Anti-inflammatory 17β-Thioalkyl-16α,17α-ketal and -acetal Androstanes: A New Class of Airway Selective Steroids for the Treatment of Asthma

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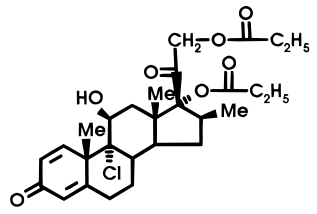
The synthesis and anti-inflammatory potencies of a new class of 17β-thioalkyl-16α,17α-ketal and -acetal androstanes are described. This new class of steroids was made by fragmentation of 2-thioxo-1,2-dihydropyrid-1-yl esters of the corresponding 17-acids to the 17-radical. The radical generated was trapped using a variety of radicophilic disulfides, giving a steroidal D-ring having acetal or ketal functionality at C-16 and C-17, together with a sulfide link at C-17. Compounds from this series bind to the glucocorticoid receptor with high potency and are functional agonists as measured by their ability to induce tyrosine aminotransferase activity in a rat hepatic cell line in vitro. These 17β-thioalkyl androstanes potently inhibit Sephadex-induced rat lung inflammation when administered directly into the airways. The high topical potency, together with a low propensity to induce systemic glucocorticoid-like side effects (rat thymus involution), provides the present compounds with a high degree of airway selectivity compared with currently available inhaled glucocorticoids. The presently described 17β-thioalkyl-16α,17α-ketal androstanes may be useful for therapies for inflammatory diseases such as asthma.

Introduction

Asthma is a chronic inflammatory disease of the airways which is characterized by variable airflow obstruction and bronchial hyperresponsiveness. Mediator and cytokine release from eosinophils, lymphocytes, and other infiltrating, inflammatory cells produces epithelial sloughing, plasma protein extravasation from the tracheobronchial microcirculation, and airway remodeling.[1,2] Bronchial mucosal inflammation is present already in patients with mild disease, and inhaled glucocorticoids are recommended in patients that require regular β_2-receptor agonist therapy to suppress the underlying inflammation.

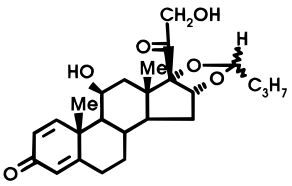
The most potent and effective anti-inflammatory agents available are the glucocorticoids. Potent glucocorticoids like dexamethasone and prednisolone with high systemic bioavailability and pronounced anti-inflammatory properties have been synthesized.[3] However, therapeutic doses of oral glucocorticoids are associated with a range of adverse reactions, the most obvious being Cushing's syndrome, altered lipid and bone metabolism, circulating hormone levels, bone erosion, and vascular effects.[3,4] Asthma is a disease of the airways and glucocorticoids for inhalation have therefore been developed in an attempt to reduce systemic side effects. However, these newer glucocorticoids, beclomethasone dipropionate (**1**) and budesonide (**2**), retain significant oral bioavailability (≥10%) and together with drug absorbed over the tracheobronchial mucosa result in significant plasma levels and systemic side effects at therapeutic doses.[3,4] Plasma levels of cortisone are reduced and the function of the hypothalamine−pituitary−adrenal (HPA) axis is suppressed but more importantly are the osteoporosis and the reduced rate of bone growth in children.[3,5]

The most recently introduced glucocorticoid for inhalation use in asthma is fluticasone propionate (**3**).



Beclomethasone Dipropionate

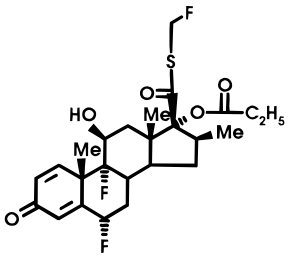
1



Budesonide

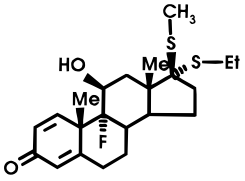
2

Although claimed to have a lower oral bioavailability, the use of this drug is associated with similar systemic adverse reactions as those produced by the other two new glucocorticoids.[6] These side effects have led to the questioning of the long-term safety of inhaled glucocorticoids in large parts of the population, and in children in particular.[5] A novel topically airway selective glucocorticoid is therefore highly desirable for the safe treatment of subjects with asthma.



Fluticasone propionate

3



Tipredane

4

Previous work has indicated the importance of the 16α,17α-ketal substitution for increasing glucocorticoid potency through increased binding to a hydrophobic site in the glucocorticoid receptor.[7] Furthermore, this functionality is labile and is metabolized by microsomal mono-oxygenases in the liver, the site of attack being

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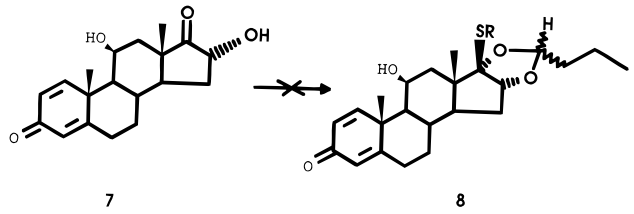
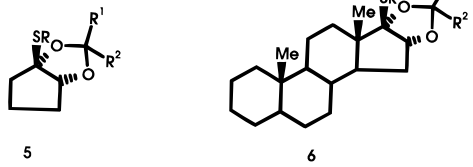
Scheme 1



7 8

the ketal/acetal carbon atom. Oxygenation is followed by hydrolytic decomposition, giving 16α-hydroxyprednisolone, an essentially inactive fragmentation product.[8]

The aim of the present work was to retain the 16α,17α-ketal and/or -acetal functionality, which is associated with high potency at the glucocorticoid receptor, while introducing novel functionality around the D-ring which would further enhance systemic metabolism. Synthesis centered around compounds incorporating the novel 3a-(alkylthio)-1,3-dioxo[3.3]bicyclooctane skeleton (**5**) into the D-ring position of the steroid nuclear backbone. These molecules, together with those combining further changes in functionalities in the A-ring of the androstane skeleton (**6**), have produced a novel class of compounds, 17β-thioalkyl-16α,17α-ketal/acetal androstanes, with high potency at the glucocorticoid receptor. These compounds possess anti-inflammatory properties and have indicated remarkably improved airway selectivity when compared to currently available glucocorticoids in preclinical models. A detailed pharmacological investigation of the HPA axis is in press.[9]



5 6

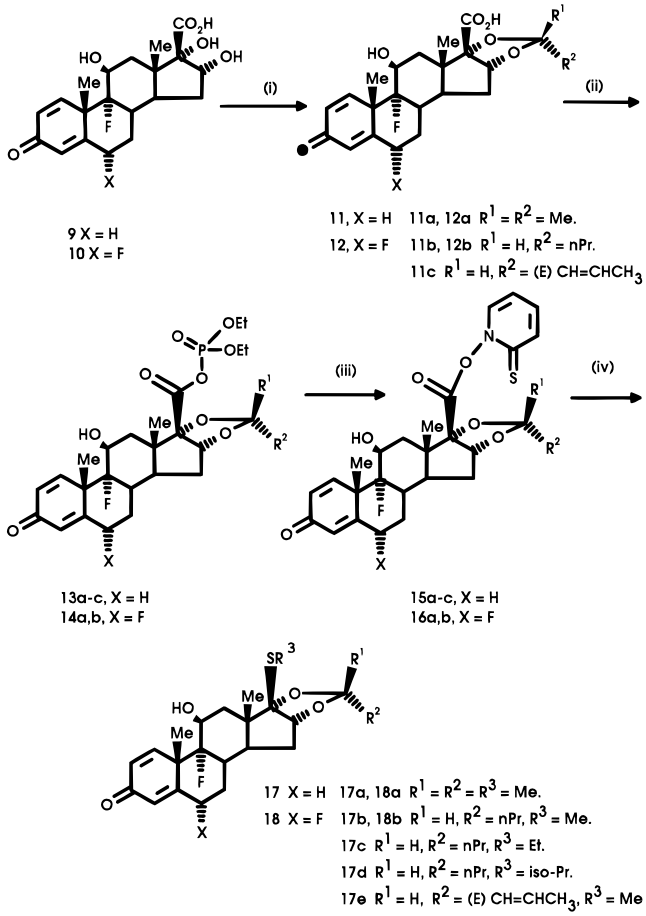
Chemistry

Application of normal ionic chemistry failed to yield our target molecules. When, for example, acetal or ketal formation was attempted on the 16α-hydroxy-17-keto steroids **7** in the presence of mercaptans (Scheme 1), no products with the desired skeleton **8** were obtained.

