, marked. *b*) Ten volunteers were used. *c*) 21-Acetoxy-11β,17α-dihydroxy-4-pregnene-3,20-dione (0.1 w/w%). *d*) 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (**1**). *e*) 9α-Fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione. *f*) Seven volunteers were used. *g*) $p<0.05$ for BV. *h*) $p<0.05$ for MP, using Wilcoxon's signed-ranks test.[7]

seven or ten healthy male volunteers according to the closed patch method (Finn Chamber, Epitest Ltd. Oy) and left undisturbed for 16 h. After removal of the ointment, the vasoconstrictive activities were evaluated twice (after 2 and 6 h). The degrees of blanching assessed independently by two evaluators were scored and averaged, and statistical analysis was carried out by using Wilcoxon's signed-ranks test.[7] The results are shown in Table III.

The compounds other than **3a**, $\mathbf{4d}_6$, $\mathbf{4e}_3$, $\mathbf{4g}_1$ and $\mathbf{4g}_2$ were significantly ($p<0.05$) more potent than the mother compound (**1**). In particular, the activities of the sixteen compounds, **3b—g**, $\mathbf{4b}_{7,9,10}$, $\mathbf{4c}_{1-3,6}$, $\mathbf{4d}_{2,5}$ and $\mathbf{4e}_2$, were equal to or greater ($p<0.05$) than that of 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV). On the other hand, the activities of $\mathbf{4a}_3$, $\mathbf{4a}_4$ and $\mathbf{4b}_2$ were relatively weak and were remarkably decreased after 6 h.

TABLE IV. Vasoconstriction Activity Ratios of Compounds **3** and **4** with Respect to Betamethasone 17-Valerate (BV)

17-Position	21-Position									
	OH	OCOMe (C2)[a]	OCOEt (C3)	OCO-*n*-Pr (C4)	OCO-iso-Pr (C4)	OCO-*n*-Bu (C5)	OCOPh (C7)	$OCOCH=CH_2$ (C3)	$OCOCH_2OCH_3$ (C3)	$OCOCH_2SCH_3$ (C3)
	3a	**4a**$_1$	**4a**$_2$	**4a**$_3$	**4a**$_4$		**4a**$_7$			
OCOMe (C2)[a]	0.46[b]	0.83	0.92	0.80	0.67		0.83			
	0.36[c]	0.50	0.67	0.34	0.18		0.55			
	3b	**4b**$_1$	**4b**$_2$	**4b**$_3$	**4b**$_4$		**4b**$_7$	**4b**$_8$	**4b**$_9$	**4b**$_{10}$
OCOEt (C3)	1.00	1.04	1.00	0.94	0.89		0.98	0.65	1.19	1.07
	0.94	0.73	0.59	0.59	0.61		0.86	0.34	0.93	0.97
	3c	**4c**$_1$	**4c**$_2$	**4c**$_3$	**4c**$_4$				**4c**$_6$	
OCO-*n*-Pr (C4)	1.12	0.96	1.14	1.04	0.93				1.04	
	1.09	0.84	1.12	1.12	0.59				0.89	
	3d	**4d**$_1$	**4d**$_2$	**4d**$_3$	**4d**$_4$				**4d**$_5$	**4d**$_6$
OCO-iso-Pr (C4)	1.16	1.06	0.90	0.78	0.68				1.04	0.65
	1.21	0.70	0.72	0.70	0.60				0.82	0.57
	3e	**4e**$_1$	**4e**$_2$			**4e**$_3$				
OCO-*n*-Bu (C5)	0.83	0.85	0.78			0.26				
	0.79	0.62	0.70			0.28				
	3f	**4f**$_1$	**4f**$_2$							
OCO-iso-Bu (C5)	1.10	0.92	0.74							
	1.05	0.81	0.79							
	3g	**4g**$_1$	**4g**$_2$							
OCOPh (C7)	1.06	0.15	0.22							
	1.09	0.19	0.37							

BV = 1.00. *a*) The number of carbon atoms of the ester group is shown in parentheses. *b*) Activity ratio to BV after 2 h. *c*) Activity ratio to BV after 6 h.

For the purpose of assessing the structure–activity relationship, the ratios of the activity of the compounds **3** and **4** to that of BV were calculated and are arranged into Table IV in relation to the number of carbon atoms of the ester groups at the 17- and 21-positions. The highest activity ratio was found with compounds **3** and **4** having a butyroyl or isobutyroyl group (C4 atoms) at the 17-position.[8] In the case of the 17-ester compounds **3**, the activities of the iso forms (**3d** and **3f**) were a little higher than those of the corresponding normal forms (**3c** and **3e**). The activity of the compound having bulky ester groups at both the 17- and 21-positions was low (**4e**$_3$). The activity of the 17-benzoate (**3g**) was comparable to that of BV, but the 21-acetate (**4g**$_1$) or 21-propanoate (**4g**$_2$) showed reduced activity. The activity of 21-methoxyacetates (**4b**$_9$, **4c**$_6$ and **4d**$_5$) was potent even though the 21-ester group is as large as 21-butyrate. In addition, in the case of compounds **4**, there seems to be a relationship between the *Rf* value and the vasoconstrictive activity, and the highest activity was observed with *Rf* values of 0.39—0.41.[9]

