Studies on Topical Antiinflammatory Agents. V.[1] 17-(Alkylthio)- and Methoxyalkanoates of Corticosteroids

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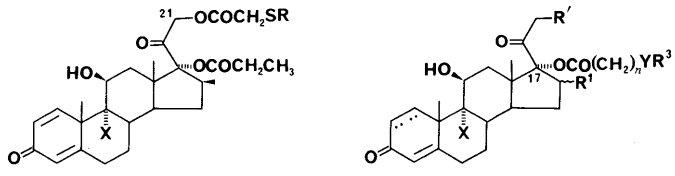
As part of our search for new topical antiinflammatory agents, a series of corticosteroid 17-(alkylthio)- and methoxyalkanoate derivatives was prepared and tested for vasoconstrictive activities. Several compounds were proved to have activity superior or comparable to that of 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV). Among these compounds, 21-chloro-11β-hydroxy-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (5Aa) was found to have the most potent activity, being more active than BV. The structure–activity relationships of the series revealed that introduction of a (methylthio)acetate function into the 17-position as well as the 21-position of corticosteroids was effective for enhancing the topical antiinflammatory activity.

Keywords corticosteroid; antiinflammatory agent; vasoconstrictive activity; 21-chloro-11β-hydroxy-17α-(methylthio)-acetoxy-4-pregnene-3,20-dione; structure–activity relationship

We recently reported[1] that corticosteroid 21-derivatives having sulfur-containing moieties at the 21-ester chain (I) (Chart 1) displayed potent vasoconstrictive activity due to a topical antiinflammatory activity. The results showed that the (methylthio)acetate function is a good replacement for the 21-hydroxy group of corticosteroids. As an extension of our studies aimed at finding novel compounds with high topical antiinflammatory activity, we have sought to elucidate the possible roles of similar functional groups at the 17-position including another hydroxy function in the dihydroxyacetone side chain. In order to determine the effect of sulfur and oxygen atoms introduced into the 17-ester chain upon the activity and to establish structure–activity relationships, in this paper we describe the synthesis and biological activities of a new series of 17-(alkylthio)alkanoates and 17-methoxyacetates (II) (Chart 1).

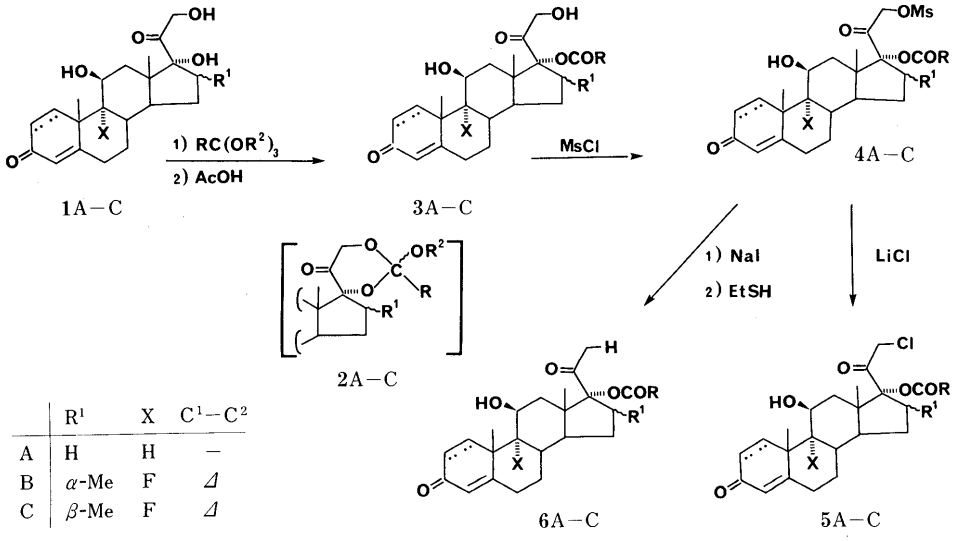


I II

Chart 1

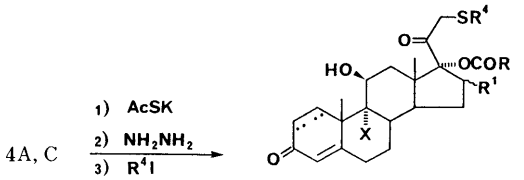
Chemistry

The 17-(alkylthio)alkanoates and 17-methoxyacetates of corticosteroids listed in Table I were prepared by the methods shown in Charts 2 and 3. Sixteen 17-ortho esters (**2A**—C) were prepared from the corresponding corticosteroids, namely 11β,17α,21-trihydroxy-4-pregnene-3,20-dione (hydrocortisone, **1A**), 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (dexamethasone, **1B**) and betamethasone (**1C**), respectively, by exchange reaction with the appropriate ortho esters. Next, these ortho esters (**2A**—C) were hydrolyzed with aqueous acetic acid in MeOH to give the 17-esters (**3A**—C). Mesylation of **3A**—C with MsCl in pyridine afforded the 21-mesyl derivatives (**4A**—C). Chlorination of **4A**—C with lithium chloride (LiCl) in *N*,*N*-dimethylformamide (DMF)/acetonitrile provided **5A**—C in 50—94% yields. Iodination of **4A**—C with sodium iodide in DMF/acetonitrile gave the 21-iodides. Without purification, reductive removal of the iodo group was carried out by using ethanethiol to afford



	R¹	X	C¹–C²
A	H	H	–
B	α-Me	F	Δ
C	β-Me	F	Δ

Chart 2



7A, C : R^4=Ac
8A, C : R^4=H
9A, C : R^4=Me, Et

$R=-(CH_2)_nYR^3$

	a	b	c	d	e	f	g
R^3	Me	Et	iso-Pr	Me	Me	Et	iso-Pr
n	1	1	1	1	2	2	2
Y	S	S	S	O	S	S	S

Chart 3

the 21-deoxy derivatives (**6**A—C) in overall yields of 39—94%. Thus, under mild conditions, the group $-CH_2OMs$ could be reduced to methyl. This reduction method has advantages in that no protection of the carbonyl groups at positions 3 and/or 20 is required. Reaction of **4**A and **4**C with potassium thioacetate provided the 21-acetylthio compounds (**7**A,C), which were then hydrolyzed with hydrazine hydrate to give the 21-mercapto derivatives (**8**A, C, respectively).

Alkylation of **8**A and **8**C with alkyl iodide in the presence of triethylamine yielded the 21-alkylthio compounds (**9**A,C) in 48—88% yields (Chart 3).

Safety of the Compounds Tested Before application to volunteers, the safety of all the compounds was checked by the method reported previously.[2]

Biological Results and Discussion

Primary Skin-Irritating Activity All the compounds were evaluated at 1, 2, 3 and 7 d in rabbits by the Draize method.[3] It was considered that none of the tested compounds exhibits primary skin irritation.

Mutagenicity All the compounds tested were negative in Ames' spot test[4] against *Salmonella typhimurium* TA98 and TA100. 2-Aminoanthracene, 2-nitrofluorene and *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine were used as positive controls.