Recourse was hence made to radical chemistry. It was anticipated that the steric integrity of a preformed 16α,17α-acetal or -ketal, bearing a group at C-17 that could fragment to a 17-radical, would be trapped by radicophiles such as dialkyl disulfides exclusively on the β-face, to give the 16α,17α-acetal bearing a 17β-alkylthio function (Scheme 2). The key synthon required was thus one in which a 17β-substituent was capable of collapsing to a radical. The 17β-acid functionality, after conversion to the 2-thioxo-1,2-dihydropyrid-1-yl ester ("Barton ester"),[10] proved successful.

The ideal starting materials for the preparation of both 6-H and 6α-F androstanes of this type were the 11β,16α,17α-trihydroxy-17β-carboxylic acids **9** and **10**. Reaction with aldehydes and ketones would yield the corresponding acetals and ketals **11** and **12**. Oxidation of triamcinolone gave the acid **9**; oxidation of triamcinolone acetonide gave the corresponding acetonide **11a**. Acetalization of the acid **9** with butanal gave the

Scheme 2[a]



9 X = H
10 X = F

11, X = H 11a, 12a $R^1 = R^2$ = Me.
12, X = F 11b, 12b R^1 = H, R^2 = nPr.
11c R^1 = H, R^2 = (E) CH=CHCH$_3$

13a-c, X = H
14a,b, X = F

15a-c, X = H
16a,b, X = F

17 X = H 17a, 18a $R^1 = R^2 = R^3$ = Me.
18 X = F 17b, 18b R^1 = H, R^2 = nPr, R^3 = Me.
17c R^1 = H, R^2 = nPr, R^3 = Et.
17d R^1 = H, R^2 = nPr, R^3 = iso-Pr.
17e R^1 = H, R^2 = (E) CH=CHCH$_3$, R^3 = Me

[a] Reagents: (i) $R^1C(=O)R^2$, perchloric acid, THF; (ii) diethyl chlorophosphate, THF; (iii) sodium salt of 2-mercaptopyridine *N*-oxide, DMF; (iv) R^3SSR^3, dichloromethane, *hν*.

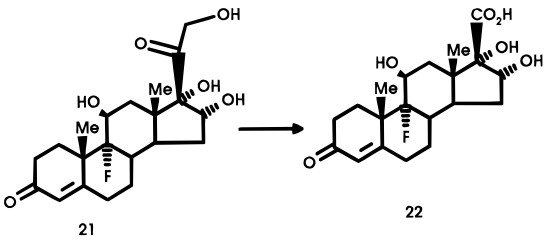
acetal **11b** (which has been prepared by another route previously[11]), and acetalization of **9** with (*E*)-2-butenal gave **11c**. The ketal **12a** has been described previously.[12] Simple hydrolysis of **12a** gave the acid **10**, which on acetalization with butanal gave the acetal **12b**.

With acetal formation, a new chiral center is formed at the C-20 position, and it was found that, by forming this acetal with a 17β-carboxylic acid group present, the *R*/*S* ratio could be favorably controlled. In general, both isomers are formed, but the 20*R*-isomer was formed preferentially and the products are depicted as thus, with the *R*/*S* ratio noted. If required, purification to homogeneity of **11b,c** and **12b** could be achieved by chromatography or crystallization.

The acids **11a**−**c** and **12a,b** were successfully activated by reaction with diethyl chlorophosphate in tetrahydrofuran. The resulting mixed anhydrides **13a**−**c** and **14a,b** were used without isolation by reaction with the sodium salt of *N*-hydroxypyridine-2-thione. This yielded the esters **15a**−**c** and **16a,b**. These esters (**15a**−**c**, **16a,b**) were sufficiently stable to allow isolation provided they were protected from light, characterization was difficult because of the photolytic instability, and the esters were generally used immediately.

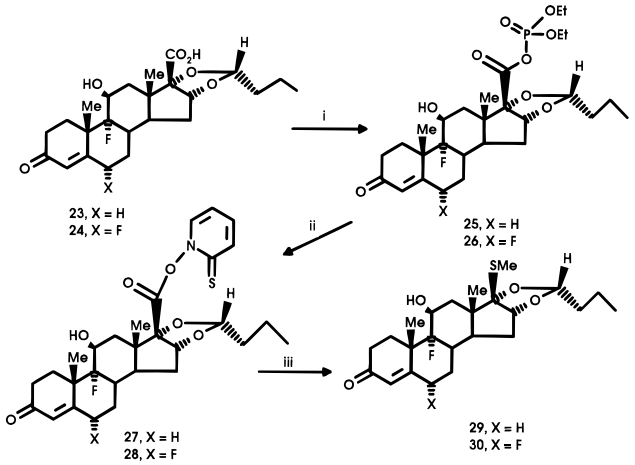
Photolysis of the esters **15a**−**c** and **16a,b**, using a tungsten lamp, generated the radical at C-17, which could be trapped with an appropriate dialkyl disulfide.[13] The dialkyl disulfide was used as solvent or in excess in dichloromethane solution. Radical fragmentation

Scheme 3[a]



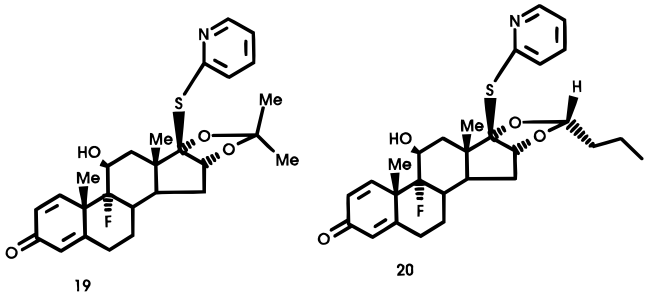
[a] Reagents: (i) potassium superoxide, 18-crown-6, DMF.

Scheme 4[a]



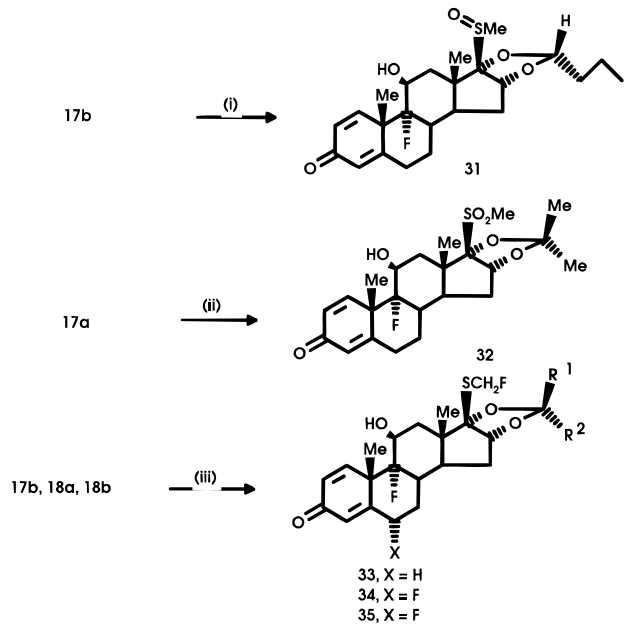
[a] Reagents: (i) diethyl chlorophosphate, THF; (ii) sodium salt of 2-mercaptopyridine *N*-oxide, DMF; (iii) MeSSMe, dichloromethane, *hν*.

and trapping occurred with complete retention of configuration at the C-17 position. Thus, trapping the radical derived from **15a**−**c** and **16a,b** with dimethyl disulfide gave the methylthio ethers **17a,b,e** and **18a,b**, while trapping the radical derived from **15b** with diethyl disulfide or diisopropyl disulfide gave the ethylthio ether **17c** and isopropylthio ether **17d**, respectively. Irradiation of the esters **15a,b** in the absence of a trapping agent led to radical fragmentation, and trapping by the 2-mercaptopyridyl functionality itself yielded the 17-thiopyrid-2-yl ethers **19** and **20**.



Of particular interest to us were compounds bearing our D-ring substitution pattern with partially reduced 'A'-ring character. In the case of the 6-H,9-F series, this was accomplished as follows. 1,2-Dihydrotriamcinolone (**21**) was oxidatively cleaved to give the 17-carboxylic acid **22** (Scheme 3). Subsequent acetalization using the above described methodology gave the acetal **23** (Scheme 4). The sequence **23** → **25** → **27** → **29** (shown in Scheme 4) was then used as described above to generate the 1,2-dihydro-17-methylthio ether **29**. In the 6,9-difluoro series, the intermediate **12b** was partially reduced by

Scheme 5[a]



[a] Reagents: (i) potassium peroxymonosulfate, aqueous acetone; (ii) *m*-chloroperoxybenzoic acid, chloroform; (iii) 2,6-di-*tert*-butyl-4-methylpyridine, 4A molecular sieve, xenon difluoride, dichloromethane.

iron pentacarbonyl/sodium hydroxide in aqueous methanol to give the 1,2-dihydro derivative **24** which was transformed into the desired product **30** by the corresponding sequence **24** → **26** → **28** → **30** (Scheme 4).