Experimental

All melting points were measured on a Yanagimoto micro melting apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-I spectrophotometer and mass spectra (MS) were determined on a Hitachi RM-50 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a Hitachi R-24 spectrometer (60 MHz) using tetramethylsilane as an internal standard in $CDCl_3$, and chemical shifts are shown in δ ppm. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. For column chromatography and PTLC, silica gel (Wako gel, C-200) and silica gel (Merck, Art. 5717) were used, respectively. The spectra of the products were consistent with the assigned structures.

General Procedure for the Preparation of 17α-Acyloxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione Derivatives (3a—g)——A 6α-methylprednisolone 17α,21-cyclic ethyl or methyl ortho ester (**2**; 1 mmol), obtained by the procedure described previously,[4b] was dissolved in MeOH (10 ml). Then, 2 N aqueous oxalic acid (1.5 ml) was added to the solution. The reaction mixture was stirred for 10 min at 40—45 °C, and concentrated *in vacuo*, then ethyl acetate (50 ml) was added and the whole was washed with water (30 ml × 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (column or PTLC) to give the product (**3**). The results are summarized in Table I. Spectral data for compounds (**3**) are as follows.

17α-Acetoxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (3a)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1710 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.95 (3H, s, C_{18}-H), 1.14 (3H, d, J=6 Hz, C_6-αCH_3), 1.45 (3H, s, C_{19}-H), 2.00 (3H, s, $COCH_3$), 4.28 (2H, s, C_{21}-H), 4.50 (1H, br, C_{11}-H), 6.02 (1H, br s, C_4-H), 6.27 (1H, dd, J= 10, 2 Hz, C_2-H), 7.28 (1H, d, J=10 Hz, C_1-H). MS *m/z*: 416 (M^+), 399, 398, 385, 356, 327, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 43.

11β,21-Dihydroxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (3b)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1725 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.98 (3H, s, C_{18}-H), 1.13 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$), 1.17 (3H, d, J=6 Hz, C_6-αCH_3), 1.46 (3H, s, C_{19}-H), 2.31 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 4.28 (2H, s, C_{21}-H), 4.48 (1H, br, C_{11}-H), 6.01 (1H, br s, C_4-H), 6.26 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS *m/z*: 430 (M^+), 413, 412, 399, 356, 327, 325, 297, 279, 239, 161, 136, 135 (base peak), 121, 91, 57.

17α-Butanoyloxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (3c)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1715 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 0.98 (3H, s, C_{18}-H), 0.96—1.05 (3H, m, $CH_2CH_2C\underline{H}_3$), 1.13 (3H, d, J=6 Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 4.28 (2H, s, C_{21}-H), 4.50 (1H, br, C_{11}-H), 6.03 (1H, br s, C_4-H), 6.27 (1H, dd, J=10, 2 Hz, C_2-H), 7.35 (1H, d, J=10 Hz, C_1-H). MS *m/z*: 444 (M^+), 427, 426, 413, 356, 327, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 71.

11β,21-Dihydroxy-17α-isobutanoyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (3d)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1710 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.95 (3H, s, C_{18}-H), 1.15 (6H, d, J=5 Hz, $-CH(C\underline{H}_3)_2$), 1.15 (3H, d, J=6 Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 4.23 (2H, s, C_{21}-H), 4.50 (1H, br, C_{11}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, d, J=10 Hz, C_1-H). MS *m/z*: 444 (M^+), 413, 358, 297, 279, 239, 225, 185, 161, 136, 135 (base peak), 121, 107, 71.

11β,21-Dihydroxy-6α-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (3e)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1725 (C=O), 1715 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 0.95 (3H, s, C_{18}-H), 0.88—1.25 (3H, m, $CH_2CH_2CH_2C\underline{H}_3$), 1.11 (3H, d, J=6 Hz, C_6-αCH_3), 1.52 (3H, s, C_{19}-H), 4.28 (2H, s, C_{21}-H), 4.52 (1H, br, C_{11}-H), 6.02 (1H, br s, C_4-H), 6.24 (1H, dd, J=10, 2 Hz, C_2-H), 7.38 (1H, d, J=10 Hz, C_1-H). MS *m/z*: 458 (M^+), 441, 440, 427, 356, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 85.