Thus, no significant toxic signs were observed in the primary skin irritation or bacterial reverse mutation tests of all the compounds.

Vasoconstrictive Activities A number of methods for evaluating topical antiinflammatory activity of corticosteroids have been described.[5-7] However, it is well known that corticosteroids that are predicted to be potent on the basis of animal studies may be much less potent than expected in humans. Only the vasoconstriction activity test is considered to be reliable for predicting the antiinflammatory potency of topical corticosteroids,[6] because a remarkably good correlation has been found between the result of this test and the topical efficacy in the clinic.[7] Using this method, for instance, clobetasol propionate[8] and betamethasone 17-valerate[9] (BV) were selected and are now widely used in the clinic. Evaluation by this method is recommended as a preclinical study for topically applied corticosteroids.[6]

The compounds prepared in this study were tested for vasoconstrictive activities in twenty healthy male volunteers by the methods reported previously.[1,2] The vasoconstrictive activities of the compounds tested were compared with that of BV, which was used as an active control for the activity. Statistical analysis was performed by Wilcoxon's signed-ranks test.[10] The results are summarized in Table I.

TABLE I. Vasoconstrictive Activity Ratios of Corticosteroid 17-(Alkylthio)- and Methoxyalkanoate Derivatives (**5**, **6** and **9**)

Compd. No.	After 2 h	After 4 h	Compd. No.	After 2 h	After 4 h
5Aa	154[d]	130[a]	**6**Aa	87	85
5Ab	87	96	**6**Ab	67[b]	57[d]
5Ac	46[d]	39[d]	**6**Ac	41[d]	28[d]
5Ad	105	102	**6**Ad	56[d]	50[d]
5Ae	59[d]	70[d]	**6**Ae	33[d]	44[d]
5Af	41[d]	39[d]	**6**Af	44[d]	35[d]
5Ag	31[d]	33[d]	**6**Ag	54[c]	37[d]
5Ba	109	82[a]	**6**Ba	120	96
5Be	66[b]	52[d]	**6**Be	63[c]	48[d]
5Bf	43[d]	39[d]	**6**Bf	71[d]	43[d]
5Bg	49[d]	48[d]	**6**Bg	60[b]	27[d]
5Ca	135[b]	114	**6**Ca	61[d]	64[d]
5Cc	46[d]	40[d]	**6**Cc	37[d]	40[d]
5Ce	44[d]	51[d]	**6**Ce	67[d]	68[d]
5Cf	35[d]	32[d]	**6**Cf	44[d]	38[d]
5Cg	39[d]	34[d]	**6**Cg	35[d]	36[d]
			9Aa	64[c]	54[d]
			9Ca-1	109	80[a]
			9Ca-2	44[d]	35[d]
			9Cc	46[d]	34[d]

Vaseline ointment (0.01%) was used. Each compound was tested on 20 volunteers. The potency is expressed as the ratio of vasoconstrictive activity to that of BV taken as 100. *a*) $p<0.1$. *b*) $p<0.05$. *c*) $p<0.02$. *d*) $p<0.01$ by BV, using Wilcoxon's signed-ranks test.[10]

The activities of six compounds, **5**Aa, **5**Ad, **5**Ba, **5**Ca, **6**Ba and **9**Ca, at 2 h were equal to or greater ($p<0.02$) than that of BV. In particular, the activities of three compounds, **5**Aa, **5**Ad and **5**Ca, were equal to or greater than that of BV at both 2 and 4 h.

Generally, the potency of the 17-acetate derivatives was higher than that of the 17-propanoate derivatives. Among the 21-chloro compounds, the activities of the 17-(methylthio)acetates (**5**Aa—Cc) were more potent than those of the corresponding 17-methoxyacetates (**5**Ad—Cd). On the other hand, in the series of 21-deoxy derivatives (**6**), the compounds showed generally weaker activities than those of the series of 21-chloro derivatives (**5**). The only exception was the 17-(methylthio)acetate (**6**Ba), whose activity was comparable to that of BV. As regards the size of terminal alkyl groups, the compounds with a methyl group showed potent activities. Lengthening of the alkyl group generally caused a decrease in activity. Our observation in this series is in accordance with our previous findings on the 21-(alkylthio)acetates.[1] Therefore the methyl group was selected as the optimum terminal substituent of the 17-position. On the other hand, among the 21-alkylthio compounds, the most active 21-methylthio(**9**Ca) was as potent as BV after 2 h, but the activity after 4 h was considerably reduced.

In conclusion, we have found a novel class of topical antiinflammatory agents, corticosteroid 17-(alkylthio)- and methoxyacetate derivatives. Introduction of the (methyl-

thio)acetate function into the 17-position as well as the 21-position of corticosteroids resulted in significant enhancement of the activity. Among the compounds synthesized in the present study, hydrocortisone 21-chloro-21-deoxy-17-(methylthio)acetate (**5Aa**) was found to have the most potent activity, being significantly more potent than BV.

Accordingly, these results lead to the conclusion that substitution of the 17-hydroxy group of corticosteroids with a (methylthio)acetate function is another potentially effective approach for obtaining higher antiinflammatory activity. It has been well demonstrated that the introduction of a (methylthio)acetate function into not only the 21-position but also the 17-position of corticosteroids has a substantial effect on topical antiinflammatory activity.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO DS-301 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian XL-200 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The chemical shifts are given in δ (ppm). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The unit (Hz) of coupling constants (J) is omitted. The fast atom bombardment (FAB) mass spectra (MS) were taken with a JEOL DX-303. The electron impact- and field-desorption mass spectra were obtained with a Shimadzu LKB-9000 and a JEOL SX-102, respectively. The extracted organic solutions were dried over $MgSO_4$. Column chromatography was carried out on Wakogel C-200.

All compounds were analyzed for C, H, F and S. The analytical results were within $\pm 0.4\%$ of the calculated values.

Preparation of Orthoesters Typical examples are given to illustrate the general procedure.

(1) (Ethylthio)acetonitrile[11]: Sodium methoxide (7.85 g) was added to a stirred and ice-cooled solution of ethanethiol (10.8 ml) in DMF (15 ml) and the reaction mixture was stirred at the same temperature for 10 min. Then chloroacetonitrile (8.4 ml) was added to the mixture under cooling with ice-water. The reaction mixture was stirred at the same temperature for 15 min, then poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% Na_2CO_3, water, 5% HCl and brine, and dried. After removal of the solvent, the residue was distilled *in vacuo* to give the product (9.28 g, 69%), bp 95 °C (28 mmHg). NMR: 1.34 (3H, t, $J=7$), 2.79 (2H, q, $J=7$), 3.32 (2H, s). The following compounds were similarly prepared. (Isopropylthio)acetonitrile[12]: Yield: 70%. bp 53 °C (5 mmHg). NMR: 1.35 (6H, d, $J=7$), 3.23 (1H, septet, $J=7$), 3.32 (2H, s). 3-(Ethylthio)propionitrile[13]: Yield 82%. bp 80 °C (6.2 mmHg). NMR: 1.28 (3H, t, $J=7$), 2.59—2.72 (4H, m), 2.78—2.88 (2H, m). 3-(Isopropylthio)propionitrile[14]: Yield 82%. bp 90 °C (8 mmHg). NMR: 1.29 (6H, d, $J=7$), 2.56—2.66 (2H, m), 2.74—2.84 (2H, m), 3.01 (1H, septet, $J=7$).