Preparation of further novel analogues of this unusual androstane could be effected by performing chemistry on the 17-thio ether products. Thus, oxidation of **17b** with oxone gave the sulfoxide **31** as a mixture of diastereoisomers. Overoxidation of **17a** gave the sulfone **32**. Fluorination of the 17-methylthio group of **17b** and **18a,b** with xenon difluoride gave the (fluoromethyl)thio ethers **33**−**35**, respectively (Scheme 5).

Biology

In order to investigate the structure−activity relationships of the compounds, they were initially tested for binding affinity to the glucocorticoid receptor (isolated from rat thymus tissue). The compounds were then examined for receptor agonist or antagonist activity by studying their ability to induce tyrosine aminotransferase (TAT) activity in rat liver H4IIE cells. All of the compounds displayed agonist activity (although compound **20** was only a very weak inducer TAT activity). The compounds' in vivo anti-inflammatory effects were examined by intratracheal administration directly into rat airways prior to administration of Sephadex particles. The ratio between inhibition of the inflammatory response and the effect on the thymus (organ involution, simultaneous measurement of the two parameters in the same animal) was obtained. Obviously, the ideal candidate would have the largest possible separation between efficacy and side effect. We hypothesize that the larger this ratio, the wider will be the clinical therapeutic ratio, and hence safety, in asthma patients.

Structure−Activity Relationships

With two exceptions, the steroids described in this paper exhibited good affinity for the glucocorticoid

Table 1. Comparative Pharmacology of Selected Compounds

compound	receptor binding IC_{50} (nM)	TAT ED_{50} (nm)	lung edema ED_{50} (mg/kg, it × 2)	thymus involution ED_{50} (mg/kg, it × 2)	topical/ systemic ratio
budesonide (**2**)	2.9	0.2	0.39	0.96	0.40
fluticasone propionate (**3**)	5.0	0.1	0.05	0.47	0.11
tipredane (**4**)	2.3	2.0	2.1	1.1	1.91
17a	1.6	0.2	0.3	0.9	0.33
17b	1.7	1.7	>1.0	1.8	>0.56
17c	3.3	1.5	>3.0	7.0	>0.43
17d	5.5	7.0	>3.0	>3.0	~1.0
17e	1.8	1.1	>3.0	1.1	>2.73
18a	2.2	0.2	1.3	3.2	0.40
18b	2.4	0.4	0.11	0.54	0.20
19	22	50	>3.0	>3.0	~1.0
20	12	>100	>3.0	>3.0	~1.0
29	2.1	0.7	3.6	5.2	0.69
30	2.2	0.3	0.06	1.0	0.06
31	3.2	23	>3.0	3.0	>1.0
32	5.3	13	2.2	1.4	1.57
33	3.3	1.2	>3.0	4	>0.75
34	4.3	1.0	0.07	1.9	0.037
35	2.2	0.3	0.3	4.6	0.065

receptor. The affinity was markedly reduced with increasing size of the R^3 substituent. Thus, replacing the methylthio group with ethylthio and isopropylthio decreased affinity by 2- and 4-fold, respectively. The pyridylthio-substituted compounds were about 10 times less potent than the methylthio substituent. There was also a trend of lower affinity for the glucocorticoid receptor in compounds with groups of increased polarity at C-17 (methylsulfonyl and methylsulfinyl being less active than methylthio). It is interesting to note that tipredane (**4**) (a 17-methylmercapto compound) undergoes metabolic sulfoxidation.[14] A similar metabolic transformation would be expected, therefore, to be an important inactivation pathway in our series. Introduction of a fluoro group in the 17β-side chain does not markedly enhance potency of binding to the steroid receptor. It would appear that the optimal R^3 substituent in the present series of androstane compounds is methyl with the sulfur atom in its lowest oxidation state.

The functional assay data (induction of TAT) served to measure the compounds' ability to penetrate the whole cell and to determine whether the compounds were agonists or antagonists. The TAT data are in general agreement with the findings of the binding studies in that activity is sensitive to increases in both size and polarity in the 17β-position. However, compared with the binding data, the potency differences were accentuated in the whole cell experiments, indicating that they are a function of both absorption through the cell membrane and of affinity for the receptor. Thus, the trends observed in the binding assay were mirrored in the functional assay whereby both an increased size in the R^3 region and oxidation of the sulfur atom also reduced potency.

In this limited series of androstanes, 6α-fluoro incorporation and/or partial A-ring saturation gave compounds approximately equiactive to parent compounds. However, the major aim of the present program of work was the synthesis of compounds with high topical but low systemic potency. This was achieved in the present series. The order of selectivity for the reference steroids examined was fluticasone propionate > budesonide > tipredane. Four compounds in the current series showed selectivity greater than that of budesonide using the ratio between topical to systemic potency, and three compounds were considerably more selective than fluticasone propionate. These data may be in accordance with the expected deactivation of the glucocorticoid steroid by sulfur oxidation followed by hydrolytic decomposition to inert 16-hydroxy-17-keto androstanes.

Taken together, these results suggest that fluorination at the 6α-position or reduction of the 1,2-double bond in compound **18b** to give compound **30** increases the anti-inflammatory potency and selectivity in vivo in these substituted androstanes.

Summary

The chemical syntheses and structure−activity relationship of a novel series of 17β-thioalkyl-16α,17α-ketal and -acetal androstanes as selective glucocorticoid topical anti-inflammatory agents are described. Optimal selectivity for the airways within the series is achieved by reduction of the 1,2-double bond in the A-ring or by fluorination at the 6α-position of the steroid B-ring. Three compounds have shown greater selectivity than fluticasone propionate in topical versus systemic activity. As indicated by the effects on airway inflammation versus thymus involution, it is anticipated that these compounds will be potent anti-inflammatory agents by the inhalation route but have little propensity to produce glucocorticoid-like systemic side effects.[9]

Experimental Section

Reagents, starting materials, and solvents were purchased from common commercial suppliers and used as received or distilled from the appropriate drying agent. Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. All organic solutions were dried over magnesium sulfate. Concentration refers to evaporation under aspirator vacuum using a Buchi rotary evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40−63 μm) with the solvent system indicated. Yields are not optimized. NMR spectroscopic data were recorded on a Varian VXR 400 MHz instrument and are consistent with the assigned structures. NMR data are reported in ppm downfield relative to internal TMS (0 ppm) as standard. Melting points are uncorrected. Elemental analyses were performed by the Analytical Department at Rhône-Poulenc Rorer.

9α-Fluoro-11β,16α,17α-trihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (9). A stirred solution of triamcinolone (15.0 g, 38 mmol) in DMF (150 mL) was treated with K_2CO_3 (15.0 g, 0.11 mol) and then with H_2O_2 (27% aqueous

solution, 15 mL, 61 mmol), with a slight exotherm (temperature rose to 38 °C), and the mixture was stirred for 1 h. MeOH (50 mL) was added and stirring continued for 6 h. A further volume of H_2O_2 (10 mL, 41 mmol) was added and stirring continued for a further 16 h. The reaction mixture was poured into H_2O (2.5 L), and the solution was extracted twice with EtOAc (1.5 and 1 L). The aqueous phase was acidified with concentrated HCl (20 mL) and left to stand to give two crops of **9** (6.5 g, 45%): mp 320 °C dec; ^{1}H NMR (DMSO-d_6) 0.95 (s, 3H), 1.28−1.4 (m, 2H), 1.49 (s, 3H), 1.58 (bd, 1H, J = 14 Hz), 1.72−1.85 (m, 2H), 2.0−2.18 (m, 2H), 2.24−2.42 (m, 2H), 2.55−2.7 (m, 1H), 4.13 (m, 1H), 4.73 (bd, 1H, J = 9 Hz), 5.2 (bs, 1H), 5.25 (m, 1H), 6.0 (s, 1H), 6.22 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{20}H_{25}FO_6$) C, H.

Preparation of 6α,9α-Difluoro-11β,16α,17α-trihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (10). A stirred solution of the acetonide **12a**[11] (75.0 g, 0.17 mol) in HCOOH (1.5 L), under N_2, was heated at 80 °C for 2.5 h. The reaction mixture was concentrated to give a tan solid which was taken up in more HCOOH (400 mL) and stirred at 80 °C for a further 1 h. The mixture was concentrated, taken up in toluene, and concentrated again. The residue was taken up in dioxane (1.0 L) and treated with aqueous NaOH (2 M) until the pH was 10−11 and the mixture stirred for 1 h. The mixture was concentrated to remove the dioxane, but not to dryness, and taken up in more water and the pH adjusted to 7. The aqueous phase was washed with EtOAc and acidified to pH 2 to give a white precipitate which was washed with H_2O and dried to give **10** (59.1 g, 87%): mp 308−309 °C dec; ^{1}H NMR (DMSO-d_6) 0.95 (s, 3H), 1.3−1.55 (m, 5H), 1.6 (dd, 1H, J = 2, 14 Hz), 1.83 (m, 1H), 2.05 (dd, 1H, J = 3, 14 Hz), 2.2 (m, 2H), 2.42 (m, 1H), 4.14 (m, 1H), 4.75 (dd, 1H, J = 2, 9 Hz), 5.2 (bs, 1H), 5.35 (dd, 1H, J = 1.6, 4 Hz), 5.62 (dddd, 1H, J = 1.7, 6.7, 8.3, 48.5 Hz), 6.1 (s, 1H), 6.28 (dd, 1H, J = 2, 10 Hz), 7.26 (dd, 1H, J = 1.5, 10 Hz). Anal. ($C_{20}H_{24}F_2O_6$) C, H.