11β,21-Dihydroxy-17α-isovaleroyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (3f)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1710 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.90 (3H, s, C_{18}-H), 1.15 (6H, s-like, $-CH_2CH(C\underline{H}_3)_2$),

1.11 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 4.30 (2H, s, C_{21}-H), 4.50 (1H, br, C_{11}-H), 6.02 (1H, br s, C_4-H), 6.27 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.32 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 458 (M^+), 440, 356, 327, 325, 297, 279, 239, 187, 161, 136 (base peak), 135, 121, 107, 85.

17α-Benzoyloxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (3g)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1710 (C=O), 1705 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.04 (3H, s, C_{18}-H), 1.14 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 4.32 (2H, s, C_{21}-H), 4.57 (1H, br, C_{11}-H), 6.06 (1H, br s, C_4-H), 6.30 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.35 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 478 (M^+), 447, 401, 356, 338, 327, 309, 297, 279, 239, 161, 136, 135, 121, 105 (base peak), 91, 77.

General Procedure for the Preparation of 17α,21-Diacyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione Derivatives (4a—g)——a) Esterification of **3** Using Carboxylic Anhydride or Carboxylic Acid Chloride: An isolated compound (**3**; 1 mmol) or a crude product (**3**) obtained from **2** (1 mmol) by the procedure described above was dissolved in dry dichloromethane (6 ml). Then, a carboxylic anhydride (2 mmol) or a carboxylic acid chloride (2 mmol) and triethylamine (4 mmol) were added to the solution with stirring under ice cooling and the reaction mixture was stirred for 30 min to 3 h at ambient temperature. After completion of the reaction, the reaction mixture was concentrated *in vacuo* and ethyl acetate (50 ml) was added to the resulting residue. The mixture was washed with 0.5% Na_2CO_3 aq. solution (20 ml) and with water (30 ml × 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. From the resulting residue, **4** was isolated by PTLC on silica gel and crystallized from ether or ether–hexane.

b) Esterification of **3** Using Carboxylic Acid in the Presence of DCC: The reaction of an isolated **3** (1 mmol) or a crude product (**3**) obtained from **2** (1 mmol) with a carboxylic acid (4 mmol) in the presence of DCC (2 mmol) in dichloromethane (6 ml) with stirring for 24 h at ambient temperature followed by work-up similar to that described above afforded the product (**4**). The results are listed in Table II. Spectral data for **4** are as follows.

17α,21-Diacetoxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_1$)——IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1755 (C=O), 1730 (C_{17},C_{21}-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.03 (3H, s, C_{18}-H), 1.13 (3H, d, $J=7$ Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 2.05 (3H, s, C_{17}-$COCH_3$), 2.17 (3H, s, C_{21}-$COCH_3$), 4.47 (1H, br, C_{11}-H), 4.66, 4.96 (2H, dd, $J=16$ Hz, C_{21}-H), 6.01 (1H, br s, C_4-H), 6.25 (1H, dd, $J=10$ Hz, C_2-H), 7.27 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 458 (M^+), 441, 440, 338, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 43.

17α-Acetoxy-11β-hydroxy-6α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione ($4a_2$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.89—1.27 (9H, m, C_{18}-H, $CH_2C\underline{H}_3$ and C_6-αCH_3), 1.45 (3H, s, C_{19}-H), 2.02 (3H, s, $COCH_3$), 4.50 (1H, br, C_{11}-H), 4.59, 4.96 (2H, dd, $J=17$ Hz, C_{21}-H), 6.07 (1H, br s, C_4-H), 6.31 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.37 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 472 (M^+), 455, 454, 412, 346, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 57, 43.

17α-Acetoxy-21-butanoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_3$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1750 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.03 (3H, s, C_{18}-H), 1.12 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.44 (3H, s, C_{19}-H), 2.01 (3H, s, $COCH_3$), 4.46 (1H, br, C_{11}-H), 4.57, 4.94 (2H, dd, $J=17$ Hz, C_{21}-H), 6.01 (1H, br s, C_4-H), 6.26 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.27 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 486 (M^+), 479, 478, 426, 411, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 71, 43.

17α-Acetoxy-11β-hydroxy-21-isobutanoyloxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_4$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1745 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.02 (3H, s, C_{18}-H), 1.11 (3H, m, C_6-αCH_3), 1.21 (6H, d, $J=8$ Hz, $-CH(C\underline{H}_3)_2$), 1.46 (3H, s, C_{19}-H), 2.04 (3H, s, $COCH_3$), 4.47 (1H, br, C_{11}-H), 4.61, 4.95 (2H, dd, $J=16$ Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.28 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.28 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 486 (M^+), 479, 478, 426, 411, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 91,71, 43.

17α-Acetoxy-11β-hydroxy-6α-methyl-21-valeroyloxy-1,4-pregnadiene-3,20-dione ($4a_5$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1750 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.93 (3H, m, $CH_2CH_2CH_2C\underline{H}_3$), 1.03 (3H, s, C_{18}-H), 1.12 (3H, d, $J=7$ Hz, C_6-αCH_3), 1.46 (3H, s, C_{19}-H), 2.05 (3H, s, $COCH_3$), 4.49 (1H, br, C_{11}-H), 4.59, 4.94 (2H, dd, $J=16$ Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.27 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.29 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 500 (M^+), 483, 482, 440, 425, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 85, 57, 43.