(2) Trimethyl Ortho(ethylthio)acetate: Dry hydrogen chloride (3.58 g) was bubbled into a stirred and ice-cooled solution of (ethylthio)acetonitrile (9.0 g) in ether (40 ml) and MeOH (4 ml). The whole was allowed to stand at 0—5 °C for 14 d. The crystalline precipitate that formed was collected and washed with ether to give the iminoester (13.1 g, 87%). The product was used in the next reaction without further purification because of its hygroscopic character. A mixture of the iminoester (13.1 g) in MeOH (35 ml) and ether (100 ml) was refluxed for 10 h. The separated precipitate was filtered off and the filtrate was concentrated. The residual oil was distilled *in vacuo* to yield the desired product (4.46 g, 32%), bp 116 °C (33 mmHg). NMR: 1.28 (3H, t, $J=7$), 2.64 (2H, q, $J=7$), 2.92 (2H, s), 3.31 (9H, s). The following compounds were similarly prepared. Triethyl orthomethoxyacetate[15]: bp 90 °C (23 mmHg), 53%. NMR: 1.21 (9H, t, $J=7$), 3.42 (3H, s), 3.53 (2H, s), 3.61 (6H, q, $J=7$). Trimethyl ortho(methylthio)acetate: bp 76 °C (14 mmHg), 46%. NMR: 2.15 (3H, s), 2.83 (2H, s), 3.27 (9H, s). Trimethyl ortho(isopropylthio)acetate: bp 74 °C (4.4 mmHg), 36%. NMR: 1.29 (6H, d, $J=7$), 2.93 (2H, s), 3.01 (1H, m), 3.32 (9H, s). Trimethyl ortho(methylthio)propanoate[16]: bp 83 °C (9.8 mmHg), 57%. NMR: 2.00—2.10 (2H, m), 2.13 (3H, s), 2.46—2.57 (2H, m), 3.26 (9H, s). Trimethyl ortho(ethylthio)propanoate: bp 93 °C (10 mmHg). 42%. NMR: 1.27 (3H, t, $J=7$), 1.80—2.21 (2H, m), 2.38—2.80 (2H, m), 2.54 (2H, q, $J=7$), 3.21 (9H, s). Trimethyl ortho(isopropylthio)propanoate: bp 93 °C (5.8 mmHg), 18%. NMR: 1.29 (6H, d, $J=7$), 1.99—2.10 (2H, m), 2.51—2.62 (2H, m), 2.96 (1H, m), 3.26 (9H, s).

Typical examples are given to illustrate the general procedure.

11β-Hydroxy-17α,21-(1-methoxy-2-methylthioethylidenedioxy)-4-pregnene-3,20-dione (2Aa) Trimethyl ortho(methylthio)acetate (7.0 ml) was added to a mixture of hydrocortisone (**1A**, 10.0 g) in benzene (200 ml) and DMF (30 ml) followed by the addition of *p*-toluenesulfonic acid (0.2 g), and the mixture was stirred at room temperature for 4 h. Then, AcOEt was added. The extract was washed successively with 5% Na_2CO_3, H_2O and brine and dried. After removal of the solvent, the residue was used for the next step without further purification. NMR: 0.91 (3H, s), 1.45 (3H, s), 2.60—2.76 (2H, m), 2.96 (3H, s), 3.31 (3H, s), 4.03, 4.24 (2H, each d, $J=16$), 4.52 (1H, m), 5.72 (1H, br s).

11β,21-Dihydroxy-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (3Aa) A 5% aqueous AcOH solution (80 ml) was added to a solution of **2Aa** (12.3 g) in MeOH (300 ml). The mixture was refluxed for 7 h and concentrated *in vacuo*. The residue was extracted with AcOEt. The extract was washed successively with 5% Na_2CO_3, H_2O and brine, then dried and concentrated. The residue was chromatographed with $CHCl_3$–AcOEt (3 : 1) to give **3Aa** (4.85 g, 39% from **1A**) as an amorphous solid. IR: 3420, 2920, 1720, 1660 cm^{-1}. NMR: 0.96 (3H, s), 1.45 (3H, s), 2.21 (3H, s), 3.16 (2H, s), 4.35 (2H, br s), 4.51 (1H, m), 5.70 (1H, br s).

The following compounds were similarly prepared.

17α-(Ethylthio)acetoxy-11β,21-dihydroxy-4-pregnene-3,20-dione (3Ab) Amorphous, 61%. IR: 3430, 2920, 1720, 1650 cm^{-1}. NMR: 0.95 (3H, s), 1.26 (3H, t, $J=8$), 1.44 (3H, s), 2.66 (2H, q, $J=8$), 3.19 (2H, s), 4.35 (2H, m), 4.54 (1H, m), 5.72 (1H, br s).

11β,21-Dihydroxy-17α-(isopropylthio)acetoxy-4-pregnene-3,20-dione (3Ac) Amorphous, 28%. IR: 3420, 2920, 1720, 1665 cm^{-1}. NMR: 0.96 (3H, s), 1.28 (6H, d, $J=7$), 1.45 (3H, s), 3.06 (1H, septet, $J=7$), 3.13 (2H, s), 4.35 (2H, br s), 4.54 (1H, m), 5.72 (1H, br s).

11β,21-Dihydroxy-17α-methoxyacetoxy-4-pregnene-3,20-dione[17] (3Ad) mp 187—190 °C (AcOEt–hexane), 25%. IR: 3400, 2920, 2900, 1750, 1720, 1645 cm^{-1}. NMR: 0.98 (3H, s), 1.45 (3H, s), 3.44 (3H, s), 4.04 (2H, s), 4.37 (2H, m), 4.52 (1H, m), 5.71 (1H, br s).

11β,21-Dihydroxy-17α-(methylthio)propanoyloxy-4-pregnene-3,20-dione (3Ae) Amorphous, 63%. IR: 3320, 2920, 1710, 1650 cm^{-1}. NMR: 0.95 (3H, s), 1.45 (3H, s), 2.12 (3H, s), 3.11 (1H, br s), 4.35 (2H, d, $J=4$), 4.52 (1H, m), 5.72 (1H, s).

17α-(Ethylthio)propanoyloxy-11β,21-dihydroxy-4-pregnene-3,20-dione (3Af) Amorphous, 38%. IR: 3450, 2930, 1730, 1660 cm^{-1}. NMR: 0.95 (3H, s), 1.25 (3H, t, $J=7$), 1.46 (3H, s), 4.33 (2H, s), 4.50 (1H, m), 5.70 (1H, s).