9α-Fluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (11a). A stirred solution of triamcinolone acetonide (2.9 g, 6.7 mmol) in MeOH (100 mL) was treated with K_2CO_3 (2.1 g, 15.2 mmol) and air bubbled through the mixture using a glass scinter. After 4 h the mixture was concentrated, taken up in H_2O (250 mL), and acidified to pH 9 using dilute HCl. The aqueous phase was washed with EtOAc (100 mL) and acidified to pH 2 using concentrated HCl to give a solid precipitate which was washed with H_2O and sucked dry to give **11a** as a white solid (1.9 g, 68%): mp 311−312 °C; ^{1}H NMR (DMSO-d_6) 0.94 (s, 3H), 1.16 (s, 3H), 1.3 (s, 3H), 1.3−1.43 (m, 1H), 1.47−1.62 (c, 2H), 1.49 (s, 3H), 1.68 (bd, 1H, J = 12.7 Hz), 1.78−1.95 (c, 3H), 2.33 (bdd, 1H, J = 3.4, 14 Hz), 2.44 (m, 1H), 2.63 (m, 1H), 4.15 (b, 1H), 4.95 (d, 1H, J = 5.3 Hz), 5.34 (dd, 1H, J = 2, 4 Hz), 6.0 (s, 1H), 6.22 (dd, 1H, J = 2, 10 Hz), 7.27 (d, 1H, J = 10 Hz). Anal. ($C_{23}H_{29}FO_6$) C, H.

Procedure for the Acetalization of 16α,17α-Dihydroxy Functionality: Preparation of 11b,c and 12b. (20*R*,*S*)-16α,17α-(Butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (11b). To a stirred suspension of the trihydroxy acid **9** (7.9 g, 20 mmol) in THF (65 mL) at 25 °C were added butyraldehyde (9.2 mL, 0.1 mol) and perchloric acid (0.2 g, 1.97 mmol). When the reaction mixture was homogeneous (1−5 h), the perchloric acid was neutralized by addition of Et_3N (0.2 g, 1.97 mmol). Concentration gave a solid which was dissolved in aqueous NaOH (2 M), and the resulting aqueous solution was washed several times with Et_2O. Acidification of the aqueous solution with HCl (10 M) gave a white precipitate which was filtered, washed with H_2O, and dried under vacuum (80 °C, 18 h) to give **11b** (20*R*/*S* 9/1) (8.5 g, 91.5%): mp 205 °C dec; ^{1}H NMR (DMSO-d_6) 0.85 (m, 3H), 0.96 (s, 3H), 1.22−1.46 (c, 4H), 1.50 (s, 3H), 1.49−1.61 (m, 3H), 1.70−1.97 (m, 4H), 2.33 (dd, 1H, J = 5, 9 Hz), 2.34−2.50 (m, 1H), 2.62 (dt, 1H, J = 5.6, 13.5 Hz), 4.15 (c, 1H), 4.67 (t, 0.9H, J = 5 Hz), 4.85 (d, 0.9H, J = 5 Hz), 5.08 (d, 0.1H, J = 6.7 Hz), 5.16 (t, 0.1H, J = 4.6 Hz), 5.89 (m, 1H), 6.01 (s, 1H), 6.23 (dd, 1H, J = 1.8, 10 Hz), 7.29 (d, 1H, J = 10 Hz). Anal. $C_{24}H_{31}FO_6 \cdot H_2O$ C, H.

(20*R*,*S*)-16α,17α-[(*E*)-2-Butenylidenedioxy]-9α-fluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (11c). As described above for compound **11b**, the acid **9** (8.9 g, 23.4 mmol) and crotonaldehyde (7.4 g, 105.3 mmol) afforded the acid **11c** (20*R*/*S* 4/1) (9.1 g, 90%): ^{1}H NMR (DMSO-d_6) 0.96 (s, 3H), 1.30−1.43 (m, 1H), 1.50 (s, 3H), 1.47−1.60 (m, 2H), 1.64 (dd, 0.6H, J = 2, 6 Hz), 1.68 (dd, 2.4H, J = 2, 6 Hz), 1.68−2.0 (m, 5H), 2.34 (dd, 1H, J = 3.5, 14 Hz), 2.35−2.52 (m, 1H), 2.63 (dt, 1H, J = 5.5, 14 Hz), 4.15 (c, 1H), 4.87 (d, 0.8H, J = 5 Hz), 4.95 (d, 0.8H, J = 7 Hz), 5.07 (d, 0.2H, J = 6 Hz), 5.28 (m, 0.2H), 5.33−5.40 (m, 1.8H), 5.46 (d, 0.2H, J = 6 Hz), 5.85 (m, 0.2H), 5.92 (m, 0.8H), 6.03 (s, 1H), 6.23 (dd, 1H, J = 2, 10 Hz), 7.29 (d, 1H, J = 10 Hz). Anal. $C_{24}H_{29}FO_6 \cdot 1.25H_2O$ C, H.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (12b). To a stirred suspension of 6α,9α-difluoro-11β,16α,17α-trihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid (50 g, 126 mmol) in THF (2 L) at 25 °C, under N_2, were added butyraldehyde (59.2 g, 820 mmol) and perchloric acid (1.2 g, 11.8 mmol). The reaction mixture was stirred for 16 h and then treated dropwise with Et_3N (1.2 g, 11.8 mmol). Evaporation of the solvent in vacuo gave a yellow oil which was partitioned between EtOAc (1 L) and aqueous Na_2CO_3 (2 M). The aqueous phase was decanted, washed with more EtOAc (400 mL), and acidified to pH 2 with HCl (10 M) before being extracted with Et_2O (1 L). The combined Et_2O extracts were washed with H_2O and brine, then dried, and concentrated to give a white solid which was triturated with cyclohexane before being dried under vacuum at 80 °C overnight to give **12b** (20*R*/*S* 4/1) (54.8 g, 96%) as a white solid: mp 182−183 °C; ^{1}H NMR (DMSO-d_6) 0.85 (m, 3H), 0.96 (s, 3H), 1.22−1.46 (c, 4H), 1.50 (s, 3H), 1.49−1.62 (m, 3H), 1.79 (c, 1H), 1.90−2.06 (m, 3H), 2.26 (c, 1H), 2.45−2.67 (m, 1H), 4.17 (c, 1H), 4.68 (t, 0.8H, J = 4 Hz), 4.88 (d, 0.8H, J = 5 Hz), 5.08 (d, 0.2H, J = 7 Hz), 5.19 (t, 0.2H, J = 4.5 Hz), 5.45 (dd, 1H, J = 1.6, 4 Hz), 5.63 (c, 1H), 6.10 (s, 1H), 6.29 (dd, 1H, J = 2, 10 Hz), 7.35 (dd, 1H, J = 1.5, 10 Hz). Anal. ($C_{24}H_{30}F_2O_6$) C, H.

General Procedure for the Synthesis of 17-Alkylthio Ethers: Synthesis of 9α-Fluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-17β-(methylthio)androsta-1,4-dien-3-one (17a) (11a → 13a → 15a → 17a). To a stirred solution of the acid **11a** (1.05 g, 2.5 mmol) in THF (35 mL) containing activated molecular sieves (type 4A, 1g) under an atmosphere of N_2 at 25 °C was added Et_3N (0.7 mL, 5 mmol). The mixture was stirred (0.5 h), treated dropwise (45 min) with diethyl chlorophosphate (0.54 mL, 3.75 mmol), and then stirred (90 min). The resulting mixture was filtered through a pad of Celite and the THF evaporated. The crude oil obtained was taken up in EtOAc (50 mL) and washed with HCl (1 M, 25 mL), H_2O (2 × 25 mL) and saturated brine (2 × 25 mL). The EtOAc phase was dried (Na_2SO_4), filtered, and concentrated, affording 9α-fluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylic diethyl phosphoric anhydride (**13a**) as a crude yellow oil (1.5 g) which was used without further purification in the next step.