17α-Acetoxy-11β-hydroxy-21-isovaleroyloxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_6$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.92 (3H, s, C_{18}-H), 1.03 (6H, s-like, $-CH_2CH(C\underline{H}_3)_2$), 1.08 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.45 (3H, s, C_{19}-H), 2.02 (3H, s, $COCH_3$), 4.49 (1H, br, C_{11}-H), 4.60, 4.94 (2H, dd, $J=15$ Hz, C_{21}-H), 6.02 (1H, br s, C_4-H), 6.26 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.29 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 500 (M^+), 483, 482, 440, 425, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 85, 57, 43.

17α-Acetoxy-21-benzoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_7$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1735 (C=O), 1720 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.07 (3H, s, C_{18}-H), 1.12 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.46 (3H, s, C_{19}-H), 2.08 (3H, s, $COCH_3$), 4.52 (1H, br, C_{11}-H), 4.83, 5.16 (2H, dd, $J=15$ Hz, C_{21}-H), 6.00 (1H, br s, C_4-H), 6.26 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.26 (1H, d, $J=10$ Hz, C_1-H), 7.30—8.25 (5H, m, Ph). MS *m/z*: 520 (M^+), 503, 502, 413, 385, 325, 297, 279, 161, 136, 135, 121, 105 (base peak), 77, 43.

21-Acetoxy-11β-hydroxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione ($4b_1$)——IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1755 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.15 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.12 (3H, t, $J=8$ Hz, $CH_2C\underline{H}_3$), 1.48 (3H, s, C_{19}-H), 2.18 (3H, s, $COCH_3$), 4.52 (1H, br, C_{11}-H), 4.62,

4.99 (2H, dd, J=16 Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, J=10, 2 Hz, C_2-H), 7.33 (1H, d, J=10 Hz, C_1-H). MS m/z: 472 (M^+), 455, 454, 418, 401, 398, 327, 325, 299, 297, 279, 185, 161, 136, 135, 121, 91, 57 (base peak), 43.

11β-Hydroxy-6α-methyl-17α,21-dipropanoyloxy-1,4-pregnadiene-3,20-dione (4b$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1745 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.01 (3H, s, C_{18}-H), 1.10—1.23 (9H, m, C_6-αCH$_3$ and $CH_2C\underline{H}_3$ × 2), 1.43 (3H, s, C_{19}-H), 4.46 (1H, br, C_{11}-H), 4.56, 4.92 (2H, dd, J=16 Hz, C_{21}-H), 6.02 (1H, br s, C_4-H), 6.23 (1H, dd, J=10, 2 Hz, C_2-H), 7.27 (1H, d, J=10 Hz, C_1-H). MS m/z: 486 (M^+), 469, 468, 412, 397, 356, 325, 297, 279, 189, 187, 161, 136, 135, 121, 91, 57 (base peak).

21-Butanoyloxy-11β-hydroxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_3$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 (C=O), 1730 (C=O), 1720 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.98—1.23 (9H, m, C_6-αCH$_3$, $CH_2C\underline{H}_3$ and $CH_2CH_2C\underline{H}_3$), 1.05 (3H, s, C_{18}-H), 1.47 (3H, s, C_{19}-H), 4.51 (1H, br, C_{11}-H), 4.52, 4.91 (2H, dd, J=17 Hz, C_{21}-H), 6.02 (1H, br s, C_4-H), 6.27 (1H, dd, J=10, 2 Hz, C_2-H), 7.28 (1H, d, J=10 Hz, C_1-H). MS m/z: 500 (M^+), 483, 482, 426, 411, 365, 356, 325, 297, 279, 189, 187, 161, 136 (base peak), 135, 121, 91, 71, 57.

11β-Hydroxy-21-isobutanoyloxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_4$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O), ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.25 (6H, d, J=6 Hz, –CH(C$\underline{H}_3$)$_2$), 0.97—1.20 (6H, m, C_6-αCH$_3$ and $CH_2C\underline{H}_3$), 1.47 (3H, s, C_{19}-H), 4.46 (1H, br, C_{11}-H), 4.57, 4.94 (2H, dd, J=16 Hz, C_{21}-H), 6.04 (1H, br s, C_4-H), 6.27 (1H, dd, J=10, 2 Hz, C_2-H), 7.28 (1H, d, J=10 Hz, C_1-H). MS m/z: 500 (M^+), 483, 482, 426, 365, 356, 325, 297, 279, 189, 187, 161, 136 (base peak), 135, 121, 91, 71, 57.