11β,21-Dihydroxy-17α-(isopropylthio)propanoyloxy-4-pregnene-3,20-dione (3Ag) Amorphous, 60%. IR: 3440, 2920, 1730, 1660 cm^{-1}. NMR: 0.96 (3H, s), 1.16 (6H, d, $J=7$), 1.46 (3H, s), 3.11 (1H, t, $J=5$), 4.35 (2H, d, $J=5$), 4.52 (1H, m), 5.72 (1H, br s).

9α-Fluoro-11β,21-dihydroxy-16α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (3Ba) Amorphous, 70%. IR: 3420, 2940, 1720, 1665 cm^{-1}. NMR: 1.03 (3H, d, $J=7$), 1.04 (3H, s), 1.54 (3H, s), 2.18 (3H, s), 3.19 (2H, s), 4.38 (3H, m), 6.13 (1H, br s), 6.34 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β,21-dihydroxy-16α-methyl-17α-(methylthio)propanoyloxy-1,4-pregnadiene-3,20-dione (3Be) Amorphous, 26%. IR: 3440, 2940, 1730, 1660 cm^{-1}. NMR: 0.99 (3H, d, $J=7$), 1.02 (3H, s), 1.55 (3H, s), 2.10 (3H, s), 3.16 (1H, m), 4.34 (3H, s), 4.41 (1H, m), 6.13 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

17α-(Ethylthio)propanoyloxy-9α-fluoro-11β,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (3Bf) Amorphous, 49%. IR: 3440, 2940, 1730, 1670 cm^{-1}. NMR: 0.99 (3H, d, $J=7$), 1.03 (3H, s), 1.24 (3H, t, $J=7$), 1.55 (3H, s), 2.54 (2H, q, $J=7$), 3.17 (1H, m), 4.34 (2H, s), 4.41 (1H, m), 6.14 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

9α-Fluoro-11β,21-dihydroxy-17α-(isopropylthio)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (3Bg) Amorphous, 27%. IR: 3440, 2960, 1730, 1670 cm^{-1}. NMR: 0.99 (3H, d, $J=7$), 1.02 (3H, s), 1.23 (6H, d, $J=7$), 1.53 (3H, s), 2.92 (1H, septet, $J=7$), 3.09 (1H, t, $J=5$), 3.18 (1H, m), 4.33 (2H, d, $J=5$), 4.41 (1H, m), 6.10 (1H, s), 6.35 (1H, dd, $J=10$, 2), 7.19 (1H, d, $J=10$).

9α-Fluoro-11β,21-dihydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (3Ca) Amorphous, 83%, IR: 3420, 2940, 1710, 1660 cm^{-1}. NMR: 0.87 (3H, s), 1.31 (3H, d, $J=8$), 1.50 (3H, s), 2.15 (3H, s), 3.32 (2H, s), 3.97 (2H, m), 4.21 (1H, m), 6.03 (1H, br s), 6.23 (1H, dd, $J=10$, 2), 7.30 (1H, d, $J=10$).

9α-Fluoro-11β,21-dihydroxy-17α-(isopropylthio)acetoxy-16β-methyl-1,4-pregnadiene-3,20-dione (3Cc) Amorphous, 73%. IR: 3400, 2930, 1720,

1660 cm^{-1}. NMR: 0.98 (3H, s), 1.26, 1.27 (6H, each d, J=7), 1.42 (3H, d, J=8), 1.56 (3H, s), 3.06 (1H, septet, J=7), 3.16 (1H, t, J=5), 3.22 (2H, s), 4.07, 4.21 (2H, each dd, J=18, 5), 4.44 (1H, m), 6.14 (1H, br s), 6.35 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

9α-Fluoro-11β,21-dihydroxy-16β-methyl-17α-(methylthio)propanoyloxy-1,4-pregnadiene-3,20-dione (3Ce) mp 196.5—198.5 °C (from AcOEt–hexane). 50%. IR: 3380, 2930, 1730, 1650 cm^{-1}. NMR: 0.98 (3H, s), 1.41 (3H, d, J=7), 1.56 (3H, s), 2.11 (3H, s), 3.14 (1H, dd, J=5, 4), 4.04 (1H, dd, J=18, 5), 4.22 (1H, dd, J=18, 4), 4.44 (1H, m), 6.14 (1H, s), 6.56 (1H, dd, J=10, 2), 7.21 (1H, d, J=10).

17α-(Ethylthio)propanoyloxy-9α-fluoro-11β,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (3Cf) Amorphous, 55%. IR: 3450, 2930, 1740, 1670 cm^{-1}. NMR: 0.97 (3H, s), 1.24 (3H, t, J=7), 1.42 (3H, d, J=7), 1.55 (3H, s), 2.54 (2H, q, J=7), 4.03, 4.22 (2H, each d, J=18), 4.43 (1H, m), 6.14 (1H, s), 6.35 (1H, dd, J=10, 2), 7.23 (1H, d, J=10).

9α-Fluoro-11β,21-dihydroxy-17α-(isopropylthio)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (3Cg) Amorphous, 68%. IR: 3440, 2930, 1730, 1660 cm^{-1}. NMR: 0.97 (3H, s), 1.25 (6H, d, J=7), 1.41 (3H, d, J=7), 1.55 (3H, s), 2.92 (1H, septet, J=7), 4.02, 4.22 (2H, each d, J=18), 4.43 (1H, m), 6.13 (1H, s), 6.36 (1H, dd, J=10, 2), 7.20 (1H, d, J=10).

11β-Hydroxy-21-methylsulfonyloxy-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (4Aa) Mesyl chloride (0.40 ml) was added dropwise to a stirred solution of **3**Aa (1.50 g) in dry pyridine (25 ml) under ice-cooling. The reaction mixture was stirred for an additional 1 h and then poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% HCl, H_2O, saturated $NaHCO_3$ and brine, dried and concentrated to give **4**Aa (1.67 g, 95%) as an amorphous solid. NMR: 1.00 (3H, s), 1.45 (3H, s), 2.21 (3H, s), 3.17 (2H, s), 3.20 (3H, s), 4.51 (1H, m), 4.98, 5.01 (2H, each d, J=16), 5.70 (1H, br s).

This product was used for the next step without further purification. The following compounds were similarly prepared.

4Ab: Amorphous, 99%. NMR: 1.00 (3H, s), 1.27 (3H, t, J=7), 1.45 (3H, s), 2.67 (2H, q, J=7), 3.21 (5H, s), 4.51 (1H, m), 4.97, 5.00 (2H, each d, J=16), 5.71 (1H, br s).

4Ac: Amorphous, 99%. NMR: 1.00 (3H, s), 1.29 (6H, d, J=7), 1.46 (3H, s), 3.07 (1H, septet, J=7), 3.22 (3H, s), 3.24 (2H, s), 4.53 (1H, m), 4.97, 5.00 (2H, each d, J=16), 5.72 (1H, br s).

4Ad: Amorphous, 96%. NMR: 1.02 (3H, s), 1.45 (3H, s), 3.21 (3H, s), 3.44 (3H, s), 4.06 (2H, s), 4.51 (1H, m), 4.92, 5.05 (2H, each d, J=16), 5.71 (1H, br s).