In a reaction vessel protected from light, a stirred solution of the anhydride **13a** (3.4 g) in DMF (30 mL) containing activated molecular sieves (type 4A, 5g) under N_2 was treated at 20 °C with the sodium salt of 2-mercaptopyridine *N*-oxide (1.13 g, 7.6 mmol). After the reaction was completed (TLC), the reaction mixture was filtered and the filtrate poured into ice cold H_2O (150 mL). The yellow precipitate formed was collected by filtration, washed with cold water, dissolved in CH_2Cl_2 (100 mL), washed with cold H_2O and saturated brine, dried, and concentrated (20 °C, 13 mmHg) to give 2-thioxo-1,2-dihydropyrid-1-yl 9α-fluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylate ester (**15a**) (2.5 g) as a bright yellow solid, which was used directly in the next step. All the above procedures were carried out with exclusion of light as far as possible.

A solution of the ester **15a** (2.1 g, 3.96 mmol) in MeSSMe (80 mL) was irradiated with a tungsten lamp (300 W) at −8 °C under N_2 until the reaction was complete (1−3 h). MeSSMe was removed under reduced pressure and the residue purified by chromatography ($CHCl_3$). The solid obtained after evaporation of the solvent was recrystallized (EtOAc) to give **17a** (0.45 g in 7% yield for last three steps), as a white solid: mp 225

°C; ^{1}H NMR (DMSO-d_6) 1.13 (s, 3H), 1.27−1.39 (m, 1H), 1.33 (s, 3H), 1.44 (dd, 1H, J = 6, 13 Hz), 1.50 (s, 3H), 1.54 (s, 3H), 1.59 (m, 1H), 1.68 (d, 1H, J = 13 Hz), 1.81 (c, 1H), 1.93−2.03 (m, 2H), 2.11 (s, 3H), 2.35 (dt, 1H, J = 4, 13 Hz), 2.4 (m, 1H), 2.63 (m, 1H), 4.13 (c, 1H), 4.39 (d, 1H, J = 6 Hz), 5.34 (c, 1H), 6.01 (s, 1H), 6.23 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{23}H_{31}FO_4S$) C, H.

(20*R*)-16α,17α-(Butylidenedioxy)-9α-fluoro-11β-hydroxy-17β-(methylthio)androsta-1,4-dien-3-one (17b) (11b → 13b → 15b → 17b). As described above for compound **13a**, the acid **11b** (6.4 g, 15.2 mmol) gave (20*R*,*S*)-16α,17α-(butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic diethyl phosphoric anhydride (**13b**) as a yellow oil (7.5 g) which was used as such.

As described above for compound **15a**, the mixed anhydride **13b** (4.2 g) gave 2-thioxo-1,2-dihydropyrid-1-yl (20*R*,*S*)-16α,17α-(butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (**15b**) (3 g) which was used as such.

As described above for compound **17a**, a solution of the ester **15b** (2g) in DMF (5 mL) and MeSSMe (75 mL) was irradiated. After workup, the powder obtained was recrystallized from EtOAc to give **17b** (0.63 g, in 25% yield for last three steps) as a white solid in a stereoisomeric purity greater than 98%: mp 187 °C; ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J = 7.5 Hz), 1.17 (s, 3H), 1.23−1.61 (m, 7H), 1.50 (s, 3H), 1.61 (m, 1H), 1.80 (m, 1H), 1.93−2.05 (m, 2H), 2.09 (s, 3H), 2.33 (dd, 1H, J = 3.5, 14 Hz), 2.4 (m, 1H), 2.64 (m, 1H), 4.12 (c, 1H), 4.14 (d, 1H, J = 5.5 Hz), 5.12 (t, 1H, J = 4.3 Hz), 5.34 (dd, 1H, J = 2, 4 Hz), 6.01 (t, 1H, J = 1.5 Hz), 6.23 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{24}H_{33}FO_4S$) C, H.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-17β-(ethylthio)-9α-fluoro-11β-hydroxyandrosta-1,4-dien-3-one (17c) (15b → 17c). The ester **15b** (1 g, 1.9 mmol) was dissolved in dimethylformamide (5 mL) and diethyl disulfide (35 mL) and irradiated at −40 °C for 3 h under a N_2 atmosphere. The solvents were removed in vacuo (70 °C, 0.4 mmHg), and the residue was purified by chromatography ($CHCl_3$). The solid obtained after evaporation of the solvent was recrystallized (EtOAc and *n*-hexane) to give **17c** (20 *R*/*S* 6/1) as a white solid (0.30 g, 35%): mp 228−229 °C; ^{1}H NMR (DMSO-d_6) 0.87 (t, 2.55H, J = 7.4 Hz), 0.89 (t, 0.45H, J = 7.4 Hz), 1.07 (s, 0.45H), 1.17 (m, 5.55H), 1.27−1.46 (m, 4H), 1.49 (s, 0.45H), 1.50 (s, 2.55H), 1.50−1.60 (m, 3H), 1.71 (d, 1H, J = 14 Hz), 1.80 (m, 1H), 1.95 (m, 1H), 2.02 (dt, 1H, J = 3.5, 10.7 Hz), 2.33 (m, 1H), 2.33−2.47 (m, 1H), 2.64 (m, 1H), 2.68 (m, 2H), 4.12 (d, 0.85H, J = 5.5 Hz), 4.13 (c, 1H), 4.75 (d, 0.15H, J = 7 Hz), 5.07 (t, 0.15H, J = 5.5 Hz), 5.15 (t, 0.85H, J = 5 Hz), 5.33 (c, 0.85H), 5.38 (c, 0.15H), 6.0 (s, 1H), 6.22 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{25}H_{35}FO_4S$) C, H.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-9α-fluoro-11β-hydroxy-17β-(isopropylthio)androsta-1,4-dien-3-one (17d) (15b → 17d). The ester **15b** (2.40 g, 4.5 mmol) dissolved in DMF (10 mL) and diisopropyl disulfide (40 mL) was treated as described above for compound **17a**. Recrystallization (EtOAc and petroleum spirit) gave **17d** (20*R*/*S* 6/1) as a white solid (0.6 g, 28%): mp 235 °C; ^{1}H NMR (DMSO-d_6) 0.88 (t, 2.55 H, J = 7.5 Hz), 0.92 (t, 0.45H, J = 7.5 Hz), 1.05 (s, 0.45H), 1.17 (s, 2.55 H), 1.23 (d, 3H, J = 7 Hz), 1.28 (d, 3H, J = 7 Hz), 1.30−1.45 (m, 4H), 1.49 (s, 0.45H), 1.50 (s, 2.55H), 1.50−1.63 (m, 3H), 1.67−1.84 (m, 2H), 1.95 (m, 1H), 2.07 (dt, 1H, J = 3.5, 10 Hz), 2.32 (dd, 1H, J = 3.5, 14 Hz), 2.35−2.50 (m, 1H), 2.63 (m, 1H), 3.42 (m, 1H), 4.08 (d, 0.85H, J = 4.5 Hz), 4.15 (c, 1H), 4.73 (d, 0.15H, J = 6 Hz), 5.08 (t, 0.15H, J = 4.5 Hz), 5.16 (t, 0.85H, J = 4.5 Hz), 5.37 (c, 1H), 6.02 (s, 1H), 6.23 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{26}H_{37}F_2O_4S$) C, H.

(20*R*)-16α,17β-[(*E*)-2-Butenylidenedioxy]-9α-fluoro-11β-hydroxy-17β-(methylthio)androsta-1,4-dien-3-one (17e) (11c → 13c → 15c → 17e). As described above for compound **13a**, the acid **11c** (6.4 g, 15.2 mmol) afforded the crude (20*R*,*S*)-16α,17α-(butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic diethyl phosphoric anhydride (**13c**) as a yellow oil (7.5 g) which was used as such.

As described above for compound **15a**, the mixed anhydride **13c** (2 g) gave after workup the ester 2-thioxo-1,2-dihydropyrid-1-yl (20*R*,*S*)-16α,17α-[(*E*)-2-butenylidenedioxy]-9α-fluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (**15c**) (1.90 g) which was used as such.

As described above for compound **17a**, the ester **15c** (1.85 g) gave, after recrystallization (Et_2O), **17e** as a white solid (0.25 g, 14% for last three steps) in a stereoisomeric purity greater than 96%: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) 1.17 (s, 3H), 1.33 (m, 1H), 1.44 (dd, 1H, J = 6, 13 Hz), 1.50 (s, 3H), 1.57 (m, 1H), 1.69 (m, 3H), 1.71 (m, 1H), 1.80 (m, 1H), 1.92−2.04 (m, 2H), 2.10 (s, 3H), 2.33 (m, 1H), 2.30−2.50 (m, 1H), 2.63 (m, 1H), 4.11 (c, 1H), 4.18 (d, 1H, J = 5.5 Hz), 5.35 (c, 1H), 5.37−5.45 (m, 2H), 5.96 (m, 1H), 6.02 (s, 1H), 6.24 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{24}H_{31}FO_4S$) C, H.