11β-Hydroxy-6α-methyl-17α-propanoyloxy-21-valeroyloxy-1,4-pregnadiene-3,20-dione (4b$_5$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1745 (C=O), 1730 ($C_{17,21}$-OC=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 0.94—1.25 (6H, m, $CH_2C\underline{H}_3$ and $CH_2CH_2CH_2C\underline{H}_3$), 1.07 (3H, s, C_{18}-H), 1.14 (3H, d, J=6 Hz, C_6-αCH$_3$), 1.48 (3H, s, C_{19}-H), 4.49 (1H, br, C_{11}-H), 4.61, 4.95 (2H, dd, J=17 Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.28 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS m/z: 514 (M^+), 497, 496, 440, 425, 356, 297, 279, 189, 187, 161, 136 (base peak), 135, 91, 85, 57.

11β-Hydroxy-21-isovaleroyloxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_6$)——IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1740 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.93 (3H, s, C_{18}-H), 0.95—1.21 (6H, m, C_6-αCH$_3$ and $CH_2C\underline{H}_3$), 1.02 (6H, s, –CH_2CH(C$\underline{H}_3$)$_2$), 1.48 (3H, s, C_{19}-H), 4.48 (1H, br, C_{11}-H), 4.57, 4.94 (2H, dd, J=17 Hz, C_{21}-H), 6.01 (1H, br s, C_4-H), 6.25 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, d, J=10 Hz, C_1-CH). MS m/z: 514 (M^+), 497, 496, 440, 425, 399, 356, 325, 297, 279, 189, 187, 161, 136 (base peak), 135, 121, 91, 85, 57.

21-Benzoyloxy-11β-hydroxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_7$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1730 (C=O), 1720 (C=O), 1700 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.00—1.23 (9H, m, $CH_2C\underline{H}_3$, C_{18}-H and C_6-αCH$_3$), 1.45 (3H, s, C_{19}-H), 4.48 (1H, br, C_{11}-H), 4.83, 5.21 (2H, dd, J=16 Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, J=10, 2 Hz, C_2-H), 7.23—8.18 (6H, m, C_1-H and Ph). MS m/z: 534 (M^+), 516, 460, 399, 325, 297, 279, 161, 136, 135, 121, 105 (base peak), 77, 57.

21-Acryloyloxy-11β-hydroxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_8$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1735 (C=O), 1725 (C=O), 1720 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.05 (3H, s, C_{18}-H), 1.02—1.21 (6H, m, C_6-αCH$_3$ and $CH_2C\underline{H}_3$), 1.46 (3H, s, C_{19}-H), 4.51 (1H, br, C_{11}-H), 4.69, 5.01 (2H, dd, J=15 Hz, C_{21}-H), 5.85—6.50 (5H, m, C_4-H, C_2-H and $C\underline{H}$=$C\underline{H}_2$), 7.33 (1H, d, J=10 Hz, C_1-H). MS m/z: 484 (M^+), 467, 466, 410, 349, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 91, 57, 55.

11β-Hydroxy-21-methoxyacetoxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_9$)——IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1760 (C=O), 1735 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.22 (3H, d, J=6 Hz, C_6-αCH$_3$), 1.46 (3H, s, C_{19}-H), 3.48 (3H, s, OCH_3), 4.20 (2H, s, $COCH_2O$), 4.60 (1H, br, C_{11}-H), 4.68, 5.04 (2H, dd, J=16 Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.30 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS m/z: 502 (M^+), 484, 428, 367, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 74, 73, 57, 45.

11β-Hydroxy-6α-methyl-21-(methylthio)acetoxy-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_{10}$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1745 (C=O), 1730 (C=O), 1715 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.12 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$), 1.46 (3H, s, C_{19}-H), 2.25 (3H, s, SCH_3), 3.31 (2H, s, $COCH_2S$), 4.53 (1H, br, C_{11}-H), 4.69, 5.05 (2H, dd, J=17 Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.29 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS m/z: 518 (M^+), 426, 356, 325, 309, 297, 279, 161, 136, 135, 121, 91, 61 (base peak), 57.

21-Acetoxy-17α-butanoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4c$_1$)——IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1755 (C=O), 1725 (C=O), 1720 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.96 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H}_3$), 1.06 (3H, s, C_{18}-H), 1.15 (3H, s, d, J=6 Hz, C_6-αCH$_3$), 1.48 (3H, s, C_{19}-H), 2.19 (3H, s, $COCH_3$), 4.48 (1H, br, C_{11}-H), 4.63, 4.97 (2H, dd, J=17 Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.26 (1H, dd, J=10, 2 Hz, C_2-H), 7.31 (1H, d, J=10 Hz, C_1-H). MS m/z: 486 (M^+), 469, 468, 398, 356, 325, 297, 279, 263, 189, 161, 136 (base peak), 135, 121, 91, 71, 43.