4Ae: Amorphous, 86%. NMR: 1.00 (3H, s), 1.46 (3H, s), 2.14 (3H, s), 3.22 (3H, s), 4.52 (1H, m), 5.00 (2H, s), 5.72 (1H, s).

4Af: mp 143—145 °C (from EtOH), 82%. NMR: 0.99 (3H, s), 1.26 (3H, t, J=7), 1.45 (3H, s), 2.56 (2H, q, J=7), 3.20 (3H, s), 4.50 (1H, m), 4.99 (2H, s), 5.70 (1H, s).

4Ag: mp 145—146 °C (from EtOH), 91%. NMR: 0.99 (3H, s), 1.26 (6H, d, J=7), 1.45 (3H, s), 3.21 (3H, s), 4.52 (1H, m), 5.00 (2H, s), 5.72 (1H, s).

4Ba: Amorphous, 96%. NMR: 1.02 (3H, d, J=7), 1.07 (3H, s), 1.54 (3H, s), 2.21 (3H, s), 3.22 (5H, s), 4.42 (1H, m), 4.88, 4.93 (2H, each d, J=16), 6.13 (1H, br s), 6.35 (1H, dd, J=10, 2), 7.20 (1H, d, J=10).

4Be: Amorphous, 91%. NMR: 0.95 (3H, d, J=7), 1.07 (3H, s), 1.55 (3H, s), 2.25 (3H, br s), 3.23 (3H, s), 3.27 (1H, m), 4.42 (1H, m), 4.92 (2H, s), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.23 (1H, d, J=10).

4Bf: Amorphous, 95%. NMR: 0.96 (3H, d, J=7), 1.07 (3H, s), 1.24 (3H, t, J=7), 2.55 (2H, q, J=7), 3.23 (3H, s), 3.28 (1H, m), 4.41 (1H, m), 4.92 (2H, s), 6.15 (1H, s), 6.37 (1H, dd, J=10, 2), 7.23 (1H, d, J=10).

4Bg: Amorphous, 95%. NMR: 0.95 (3H, d, J=7), 1.07 (3H, s), 1.24 (6H, d, J=7), 1.55 (3H, s), 2.93 (1H, septet, J=7), 3.27 (3H, s), 3.29 (1H, m), 4.41 (1H, m), 4.92 (2H, s), 6.13 (1H, s), 6.35 (1H, dd, J=10, 2), 7.21 (1H, d, J=10).

4Ca: Amorphous, 99%. NMR: 1.03 (3H, s), 1.39 (3H, d, J=7), 1.56 (3H, s), 2.24 (3H, s), 3.17, 3.20 (2H, each d, J=15), 3.24 (3H, s), 4.42 (1H, m), 4.79, 4.87 (2H, each d, J=16), 6.15 (1H, br s), 6.37 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

4Cc: Amorphous, 99%. NMR: 1.04 (3H, s), 1.27, 1.30 (6H, each d, J=7), 1.56 (3H, s), 3.08 (1H, septet, J=7), 3.23 (3H, s), 4.44 (1H, m), 4.78, 4.86 (2H, each d, J=16), 6.15 (1H, br s), 6.36 (1H, dd, J=10, 2), 7.21 (1H, d, J=10).

4Ce: Amorphous, 99%. NMR: 1.02 (3H, s), 1.37 (3H, d, J=7), 2.12 (3H, s), 3.22 (3H, s), 4.43 (1H, m), 4.79, 4.88 (2H, each d, J=17), 6.14 (1H, s), 6.37 (1H, dd, J=10, 2), 7.21 (1H, d, J=10).

4Cf: Amorphous, 93%. NMR: 1.02 (3H, s), 1.25 (3H, t, J=7), 1.37 (3H, d, J=7), 1.56 (3H, s), 2.56 (2H, q, J=7), 3.23 (3H, s), 4.43 (1H, m), 4.80, 4.88 (2H, each d, J=17), 6.13 (1H, s), 6.36 (1H, dd, J=10, 2), 7.21 (1H, d, J=10).

4Cg: Amorphous, 96%. NMR: 1.02 (3H, s), 1.26 (6H, d, J=7), 1.37 (3H, d, J=7), 1.56 (3H, s), 2.93 (1H, septet, J=7), 3.22 (3H, s), 4.43 (1H, m), 4.84 (2H, s), 6.13 (1H, s), 6.36 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

21-Chloro-11β-hydroxy-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (5Aa) A mixture of **4**Aa (0.70 g), LiCl (1.40 g) in DMF (14 ml) and CH_3CN (14 ml) was refluxed for 4 h. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with brine, dried and concentrated *in vacuo*. The residue was subjected to column chromatography with AcOEt–hexane (1 : 2) as an eluent. The product obtained from the main fraction was recrystallized from EtOH to give **5**Aa (0.58 g, 93%) as colorless prisms. mp 176—180 °C. $C_{24}H_{33}ClO_5S$. EI-MS m/z: 468 (M^+). IR: 3360, 2920, 1730, 1720, 1640 cm^{-1}. NMR: 0.99 (3H, s), 1.45 (3H, s), 2.22 (3H, s), 3.18 (2H, s), 4.24, 4.30 (2H, each d, J=12), 4.52 (1H, m), 5.71 (1H, br s).

The following compounds were similarly prepared.

21-Chloro-17α-(ethylthio)acetoxy-11β-hydroxy-4-pregnene-3,20-dione (5Ab) mp 160—162 °C (from AcOEt–hexane), 94%. $C_{25}H_{35}ClO_5S$. FAB-MS m/z: 483 $(M+H)^+$. IR: 3360, 2920, 1720, 1635 cm^{-1}. NMR: 0.99 (3H, s), 1.28 (3H, t, J=7), 1.46 (3H, s), 2.68 (2H, q, J=7), 3.22 (2H, s), 4.24, 4.28 (2H, each d, J=15), 4.55 (1H, m), 5.73 (1H, br s).

21-Chloro-11β-hydroxy-17α-(isopropylthio)acetoxy-4-pregnene-3,20-dione (5Ac) mp 146—148 °C (from EtOH–H_2O), 90%. $C_{26}H_{37}ClO_5S$. FAB-MS m/z: 497 $(M+H)^+$. IR: 3360, 2920, 1725, 1640 cm^{-1}. NMR: 0.98 (3H, s), 1.28 (6H, d, J=7), 1.45 (3H, s), 3.07 (1H, septet, J=7), 3.24 (2H, s), 4.24, 4.26 (2H, each d, J=15), 4.55 (1H, m), 5.72 (1H, br s).

21-Chloro-11β-hydroxy-17α-methoxyacetoxy-4-pregnene-3,20-dione (5Ad) mp 179—181 °C (from AcOEt–hexane), 75%. $C_{24}H_{33}ClO_6$. FAB-MS m/z: 453 $(M+H)^+$. IR: 3400, 2920, 1730, 1640 cm^{-1}. NMR: 1.00 (3H, s), 1.45 (3H, s), 3.44 (3H, s), 4.06 (2H, s), 4.20, 4.35 (2H, each d, J=15), 4.52 (1H, m), 5.72 (1H, br s).