6α,9α-Difluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-17β-(methylthio)androsta-1,4-dien-3-one (18a) (12a → 14a → 16a → 18a). As described above for compound **13a**, the acid **12a**[11] (7.04 g, 16 mmol) gave 6α,9α-difluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylic diethyl phosphoric anhydride (**14a**) as a white foam (9.8 g) which was used as such.

As described above for compound **15a**, the mixed anhydride **14a** (9.7 g) gave 2-thioxo-1,2-dihydropyrid-1-yl 6α,9α-difluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylate (**16a**) (8.41 g) which was used as such.

As described above for compound **17a**, the ester **16a** (2.5 g) gave after purification by chromatography (CH_2Cl_2/MeOH 19/1) and crystallization (CH_3CN) **18a** (0.46 g, 21% for last three steps) as a white solid: mp 255−256 °C; ^{1}H NMR (DMSO-d_6) 1.13 (s, 3H), 1.33 (s, 3H), 1.45 (m, 2H), 1.50 (s, 3H), 1.55 (s, 3H), 1.63 (m, 1H), 1.70 (d, 1H, J = 13 Hz), 1.96−2.09 (m, 2H), 2.12 (s, 3H), 2.26 (m, 1H), 2.45−2.62 (m, 1H), 4.13 (c, 1H), 4.42 (d, 1H, J = 6 Hz), 5.41 (dd, 1H, J = 2, 4 Hz), 5.63 (dddd, 1H, J = 1.7, 6.5, 8.4, 48.5 Hz), 6.10 (s, 1H), 6.29 (dd, 1H, J = 2, 10 Hz), 7.25 (dd, 1H, J = 1.5, 10 Hz). Anal. ($C_{23}H_{30}F_2O_4S$) C, H.

(20*R*)-16α,17α-(Butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-17β-(methylthio)androsta-1,4-dien-3-one (18b) (12b → 14b → 16b → 18b). As described above for compound **13a**, the acid **12b** (14.5 g, 32 mmol) gave (20*R*,*S*)-16α,17α-(butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic diethyl phosphoric anhydride (**14b**) (19.5 g crude) which was used as such.

As described above for compound **15a**, the mixed anhydride **14b** (19.5 g) gave after workup 2-thioxo-1,2-dihydropyrid-1-yl (20*R*,*S*)-16α,17α-(butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (**16b**) (19.5 g) which was used as such.

As described above for compound **17a**, the ester **16b** (19.5 g) was dissolved in CH_2Cl_2 (40 mL) and MeSSMe (430 mL) and irradiated. The reaction mixture was concentrated; the residue was taken up in EtOAc (400 mL) and washed successively with HCl (1 M, 2 × 200 mL), H_2O (200 mL), and brine (2 × 200 mL). The EtOAc solution was dried and concentrated to give a pale yellow foam (20*R*/*S* 4/1) (13.1 g) which was resolved by preparative HPLC using a Dynamax RP-18 column and MeOH/H_2O as mobile phase. The compound **18b**, in a stereoisomeric purity of greater than 99%, was obtained as a white solid (6.55 g, 45% for last three steps): mp 204−206 °C; $[\alpha]^{26}_D$ = +108° (c = 0.067, CH_3CN); ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J = 7.5 Hz), 1.16 (s, 3H), 1.33−1.43 (m, 3H), 1.43−1.54 (m, 1H), 1.50 (s, 3H), 1.54−1.63 (m, 3H), 1.73 (d, 1H, J = 12 Hz), 1.97−2.08 (m, 2H), 2.10 (s, 3H), 2.26 (c, 1H), 2.48−2.63 (m, 1H), 4.14 (c, 1H), 4.15 (d, 1H, J = 5.3 Hz), 5.12 (t, 1H, J = 4.4 Hz), 5.43 (c, 1H), 5.63 (dm, 1H, J = 48.5 Hz), 6.1 (s, 1H), 6.29 (dd, 1H, J = 2, 10 Hz), 7.26 (d, 1H, J = 10 Hz). Anal. ($C_{24}H_{32}F_2O_4S$) C, H.

9α-Fluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-17β-(2-pyridylthio)androsta-1,4-dien-3-one Hydrate (19). The ester **15a** (9 g) was dissolved in dichloromethane (300 mL) and irradiated with a tungsten lamp (300 W) under an atmosphere of nitrogen. The temperature was maintained at 20 °C by external cooling, and irradiation was continued until the reaction mixture became colorless to give after workup a white solid (2.9 g). Recrystallization (Et_2O) gave **19** as a yellow solid (0.63 g, 7%): mp 183−186 °C; ^{1}H NMR (DMSO-d_6) 1.14−1.22 (m, 4H), 1.25−1.42 (m, 1H), 1.38 (s, 3H), 1.47 (s, 3H), 1.47−1.55 (m, 1H), 1.59 (s, 3H), 1.62−1.75 (m, 1H), 1.78−1.92

(m, 2H), 1.93−2.05 (m, 1H), 2.29−2.48 (m, 2H), 2.55−2.67 (m, 1H), 3.98 (c, 1H), 4.69 (d, 1H, J = 6.2 Hz), 5.29 (dd, 1H, J = 1.6, 5 Hz), 6.0 (s, 1H), 6.19 (dd, 1H, J = 1.8, 10 Hz), 7.2 (d, 1H, J = 10 Hz), 7.24 (m, 1H), 7.67−7.75 (m, 2H), 8.45 (m, 1H). Anal. ($C_{27}H_{32}FNO_4S\cdot H_2O$) C, H, N.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-9α-fluoro-11β-hydroxy-17β-(2-pyridylthio)androsta-1,4-dien-3-one (20). The ester **15b** (0.60 g, 1.1 mmol) was dissolved in CH_2Cl_2 (50 mL) and irradiated with a tungsten lamp (300 W) under N_2. The temperature was maintained at 20 °C by external cooling, and irradiation was continued until the reaction mixture became colorless (45 min). The reaction mixture was concentrated and the product isolated by chromatography ($CHCl_3$). Recrystallization (EtOAc and petroleum spirit) gave **20** (20*R*/*S* 6/1) (0.15 g, 27%) as a white solid: mp 215 °C; ^{1}H NMR (DMSO-d_6) 0.75 (t, 0.45H, J = 7 Hz), 0.88 (t, 2.55H, J = 7 Hz), 1.17 (m, 1H), 1.20 (s, 3H), 1.22−1.45 (m, 3H), 1.46 (s, 3H), 1.45−1.55 (m, 2H), 1.56−1.69 (m, 2H), 1.82 (m, 2H), 1.94 (dt, 1H, J = 6, 13 Hz), 2.33 (dd, 1H, J = 4, 13 Hz), 2.40 (m, 1H), 2.62 (dt, 1H, J = 6, 13 Hz), 3.98 (c, 1H), 4.45 (d, 0.85H, J = 6 Hz), 5.03 (d, 0.15H, J = 7 Hz), 5.10 (t, 0.15H, J = 4 Hz), 5.22 (t, 0.85H, J = 4 Hz), 5.31 (c, 0.85H), 5.38 (c, 0.15H), 6.0 (s, 1H), 6.19 (dd, 0.85H, J = 2, 12 Hz), 6.21 (dd, 0.15H, J = 2, 12 Hz), 7.20 (d, 0.85H, J = 10 Hz), 7.25 (d, 0.15H, J = 10 Hz), 7.29 (m, 1H), 7.66 (m, 1H), 7.72 (m, 1H), 8.48 (m, 1H). Anal. ($C_{28}H_{34}FNO_4S$) C, H, N.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-9α-fluoro-11β-hydroxy-17β-(methylthio)androst-4-en-3-one (29) (21 → 22 → 23 → 25 → 27 → 29). To a stirred mixture of 9α-fluoro-11β,16α,17α-21-tetrahydroxypregn-4-ene-3,20-dione (**21**) (2 g, 5 mmol) in dry DMF (30 mL) was added potassium superoxide (1.4 g, 20 mmol) followed by 18-crown-6 (1.3 g, 5 mmol), and cooling was used to maintain the temperature below 38 °C. The reaction mixture was stirred (30 min), treated with H_2O (300 mL), adjusted (pH 9), washed with EtOAc, and acidified (concentrated HCl) to pH 2. The aqueous acidic mixture was extracted with EtOAc (×3), and the combined organic extracts were washed with brine, dried, and concentrated to give 9α-fluoro-11β,16α,17α-trihydroxy-3-oxoandrost-4-ene-17β-carboxylic acid (**22**) (0.9 g, 46%) as a white solid: mp 267−269 °C dec; ^{1}H NMR (DMSO-d_6) 0.92 (s, 3H), 1.35 (m, 2H), 1.47 (s, 3H), 1.55 (d, 1H, J = 14 Hz), 1.65 (m, 1H), 1.97 (m, 1H), 2.03 (m, 1H), 2.22 (c, 6H), 2.4 (m, 1H), 2.53 (m, 1H), 4.1 (c, 1H), 4.5 (b, 1H), 4.75 (m, 1H), 4.95 (m, 1H), 5.2 (d, 1H, J = 6 Hz), 5.66 (s, 1H). Anal. ($C_{20}H_{29}FO_6$) C, H.