17α-Butanoyloxy-11β-hydroxy-6α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4c$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 (C=O), 1720 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.02 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$ and $CH_2CH_2C\underline{H}_3$), 1.02 (3H, s, C_{18}-H), 1.18 (3H, d, J=6 Hz, C_6-αCH$_3$), 1.44 (3H, s, C_{19}-H), 4.48 (1H, br, C_{11}-H), 4.56, 4.91 (2H, dd, J=16 Hz, C_{21}-H), 6.00 (1H, br s, C_4-H), 6.24 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, d, J=10 Hz, C_1-H). MS m/z: 500 (M^+), 483, 482, 413, 325, 297, 279, 161, 136 (base peak), 135, 121, 71, 57.

17α,21-Dibutanoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4c$_3$)——IR ν_{max}^{KBr} cm^{-1}: 3380 (OH),

1740 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.97 (3H, s, C_{18}-H), 1.07 (6H, s-like, $CH_2CH_2C\underline{H}_3 \times 2$), 1.15 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 4.53 (1H, br, C_{11}-H), 4.62, 4.98 (2H, dd, $J=16$ Hz, C_{21}-H), 6.09 (1H, br s, C_4-H), 6.32 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.34 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 514 (M^+), 496, 427, 325, 297, 279, 161, 136, 135, 121, 71 (base peak).

17α-Butanoyloxy-11β-hydroxy-21-isobutanoyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4c$_4$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.95 (3H, m, $CH_2CH_2C\underline{H}_3$), 1.05 (3H, s, C_{18}-H), 1.23 (6H, d, $J=6$ Hz, $-CH(C\underline{H}_3)_2$), 1.10—1.18 (3H, m, C_6-αCH_3), 1.46 (3H, s, C_{19}-H), 4.52 (1H, br, C_{11}-H), 4.60, 4.95 (2H, dd, $J=18$ Hz, C_{21}-H), 6.08 (1H, br s, C_4-H), 6.32 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.32 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 514 (M^+), 497, 496, 426, 379, 356, 325, 297, 279, 205, 189, 187, 161, 136, 135, 121, 91, 71 (base peak).

21-Acryloyloxy-17α-butanoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4c$_5$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1725 (C=O), 1720 (C=O), 1655 (C=O). MS *m/z*: 498 (M^+), 481, 480, 410, 356, 325, 297, 279, 189, 187, 161, 136 (base peak), 135, 121, 91, 71, 55.

17α-Butanoyloxy-11β-hydroxy-21-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione (4c$_6$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1760 (C=O), 1745 (C=O), 1725 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.92—1.08 (3H, m, $CH_2CH_2C\underline{H}_3$), 1.04 (3H, s, C_{18}-H), 1.10 (3H, d, $J=6$ Hz, C_6-αCH_3), 1.44 (3H, s, C_{19}-H), 3.48 (3H, s, OCH_3), 4.18 (2H, s, $COCH_2O$), 4.51 (1H, br, C_{11}-H), 4.67, 5.00 (2H, dd, $J=15$ Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.27 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 516 (M^+), 499, 498, 428, 381, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 73, 71, 60, 45.

17α-Butanoyloxy-11β-hydroxy-6α-methyl-21-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4c$_7$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1720 (C=O), 1710 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.07 (3H, s, C_{18}-H), 1.48 (3H, s, C_{19}-H), 2.25 (3H, s, SCH_3), 3.34 (2H, s, $COCH_2$), 4.52 (1H, m, C_{11}-H), 4.69, 5.02 (2H, dd, $J=15$ Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.33 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 532 (M^+), 443, 429, 425, 397, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak).

21-Acetoxy-11β-hydroxy-17α-isobutanoyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4d$_1$)——IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1750 (C=O), 1730 (C=O), 1725 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.03 (3H, s, C_{18}-H), 1.10 (3H, m, C_6-αCH_3), 1.13 (6H, d, $J=8$ Hz, $-CH(C\underline{H}_3)_2$), 1.43 (3H, s, C_{19}-H), 2.17 (3H, s, $COCH_3$), 4.50 (1H, br, C_{11}-H), 4.59, 4.94 (2H, dd, $J=14$ Hz, C_{21}-H), 6.06 (1H, br s, C_4-H), 6.28 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.26 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 486 (M^+), 469, 468, 398, 351, 325, 297, 279, 161, 136, 135, 121, 91, 71, 43 (base peak).

11β-Hydroxy-17α-isobutanoyloxy-6α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4d$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3390 (OH), 1740 (C=O), 1720 (C=O), 1710 (C=O), 1645 (C=O). ^{1}H-NMR ($CDCl_3$): 1.08—1.32 (15H, m, $-CH(C\underline{H}_3)_2$, $CH_2C\underline{H}_3$, C_{18}-H and C_6-αCH_3), 1.46 (3H, s, C_{19}-H), 4.52 (1H, br, C_{11}-H), 4.63, 4.96 (2H, dd, $J=16$ Hz, C_{21}-H), 6.00 (1H, br s, C_4-H), 6.23 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.28 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 500 (M^+), 482, 413, 325, 297, 279, 161, 136 (base peak), 135, 121, 71, 57.