21-Chloro-11β-hydroxy-17α-(3-methylthio)propanoyloxy-4-pregnene-3,20-dione (5Ae) mp 162—164 °C (from EtOH), 88%. $C_{25}H_{35}ClO_5S$. EI-MS m/z: 482 (M^+). IR: 3370, 2920, 2900, 1720, 1635 cm^{-1}. NMR: 0.98 (3H, s), 1.46 (3H, s), 2.14 (3H, s), 4.22, 4.32 (2H, each d, J=15), 4.52 (1H, m), 5.72 (1H, br s).

21-Chloro-17α-(3-ethylthio)propanoyloxy-11β-hydroxy-4-pregnene-3,20-dione (5Af) mp 133—134 °C (from AcOEt–hexane), 92%. $C_{26}H_{37}ClO_5S$. FAB-MS m/z: 497 $(M+H)^+$. IR: 3360, 2900, 1720, 1630 cm^{-1}. NMR: 0.98 (3H, s), 1.26 (3H, t, J=8), 1.46 (3H, s), 2.58 (2H, q, J=8), 4.23, 4.32 (2H, each d, J=15), 4.53 (1H, m), 5.72 (1H, s).

21-Chloro-11β-hydroxy-17α-(3-isopropylthio)propanoyloxy-4-pregnene-3,20-dione (5Ag) mp 151—155 °C (from EtOH), 82%. $C_{27}H_{39}ClO_5S$. FAB-MS m/z: 511 $(M+H)^+$. IR: 3420, 2930, 1730, 1650 cm^{-1}. NMR: 0.98 (3H, s), 1.27 (6H, d, J=6), 1.46 (3H, s), 4.23, 4.32 (2H, each d, J=16), 4.54 (1H, m), 5.72 (1H, s).

21-Chloro-9α-fluoro-11β-hydroxy-16α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (5Ba) mp 196—198 °C (from AcOEt–hexane), 90%. $C_{25}H_{32}ClFO_5S$. FAB-MS m/z: 499 $(M+H)^+$. IR: 3300, 2920, 1723, 1655 cm^{-1}. NMR: 0.98 (3H, d, J=7), 1.09 (3H, s), 1.55 (3H, s), 2.22 (3H, s), 3.20, 3.23 (2H, each d, J=16), 4.12, 4.15 (2H, each d, J=16), 4.43 (1H, m), 6.13 (1H, br s), 6.36 (1H, dd, J=10, 2), 7.19 (1H, d, J=10).

21-Chloro-9α-fluoro-11β-hydroxy-16α-methyl-17α-(3-methylthio)propanoyloxy-1,4-pregnadiene-3,20-dione (5Be) mp 191—192 °C (from EtOH), 50%. $C_{26}H_{34}ClFO_5S$. FAB-MS m/z: 513 $(M+H)^+$. IR: 3370, 3260, 2920, 2880, 1730, 1660 cm^{-1}. NMR: 0.92 (3H, d, J=7), 1.08 (3H, s), 1.54 (3H, s), 2.10 (3H, s), 3.26—3.48 (1H, m), 4.09, 4.18 (2H, each d, J=14), 4.42 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, J=10, 2), 7.20 (1H, d, J=10).

21-Chloro-17α-(3-ethylthio)propanoyloxy-9α-fluoro-11β-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (5Bf) mp 162—164 °C (from EtOH), 60%. $C_{27}H_{36}ClFO_5S$. FAB-MS m/z: 527 $(M+H)^+$. IR: 3360, 3240, 2920, 2860, 1730, 1650 cm^{-1}. NMR: 0.92 (3H, d, J=7), 1.08 (3H, s), 1.23 (3H, t, J=7), 1.55 (3H, s), 2.55 (2H, q, J=7), 3.26—3.50 (1H, m), 4.09, 4.18 (2H, each d, J=15), 4.41 (1H, m), 6.14 (1H, s), 6.36 (1H, dd, J=10, 2), 7.20 (1H, d, J=10).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(3-isopropylthio)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (5Bg) mp 90—95 °C (from EtOH–H_2O), 70%. $C_{28}H_{38}ClFO_5S$. FAB-MS m/z: 541 $(M+H)^+$. IR: 3400, 2920, 2860, 1725, 1655 cm^{-1}. NMR: 0.92 (3H, d, J=7), 1.07 (3H, s), 1.24 (6H, d, J=7), 1.55 (3H, s), 2.93 (1H, septet, J=7), 3.28—3.49 (1H, m), 4.09, 4.18 (2H, each d, J=15), 4.42 (1H, m), 6.13 (1H, s), 6.36 (1H, dd, J=10, 2), 7.19 (1H, d, J=10).

21-Chloro-9α-fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (5Ca) mp 200—203 °C (from EtOH), 94%. $C_{25}H_{32}ClFO_5S$. EI-MS m/z: 498 (M^+). IR: 3225, 2920, 1740, 1730, 1650 cm^{-1}. NMR: 0.88 (3H, s), 1.30 (3H, d, J=8), 1.50 (3H, s), 2.15 (3H,

s), 3.39 (2H, s), 4.24 (1H, m), 4.24, 4.30 (2H, each d, $J=12$), 6.05 (1H, br s), 6.25 (1H, dd, $J=10$), 7.31 (1H, d, $J=10$).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(isopropylthio)acetoxy-16β-methyl-1,4-pregnadiene-3,20-dione (5Cc) mp 207—210 °C (from AcOEt–hexane), 74%. $C_{27}H_{36}ClFO_5S$. FAB-MS *m/z*: 527 $(M+H)^+$. IR: 3410, 2940, 2910, 1725, 1653 cm^{-1}. NMR: 1.05 (3H, s), 1.26, 1.28 (6H, each d, $J=7$), 1.39 (3H, d, $J=8$), 1.56 (3H, s), 3.06 (1H, septet, $J=7$), 3.22 (2H, s), 4.10 (2H, s), 4.45 (1H, m), 6.13 (1H, br s), 6.35 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

21-Chloro-9α-fluoro-11β-hydroxy-16β-methyl-17α-(3-methylthio)propanoyloxy-1,4-pregnadiene-3,20-dione (5Ce) mp 178—180 °C (from EtOH), 64%. $C_{26}H_{34}ClFO_5S$. FD-MS *m/z*: 512 (M^+). IR: 3300, 2950, 1730, 1660 cm^{-1}. NMR: 1.01 (3H, s), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.11 (3H, s), 4.10 (2H, s), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

21-Chloro-17α-(3-ethylthio)propanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (5Cf) mp 152—154 °C (from EtOH), 77%. $C_{27}H_{36}ClFO_5S$. FAB-MS *m/z*: 527 $(M+H)^+$. IR: 3490, 2920, 2880, 1740, 1670 cm^{-1}. NMR: 1.01 (3H, s), 1.24 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 1.55 (3H, s), 2.56 (2H, q, $J=7$), 4.11 (2H, s), 4.45 (1H, m), 6.15 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(3-isopropylthio)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (5Cg) mp 168—171 °C (from AcOEt–hexane), 92%. $C_{28}H_{38}ClFO_5S$. FAB-MS *m/z*: 541 $(M+H)^+$. IR: 3440, 2950, 1740, 1660 cm^{-1}. NMR: 1.01 (3H, s), 1.25 (6H, d, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.93 (1H, septet, $J=7$), 4.12 (2H, s), 4.44 (1H, m), 6.14 (1H, s), 6.35 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