As described above for compound **11b**, the acid **22** (2.4 g) gave (5/2) (20*R*,*S*)-16α,17α-(butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrost-4-ene-17β-carboxylic acid (**23**) (2.15 g 78%): mp 146−148 °C dec; ^{1}H NMR (DMSO-d_6) 0.87 (m, 3H), 0.94 (s, 3H), 1.22−1.46 (c, 4H), 1.50 (s, 3H), 1.49−1.61 (m, 3H), 1.65−1.82 (m, 2H), 1.9−2.02 (m, 3H), 2.19−2.6 (m, 6H), 4.12 (b, 1H), 4.67 (t, 0.7H, J = 4 Hz), 4.85 (m, 0.7H), 5.05 (m, 1.3H), 5.19 (t, 0.3H, J = 4 Hz), 5.68 (s, 1H). Anal. ($C_{24}H_{33}FO_6$) C, H.

As described above for compound **13a**, the acid **23** (2.1 g) gave (20*R*,*S*)-16α,17α-(butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrost-4-ene-17β-carboxylic diethyl phosphoric anhydride (**25**) (2.8 g).

As described above for compound **15a**, the mixed anhydride **25** (2.8 g) gave 2-thioxo-1,2-dihydropyrid-1-yl (20*R*,*S*)-16α,17α-(butylidenedioxy)-9α-fluoro-11β-hydroxy-3-oxoandrost-4-ene-17β-carboxylate (**27**) (2.4 g).

As described above for compound **17a**, the ester **27** (2.4 g), after purification by chromatography (Et_2O and petroleum spirit, 9:1) and recrystallization (cyclohexane), gave **29** (20*R*/*S* 9/1) as a white solid (0.58 g, 27% for last three steps): mp 161−163 °C; ^{1}H NMR (DMSO-d_6) 0.89 (t, 3H, J = 7.5 Hz), 1.05 (s, 0.3H), 1.14 (s, 2.7H), 1.25−1.75 (m, 9H), 1.48 (s, 0.3H), 1.49 (s, 2.7H), 1.92−2.10 (m, 3H), 2.03 (s, 0.3H), 2.09 (s, 2.7H), 2.18−2.60 (m, 6H), 4.10 (c, 1H), 4.13 (d, 0.9H, J = 5.5 Hz), 4.75 (d, 0.1H, J = 5.5 Hz), 5.03 (c, 0.9H), 5.06 (c, 0.1H), 5.10 (t, 0.1H, J = 4.3 Hz), 5.14 (t, 0.9H, J = 4.3 Hz), 5.68 (d, 1H, J = 1.3 Hz). Anal. ($C_{24}H_{35}FO_4S$) C, H.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-17β-(methylthio)androst-4-en-3-one (30) (12b → 24 → 26 → 28 → 30). To a degassed (N_2) solution of MeOH (250 mL) and H_2O (15 mL) was added NaOH (5.52 g, 138 mmol). To the resulting solution was added the acid **12b** (12.48 g, 27.6 mmol) in one portion, and the suspension was stirred until a yellow solution was obtained. The reaction mixture was treated dropwise at room temperature with iron pentacarbonyl (36.31 mL, 276 mmol) and then heated at 50 °C (20 h) under N_2. The cooled reaction mixture was poured into an ice-cold aqueous solution of H_2SO_4 (4 M, 1 L), and the aqueous phase was extracted with CH_2Cl_2 (750 mL). The organic phase was washed with brine (500 mL), dried over sodium sulfate, filtered, and concentrated to approximately one-half of the original volume. The resulting residue was filtered through a pad of silica gel, eluting first with CH_2Cl_2, then with EtOAc, and finally with a mixture of EtOAc and MeOH (1:1). Concentration gave a white foam which was triturated with diisopropyl ether to give (20*R*,*S*)-16α,17α-(butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-3-oxoandrost-4-ene-17β-carboxylic acid (**24**) (12.7 g, 88%) as an off-white solid: mp 210 °C (dec); ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J = 8 Hz), 0.93 (s, 2.7H), 0.96 (s, 0.3H), 1.25−1.60 (m, 6H), 1.49 (s, 3H), 1.75 (d, 2H, J = 13 Hz), 1.91−2.0 (m, 2H), 2.0−2.1 (m, 1H), 2.16 (c, 1H), 2.22−2.37 (m, 2H), 2.37−2.55 (m, 2H), 4.15 (c, 1H), 4.68 (t, 0.9H, J = 4 Hz), 4.89 (c, 0.9H), 5.10 (d, 0.1H, J = 6 Hz), 5.15 (c, 1H), 5.21 (t, 0.1H, J = 4 Hz), 5.50 (c, 1H), 5.70 (s, 0.1H), 5.81 (s, 0.9H). Anal. ($C_{24}H_{32}F_2O_6$) C, H.

By proceeding as described above for compound **13a**, the acid **24** (12.6 g, 27.7 mmol) gave (20*R*,*S*)-16α,17α-(butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic diethyl phosphoric anhydride (**26**) (17.2 g crude) which was used as such.

By proceeding as described above for compound **15a**, the mixed anhydride **26** (17.2 g) gave after workup the ester 2-thioxo-1,2-dihydropyrid-1-yl (20*R*,*S*)-16α,17α-(butylidenedioxy)-6α,9α-difluoro-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (**28**) (16.6 g) which was used as such.

By proceeding as described above for compound **17a**, the ester **28** (16.6 g) afforded, after workup, an off-white powder (12 g) which was purified by chromatography (Et_2O and petroleum spirit, 3:1). The white solid obtained (6 g) was recrystallized (CH_3CN) to give **30** (20*R*/*S* 9/1) (4 g) which was resolved by preparative HPLC using a Dynamax RP-18 column and MeOH/H_2O as mobile phase. The 20*R*-epimer **30** was obtained as a white solid (3.4 g, 27% for last three steps): mp 180 °C; ^{1}H NMR (DMSO-d_6) 0.89 (t, 3H, J = 7.5 Hz), 1.15 (s, 3H), 1.36−1.54 (m, 7H), 1.49 (s, 3H), 1.72 (d, 1H, J = 12.5 Hz), 1.93−2.10 (m, 3H), 2.09 (s, 3H), 2.16 (c, 1H), 2.23−2.38 (m, 2H), 2.28−2.54 (m, 2H), 4.13 (c, 1H), 4.17 (d, 1H, J = 5.4 Hz), 5.13 (c, 2H), 5.50 (dddd, 1H, J = 1.8, 6.6, 11.5, 47.5 Hz), 5.81 (s, 1H). Anal. ($C_{24}H_{34}F_2O_4S$) C, H.

(20*R*,*S*)-16α,17α-(Butylidenedioxy)-9α-fluoro-11β-hydroxy-17β-(methylsulfinyl)androsta-1,4-dien-3-one (31). The 17-methylthio ether **17b** (1.0 g, 2.3 mmol) in solution in acetone (30 mL) was treated dropwise with a solution of potassium peroxymonosulfate (0.7 g, 1.13 mmol) in H_2O (6 mL). The reaction mixture was stirred (7 h) and filtered and the filtrate concentrated to give a pale yellow gum. This gum was dissolved in $CHCl_3$ (200 mL), washed with H_2O (2 × 200 mL) and brine (200 mL), dried, and concentrated to give a pale yellow foam. This foam was purified by chromatography to give **31** (20*R*/*S* 3/1) (0.25 g, 24%) as a white solid: mp 175 °C; ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J = 7.5 Hz), 1.04 (s, 3H), 1.28−1.43 (m, 3H), 1.43−1.99 (m, 8H), 1.49 (s, 3H), 2.35 (m, 1H), 2.35−2.70 (m, 2H), 2.65 (s, 3H), 4.15 (c, 1H), 5.10 (d, 1H, J = 4.4 Hz), 5.32 (c, 1H), 5.48 (t, 1H, J = 4.4 Hz), 6.03 (s, 1H), 6.23 (dd, 1H, J = 1.8, 10 Hz), 7.27 (d, 1H, J = 10 Hz) (only major isomer is quoted). Anal. ($C_{24}H_{32}FO_5S$) C, H.