21-Butanoyloxy-11β-hydroxy-17α-isobutanoyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4d$_3$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1745 (C=O), 1730 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.00 (3H, m, $CH_2CH_2C\underline{H}_3$), 1.06 (3H, s, C_{18}-H), 1.14 (3H, m, C_6-αCH_3), 1.16 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.48 (3H, s, C_{19}-H), 4.51 (1H, br, C_{11}-H), 4.57, 4. 93 (2H, dd, $J=14$ Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.29 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.29 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 514 (M^+), 497, 496, 413, 379, 356, 325, 297, 279, 189, 161, 136, 135, 121, 91, 71, 43 (base peak).

11β-Hydroxy-17α,21-diisobutanoyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4d$_4$)——IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1740 (C=O), 1720 (C=O), 1710 (C=O), 1645 (C=O). ^{1}H-NMR ($CDCl_3$): 1.05—1.27 (18H, m, $-CH(C\underline{H}_3)_2 \times 2$, C_{18}-H and C_6-αCH_3), 1.46 (3H, s, C_{19}-H), 4.46 (1H, br, C_{11}-H), 4.55, 4.96 (2H, dd, $J=17$ Hz, C_{21}-H), 6.02 (1H, br s, C_4-H), 6.27 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.30 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 514 (M^+), 496, 427, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 71.

11β-Hydroxy-17α-isobutanoyloxy-21-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione (4d$_5$)——IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1760 (C=O), 1730 (C=O), 1715 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.07 (3H, s, C_{18}-H), 1.12 (6H, d, $J=8$ Hz, $-CH(C\underline{H}_3)_2$), 1.48 (3H, s, C_{19}-H), 3.47 (3H, s, OCH_3), 4.17 (2H, s, $COCH_2$), 4.51 (1H, m, C_{11}-H), 4.62, 4.98 (2H, dd, $J=16$ Hz, C_{21}-H), 6.06 (1H, br s, C_4-H), 6.29 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.32 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 516 (M^+), 498, 427, 381, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 73, 71. 45.

11β-Hydroxy-17α-isobutanoyloxy-6α-methyl-21-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4d$_6$)——IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1750 (C=O), 1730 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.05 (3H, s, C_{18}-H), 1.12 (6H, d, $J=8$ Hz, $-CH(C\underline{H}_3)_2$), 1.46 (3H, s, C_{19}-H), 2.25 (3H, s, SCH_3), 3.31 (2H, s, $COCH_2S$), 4.48 (1H, m, C_{11}-H), 4.60, 4.97 (2H, dd, $J=16$ Hz, C_{21}-H), 6.06 (1H, br s, C_4-H), 6.32 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.29 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 532 (M^+), 443, 429, 397, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak).

21-Acetoxy-11β-hydroxy-6α-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (4e$_1$)——IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1755 (C=O), 1730 (C=O), 1720 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.90—1.25 (3H, m, $CH_2CH_2CH_2C\underline{H}_3$), 1.02 (3H, s, C_{18}-H), 1.12 (3H, d, $J=7$ Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 2.17 (3H, s, $COCH_3$), 4.49 (1H, br, C_{11}-H), 4.63, 4.95 (2H, dd, $J=17$ Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.27 (1H, dd, $J=10$, 2 Hz, C_2-H), 7.29 (1H, d, $J=10$ Hz, C_1-H). MS *m/z*: 500 (M^+), 482, 427, 398, 365, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 85, 57, 43.

11β-Hydroxy-6α-methyl-21-propanoyloxy-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (4e$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1720 ($C_{17,21}$-OC=O), 1645 (C=O). ^{1}H-NMR ($CDCl_3$): 1.00 (6H, t, J=8 Hz, $CH_2C\underline{H}_3$ and $CH_2CH_2CH_2C\underline{H}_3$), 1.01 (3H, s, C_{18}-H), 1.16 (3H, d, J=6 Hz, C_6-αCH_3), 1.42 (3H, s, C_{19}-H), 4.47 (1H, br, C_{11}-H), 4.60, 4.96 (2H, dd, J=16 Hz, C_{21}-H), 6.00 (1H, br s, C_4-H), 6.23 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, dd, J=10 Hz, C_1-H). MS m/z: 514 (M^+), 496, 325, 297, 279, 161, 136 (base peak), 135, 121, 85, 57.