11β-Hydroxy-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (6Aa) A mixture of **4**Aa (0.60 g) and NaI (0.50 g) in DMF (7 ml) and CH_3CN (7 ml) was refluxed for 3 h. After the reaction mixture had cooled, ethanethiol (0.13 g) was added. The resulting mixture was stirred at room temperature for 20 min. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed successively with 10% Na_2CO_3, 10% HCl and brine, then dried and concentrated *in vacuo*. The residue was chromatographed with AcOEt–hexane (2 : 3) as an eluent. The product obtained was recrystallized from AcOEt–hexane to give **6**Aa (0.42 g, 85%) as colorless prisms. mp 202—203 °C. $C_{24}H_{34}O_5S$. FAB-MS *m/z*: 435 $(M+H)^+$. IR: 3360, 2910, 1710, 1635 cm^{-1}. NMR: 0.95 (3H, s), 1.45 (3H, s), 2.12 (3H, s), 2.21 (3H, s), 3.19 (2H, s), 4.51 (1H, m), 5.71 (1H, br s).

The following compounds were similarly prepared.

17α-(Ethylthio)acetoxy-11β-hydroxy-4-pregnene-3,20-dione (6Ab) mp 142—143 °C (from AcOEt–hexane), 86%. $C_{25}H_{36}O_5S$. FAB-MS *m/z*: 449 $(M+H)^+$. IR: 3470, 2920, 1718, 1660 cm^{-1}. NMR: 0.95 (3H, s), 1.26 (3H, t, $J=7$), 1.46 (3H, s), 2.12 (3H, s), 2.67 (2H, q, $J=7$), 3.23 (2H, s), 4.51 (1H, m), 5.72 (1H, br s).

11β-Hydroxy-17α-(isopropylthio)acetoxy-4-pregnene-3,20-dione (6Ac) mp 161—164 °C (from AcOEt–hexane), 66%. $C_{26}H_{38}O_5S$. FAB-MS *m/z*: 463 $(M+H)^+$. IR: 3360, 2920, 1717, 1635 cm^{-1}. NMR: 0.93 (3H, s), 1.27, 1.28 (6H, each d, $J=7$), 1.45 (3H, s), 2.10 (3H, s), 3.06 (1H, septet, $J=7$), 3.25 (2H, s), 4.53 (1H, m), 5.72 (1H, br s).

11β-Hydroxy-17α-methoxyacetoxy-4-pregnene-3,20-dione (6Ad) mp 186—189 °C (from AcOEt–hexane), 80%. $C_{24}H_{34}O_6$. FAB-MS *m/z*: 419 $(M+H)^+$. IR: 3360, 2930, 2900, 1722, 1635 cm^{-1}. NMR: 0.95 (3H, s), 1.45 (3H, s), 2.12 (3H, s), 3.45 (3H, s), 4.06 (2H, s), 4.50 (1H, m), 5.71 (1H, br s).

11β-Hydroxy-17α-(3-methylthio)propanoyloxy-4-pregnene-3,20-dione (6Ae) mp 154—156 °C (from PrOH), 63%. $C_{25}H_{36}O_5S$. FAB-MS *m/z*: 449 $(M+H)^+$. IR: 3500, 2910, 2860, 1730, 1710, 1660 cm^{-1}. NMR: 0.94 (3H, s), 1.46 (3H, s), 2.10 (3H, s), 2.12 (3H, s), 4.51 (1H, m), 5.72 (1H, br s).

17α-(3-Ethylthio)propanoyloxy-11β-hydroxy-4-pregnene-3,20-dione (6Af) mp 112—114 °C (from AcOEt–hexane), 77%. $C_{26}H_{38}O_5S$. FD-MS *m/z*: 462 (M^+). IR: 3380, 2920, 1720, 1640 cm^{-1}. NMR: 0.92 (3H, s), 1.24 (3H, t, $J=8$), 1.44 (3H, s), 2.10 (3H, s), 2.57 (2H, q, $J=8$), 4.50 (1H, m), 5.72 (1H, s).

11β-Hydroxy-17α-(3-isopropylthio)propanoyloxy-4-pregnene-3,20-dione (6Ag) mp 58—62 °C (from EtOH–H_2O), 80%. $C_{27}H_{40}O_5S \cdot 1/4\ H_2O$. FAB-MS *m/z*: 477 $(M+H)^+$. IR: 3440, 2920, 1720, 1650 cm^{-1}. NMR: 0.93 (3H, s), 1.26 (6H, d, $J=7$), 1.46 (3H, s), 2.10 (3H, s), 4.52 (1H, m), 5.72 (1H, s).

9α-Fluoro-11β-hydroxy-16α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (6Ba) mp 164—166 °C (from AcOEt–hexane), 94%. $C_{25}H_{33}FO_5S$. FAB-MS *m/z*: 465 $(M+H)^+$. IR: 3370, 2910, 1720, 1650 cm^{-1}. NMR: 0.96 (3H, d, $J=7$), 1.02 (3H, s), 1.55 (3H, s), 2.11 (3H, s), 2.21 (3H, s), 3.21, 3.23 (2H, each d, $J=12$), 4.41 (1H, m), 6.13 (1H, br s), 6.33 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16α-methyl-17α-(3-methylthio)propanoyloxy-1,4-pregnadiene-3,20-dione (6Be) mp 100—103 °C (from EtOH–H_2O), 68%. $C_{26}H_{35}FO_5S$. FAB-MS *m/z*: 479 $(M+H)^+$. IR: 3440, 2940, 1730, 1660 cm^{-1}. NMR: 0.92 (3H, d, $J=7$), 1.01 (3H, s), 1.55 (3H, s), 2.10 (3H, s), 2.11 (3H, s), 3.30—3.50 (1H, m), 4.41 (1H, m), 6.14 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

17α-(3-Ethylthio)propanoyloxy-9α-fluoro-11β-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (6Bf) mp 158—159 °C (from EtOH–hexane), 39%. $C_{27}H_{37}FO_5S$. FAB-MS *m/z*: 493 $(M+H)^+$. IR: 3360, 2920, 2860, 1730, 1700, 1655 m^{-1}. NMR: 0.92 (3H, d, $J=7$), 1.01 (3H, s), 1.24 (3H, t, $J=7$), 1.55 (3H, s), 2.10 (3H, s), 2.55 (2H, q, $J=7$), 3.30—3.50 (1H, m), 4.41 (1H, m), 6.13 (1H, s), 6.35 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-17α-(3-isopropylthio)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (6Bg) mp 175—177 °C (from EtOH–hexane), 42%. $C_{28}H_{39}FO_5S \cdot 1/4H_2O$. FAB-MS *m/z*: 507 $(M+H)^+$. IR: 3300, 2920, 2850, 1730, 1705, 1650 cm^{-1}. NMR: 0.92 (3H, d, $J=7$), 1.00 (3H, s), 1.24 (6H, d, $J=7$), 1.55 (3H, s), 2.10 (3H, s), 2.93 (1H, septet, $J=7$), 3.30—3.50 (1H, m), 4.41 (1H, m), 6.13 (1H, s), 6.35 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (6Ca) mp 217—220 °C (from AcOEt), 73%. $C_{25}H_{33}FO_5S$. FAB-MS *m/z*: 465 $(M+H)^+$. IR: 3460, 2930, 1717, 1650 cm^{-1}. NMR: 1.00 (3H, s), 1.40 (3H, s), 1.57 (3H, s), 2.05 (3H, s), 2.23 (3H, s), 3.19 (2H, br s), 4.44 (1H, m), 6.16 (1H, br s), 6.36 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-17α-(isopropylthio)acetoxy-16β-methyl-1,4-pregnadiene-3,20-dione (6Cc) mp 144—147 °C (from AcOEt–hexane), 66%. $C_{27}H_{37}FO_5S$. FAB-MS *m/z*: 493 $(M+H)^+$. IR: 3360, 2930, 1720, 1652 cm^{-1}. NMR: 0.97 (3H, s), 1.23, 1.27 (6H, each d, $J=7$), 1.37 (3H, d, $J=8$), 1.55 (3H, s), 2.02 (3H, s), 3.07 (1H, septet, $J=7$), 3.22 (2H, s), 4.43 (1H, m), 6.13 (1H, br s), 6.33 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16β-methyl-17α-(3-methylthio)propanoyloxy-1,4-pregnadiene-3,20-dione (6Ce) mp 212—213 °C (from PrOH), 50%. $C_{26}H_{35}FO_5S$. FD-MS *m/z*: 478 (M^+). IR: 3340, 2930, 2900, 1720, 1710, 1650 cm^{-1}. NMR: 0.98 (3H, s), 1.37 (3H, d, $J=7$), 1.56 (3H, s), 2.02 (3H, s), 2.11 (3H, s), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-(3-Ethylthio)propanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (6Cf) mp 185—189 °C (from EtOH), 65%. $C_{27}H_{37}FO_5S$. FAB-MS *m/z*: 493 $(M+H)^+$. IR: 3340, 2930, 1730, 1720, 1660 cm^{-1}. NMR: 0.99 (3H, s), 1.24 (3H, t, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.22 (3H, s), 2.56 (2H, q, $J=7$), 4.45 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-17α-(3-isopropylthio)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (6Cg) mp 203—205 °C (from AcOEt–hexane), 68%. $C_{28}H_{39}FO_5S$. FAB-MS *m/z*: 507 $(M+H)^+$. IR: 3360, 2960, 1730, 1660 cm^{-1}. NMR: 0.98 (3H, s), 1.24 (6H, d, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.02 (3H, s), 2.93 (1H, septet, $J=7$), 4.43 (1H, m), 6.14 (1H, s), 6.35 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

21-Acetylthio-11β-hydroxy-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (7Aa) Potassium thioacetate (1.07 g) was added to a solution of **4**Aa (1.65 g) in acetone (25 ml) and MeOH (5 ml). The mixture was refluxed for 2.5 h. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed successively with 10% Na_2CO_3, 5% HCl and brine, then dried and concentrated *in vacuo*. The residue was purified by column chromatography (eluent, AcOEt : hexane = 3 : 5) to give **7**Aa (0.79 g, 50%).

11β-Hydroxy-21-mercapto-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (8Aa) Hydrazine hydrate (0.2 ml) was added to a solution of **7**Aa (0.78 g) in tetrahydrofuran (15 ml). The mixture was stirred for 15 min at below −5 °C, then diluted with ice-water and extracted with AcOEt. The extract was washed successively with 10% HCl and brine, dried and concentrated *in vacuo*. The residue was purified by column chromatography (eluent, AcOEt : hexane = 3 : 5) to give **8**Aa (0.40 g, 56%).

11β-Hydroxy-21-methylthio-17α-(methylthio)acetoxy-4-pregnene-3,20-dione (9Aa) Triethylamine (0.35 ml) and MeI (0.16 ml) were added to a solution of **8**Aa (0.39 g) in DMF (10 ml) under cooling with ice-water. The mixture was stirred at the same temperature for 4.5 h, then diluted with ice-water. The separated crystals were collected, washed with water, and dried. The product was chromatographed using AcOEt–hexane (3 : 5) as an eluent and recrystallized from EtOH–H_2O to give **9**Aa (0.32 g, 80%) as colorless prisms. mp 76—79 °C. $C_{25}H_{36}O_5S_2$. FAB-MS *m/z*: 481 $(M+H)^+$. IR: 3420, 2910, 1720, 1655 cm^{-1}. NMR: 1.02 (3H, s), 1.46 (3H, s), 2.22 (6H, s), 3.17 (2H, s), 3.32, 3.46 (2H, each d, $J=16$), 4.50 (1H, m), 5.70 (1H, br s).

The following compounds were similarly prepared.

9α-Fluoro-11β-hydroxy-16β-methyl-21-methylthio-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (9Ca-1) mp 112—115 °C (from EtOH–H_2O), 88%. $C_{26}H_{35}FO_5S_2$. FAB-MS *m/z*: 511 $(M+H)^+$. IR: 3400, 2920, 1720, 1715, 1655 cm^{-1}. NMR: 1.06 (3H, s), 1.40 (3H, d, $J=7$), 1.56 (3H, s), 2.23 (3H, s), 2.24 (3H, s), 3.16, 3.27 (2H, each d, $J=14$), 3.23, 3.31 (2H, each d, $J=16$), 4.43 (1H, m), 6.10 (1H, br s), 6.36 (1H, dd, $J=9$, 2), 7.21 (1H, d, $J=9$).

21-Ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (9Ca-2) mp 134—136 °C (from AcOEt–hexane), 48%. $C_{27}H_{37}FO_5S_2$. FAB-MS *m/z*: 525 $(M+H)^+$. IR: 3260, 2920, 1721, 1715, 1650 cm^{-1}. NMR: 1.05 (3H, s), 1.27 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.23 (3H, s), 2.64—2.81 (2H, m), 3.14, 3.22 (2H, each d, $J=14$), 3.26, 3.34 (2H, each d, $J=16$), 4.44 (1H, m), 6.15 (1H, br s), 6.35 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-17α-(isopropylthio)acetoxy-16β-methyl-21-methylthio-1,4-pregnadiene-3,20-dione (9Cc) mp 185—188 °C (from AcOEt–hexane), 48%. $C_{28}H_{39}FO_5S_2$. FAB-MS *m/z*: 539 $(M+H)^+$. IR: 3430, 2920, 1720, 1657 cm^{-1}. NMR: 1.05 (3H, s), 1.26, 1.28 (2H, each d, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.23 (3H, s), 3.07 (1H, septet, $J=7$), 3.19, 3.33 (2H, each d, $J=14$), 3.23 (2H, s), 4.44 (1H, m), 6.23 (1H, br s), 6.36 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

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