11β-Hydroxy-6α-methyl-17α,21-divaleroyloxy-1,4-pregnadiene-3,20-dione (4e$_3$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1725 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.89—1.27 (9H, m, $CH_2CH_2CH_2C\underline{H}_3$ ×2 and C_6-αCH_3), 1.01 (3H, s, C_{18}-H), 1.46 (3H, s, C_{19}-H), 4.45 (1H, br, C_{11}-H), 4.52, 4.91 (2H, dd, J=17 Hz, C_{21}-H), 6.00 (1H, br s, C_4-H), 6.23 (1H, dd, J=10, 2 Hz, C_2-H), 7.27 (1H, d, J=10 Hz, C_1-H). MS m/z: 542 (M^+), 525, 524, 441, 356, 325, 297, 279, 161, 136, 135, 121, 85 (base peak), 57.

21-Acetoxy-11β-hydroxy-17α-isovaleroyloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4f$_1$)——IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.91 (3H, m, C_{18}-H), 1.01 (6H, d, J=3 Hz, $CH_2CH(C\underline{H}_3)_2$), 1.12 (3H, d, J=7 Hz, C_6-αCH_3), 1.45 (3H, s, C_{19}-H), 2.15 (3H, s, $COCH_3$), 4.46 (1H, m, C_{11}-H), 4.68, 4.91 (2H, dd, J=16 Hz, C_{21}-H), 6.02 (1H, br s, C_4-H), 6.26 (1H, dd, J=10, 2 Hz, C_2-H), 7.27 (1H, d, J=10 Hz, C_1-H). MS m/z: 500 (M^+), 483, 427, 365, 325, 297, 279, 189, 187, 161, 136 (base peak), 135, 121, 91, 85, 57, 43.

11β-Hydroxy-17α-isovaleroyloxy-6α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4f$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O), 1720 (C=O), 1710 (C=O), 1645 (C=O). ^{1}H-NMR ($CDCl_3$): 0.90—1.20 (15H, m, $CH_2CH(C\underline{H}_3)_2$, $CH_2C\underline{H}_3$, C_{18}-H and C_6-αCH_3), 1.42 (3H, s, C_{19}-H), 4.47 (1H, br, C_{11}-H), 4.61, 4.96 (2H, dd, J=17 Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.26 (1H, dd, J=10, 2 Hz, C_2-H), 7.33 (1H, d, J=10 Hz, C_1-H). MS m/z: 514 (M^+), 499, 497, 356, 325, 297, 279, 161, 136 (base peak), 135, 121, 107, 71, 43.

21-Acetoxy-17α-benzoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4g$_1$)——IR ν_{max}^{KBr} cm^{-1}: 3310 (OH), 1745 (C=O), 1720 (C=O), 1710 (C=O), 1645 (C=O). ^{1}H-NMR ($CDCl_3$): 1.08 (3H, s, C_{18}-H), 1.13 (3H, d, J=6 Hz, C_6-αCH_3), 1.49 (3H, s, C_{19}-H), 2.18 (3H, s, $COCH_3$), 4.49 (1H, m, C_{11}-H), 4.65, 4.99 (2H, dd, J=17 Hz, C_{21}-H), 5.99 (1H, br s, C_4-H), 6.24 (1H, dd, J=10, 2 Hz, C_2-H), 7.21—8.08 (6H, m, C_1-H and Ph). MS m/z: 520 (M^+), 503, 502, 447, 398, 325, 297, 279, 239, 161, 136, 135, 122, 121, 105 (base peak), 91, 77, 43.

17α-Benzoyloxy-11β-hydroxy-6α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4g$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 1740 (C=O), 1720 (C=O), 1705 (C=O), 1645 (C=O). ^{1}H-NMR ($CDCl_3$): 1.01—1.30 (6H, m, $CH_2C\underline{H}_3$ and C_6-αCH_3), 1.15 (3H, s, C_{18}-H), 1.52 (3H, s, C_{19}-H), 4.52 (1H, br, C_{11}-H), 4.57, 4.99 (2H, dd, J=17 Hz, C_{21}-H), 6.02 (1H, br s, C_4-H), 6.29 (1H, dd, J=10, 2 Hz, C_2-H), 7.23—8.02 (6H, m, C_1-H and Ph). MS m/z: 534 (M^+), 517, 516, 446, 412, 399, 325, 297, 279, 161, 136, 135, 121, 105 (base peak), 77, 57.

17α,21-Dibenzoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4g$_3$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1730 (C=O), 1715—1710 ($C_{17,21}$-OC=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.19 (3H, s, C_{18}-H), 1.21 (3H, d, J=7 Hz, C_6-αCH_3), 1.51 (3H, s, C_{19}-H), 4.57 (1H, br, C_{11}-H), 4.86, 5.28 (2H, dd, J=16 Hz, C_{21}-H), 6.10 (1H, br s, C_4-H), 6.38 (1H, dd, J=10, 2 Hz, C_2-H), 7.20—8.20 (11H, m, C_1-H and Ph ×2). MS m/z: 582 (M^+), 565, 460, 447, 338, 325, 297, 279, 265, 161, 145, 136, 135, 121, 105 (base peak), 91, 77.

References and Notes

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