9α-Fluoro-11β-hydroxy-16α,17α-(isopropylidenedioxy)-17β-(methylsulfonyl)androsta-1,4-dien-3-one (32). The 17-methylthio ether (**17a**) (1.4 g, 3.3 mmol) in solution in $CHCl_3$ (150 mL) was treated with 3-chloroperoxybenzoic acid (2.2 g, 6.8 mmol) at 25 °C. When the reaction was completed (TLC), the reaction mixture was treated with an aqueous solution of sodium sulfite, then washed successively with H_2O, an aqueous solution of Na_2CO_3, H_2O, and brine, dried, and concentrated. The residue obtained was purified by chromatography ($CHCl_3$/MeOH, 95:5). Recrystallization (acetone/

hexane) gave **32** (0.24 g, 16%) as a white powder: mp 180 °C; ^{1}H NMR (DMSO-d_6) 1.29 (s, 3H), 1.29−1.42 (m, 1H), 1.44 (s, 3H), 1.50 (s, 3H), 1.52 (s, 3H), 1.59 (dd, 1H, J = 6, 13 Hz), 1.73−1.88 (m, 3H), 1.99 (dt, 1H, J = 4, 13 Hz), 2.10 (dt, 1H, J = 6, 13 Hz), 2.35 (dd, 1H, J = 4, 13 Hz), 2.49−2.70 (m, 2H), 2.96 (s, 3H), 4.18 (c, 1H), 5.15 (d, 1H), J = 6 Hz), 5.40 (c, 1H), 6.03 (s, 1H), 6.24 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{23}H_{31}FO_6S$) C, H.

Syntheses of the (Fluoromethyl)thio Ethers 33−35. (20*R*)-16α,17α-(Butylidenedioxy)-9α-fluoro-17β-[(fluoromethyl)thio]-11β-hydroxyandrosta-1,4-dien-3-one (33). The compound **17b** (2.0 g, 4.58 mmol) was treated with 2,6-di-*tert*-butyl-4-methylpyridine (2.05 g, 10 mmol) and XeF_2 (0.85 g, 5.0 mmol) in CH_2Cl_2 (100 mL) as described for compound **34** to give after chromatography ($CHCl_3$) a white solid (0.6 g) which was recrystallized (EtOAc and petroleum spirit) to give **33** (20*R*/*S* 99/1) (0.25 g, 12%) as a white solid: mp 160 °C dec; ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J = 7.5 Hz), 1.09 (s, 3H, J = 14 Hz), 1.26−1.41 (m, 3H), 1.44−1.50 (m, 1H), 1.50 (s, 3H), 1.54−1.64 (m, 3H), 1.73 (d, 1H, J = 14 Hz), 1.78−2.0 (m, 3H), 2.33 (dd, 1H, J = 3.5, 14 Hz), 2.35−2.50 (m, 1H), 2.62 (m, 1H), 4.17 (c, 1H), 4.38 (d, 1H, J = 5.5 Hz), 5.09 (t, 1H, J = 4.4 Hz), 5.45 (dd, 1H, J = 1.5, 5 Hz), 5.62 (dd, 1H, J = 10, 52 Hz), 5.68 (dd, 1H, J = 10, 54 Hz), 6.01 (t, 1H, J = 1.6 Hz), 6.22 (dd, 1H, J = 2, 10 Hz), 7.28 (d, 1H, J = 10 Hz). Anal. ($C_{24}H_{32}F_2O_4S$) C, H.

6α,9α-Difluoro-17β-[(fluoromethyl)thio]-11β-hydroxy-16α,17α-(isopropylidenedioxy)androsta-1,4-dien-3-one (34). A mixture of **18a** (5.06 g, 11.5 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (5.19 g, 25.3 mmol), and activated molecular sieves (type 4A, 7.5 g) in dry CH_2Cl_2 (250 mL) was stirred for 1.5 h, under argon at 20 °C. XeF_2 (2.15 g, 12.7 mmol) was added in one portion and the mixture stirred at 20 °C (3 h). The mixture was filtered, and the filtrate was poured into H_2O (500 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic phases were washed with saturated brine (100 mL) and concentrated. The residue was taken up in EtOAc (500 mL) and washed with HCl (1 M, 3 × 250 mL), H_2O (250 mL), and brine (250 mL). The organic phase was dried and concentrated to give a white solid (3.6 g) which was purified by preparative HPLC using a Dynamax RP-18 column and MeOH/H_2O as mobile phase. Concentration followed by crystallization (CH_3CN) gave **34** (2.4 g, 46%) as a white solid: mp 261−263 °C, $[\alpha]^{26}_D$ = +162° (c = 0.057, CH_3CN); ^{1}H NMR (DMSO-d_6) 1.06 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.46−1.57 (m, 2H), 1.50 (s, 3H), 1.69 (dt, 1H, J = 6, 13 Hz), 1.73 (d, 1H, J = 13 Hz), 1.82 (dt, 1H, J = 3, 13 Hz), 2.05 (dt, 1H, J = 6, 13 Hz), 2.29 (c, 1H), 2.47−2.63 (m, 1H), 4.15 (c, 1H), 4.63 (d, 1H, J = 6 Hz), 5.52 (c, 1H), 5.62 (m, 1H), 5.70 (dd, 1H, J = 10, 54 Hz), 5.74 (dd, 1H, J = 10, 56 Hz), 6.10 (s, 1H), 6.29 (dd, 1H, J = 2, 10 Hz), 7.25 (dd, 1H, J = 2, 10 Hz). Anal. ($C_{23}H_{29}F_3O_4S$) C, H.

(20*R*)-16α,17α-(Butylidenedioxy)-6α,9α-difluoro-17β-[(fluoromethyl)thio]-11β-hydroxyandrosta-1,4-dien-3-one (35). The compound **18b** (1.7 g, 3.5 mmol) was treated with 2,6-di-*tert*-butyl-4-methylpyridine (1.57 g, 7.66 mmol) and XeF_2 (0.65 g, 3.8 mmol) in CH_2Cl_2 (100 mL), as described above for compound **34**. After workup, the white powder obtained (1.3 g) was purified by chromatography ($CHCl_3$) to give **35** (20*R*/*S* 99/1) as a white solid (0.32 g, 19%): mp 145−146 °C; ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H, J = 7.5 Hz), 1.08 (s, 3H), 1.31−1.50 (m, 3H), 1.50 (s, 3H), 1.50−1.55 (m, 1H), 1.53−1.68 (m, 3H), 1.75 (d, 1H, J = 13 Hz), 1.88 (dt, 1H, J = 3.5, 14 Hz), 2.03 (m, 1H), 2.27 (c, 1H), 2.50−2.66 (m, 1H), 4.17 (c, 1H), 4.40 (d, 1H), 5.11 (t, 1H), 5.53−5.60 (m, 1.5H), 5.62 (dd, 1H, J = 10.6, 52 Hz), 5.65−5.74 (m, 0.5H), 5.69 (dd, 1H, J = 10.6, 54 Hz), 6.11 (s, 1H), 6.30 (dd, 1H, J = 2, 10 Hz), 7.24 (dd, 1H, J = 1.6, 10 Hz). Anal. ($C_{24}H_{31}F_3O_4S$) C, H.

Biological Methods. Steroid Binding to the Rat Thymus Glucocorticoid Receptor. Thymi of male adrenalectomized rats were removed, homogenized in 3-(*N*-morpholino)propanesulfonic acid dithiothreitol buffer, and centrifuged at 100000*g*. The supernatant cytosol was used as the source of receptor. Steroid (1−16 nM in doubling dilutions) and [^{3}H]-dexamethasone (4 nM) were equilibrated with receptor for 24 h at 4 °C. Bound [^{3}H] dexamethasone was separated from free dexamethasone by a dextran-coated charcoal technique and quantified by liquid scintillation counting. The IC_{50} (concentration reducing [^{3}H]dexamethasone binding by 50%) was calculated from the plot of the fraction bound against added steroid concentration.

Induction of Tyrosine Aminotransferase Activity. Rat liver H4IIE cells were cultured for 4 days until the cells were confluent. The medium was replaced by fresh medium, containing the steroid under test (0−100 nM) which was added to triplicate wells. After overnight incubation as above, the medium was removed, the cells were lysed, and the extract was equilibrated at 37 °C with α-ketoglutarate and pyridoxal phosphate in phosphate buffer, pH 7.3, in a final volume of 1 mL. Tyrosine aminotransferase activity was initiated by adding tyrosine and incubating at 37 °C for 10 min. The reaction was stopped by adding aqueous sodium hydroxide solution (10 M). The ultraviolet absorbance of the *p*-hydroxybenzaldehyde was measured by a plate reader at 340 nm. The maximal absorbance change achieved with the standard (dexamethasone) was used as a reference. The absorbance change for each concentration of steroid under test was calculated as a fraction of the maximal absorption achievable and plotted against steroid concentration. The ED_{50} was determined as the concentration causing an increase in tyrosine aminotransferase activity of 50% of the maximum achievable.

Inhibition of Rat Lung Edema and Suppression of Thymus Weight in Vivo. Test compounds were suspended in 1% carboxymethyl cellulose/0.2% Tween 80 at double the required strength and sonicated to form a suspension. This was administered intratracheally (it) to male rats (Sprague−Dawley strain, six in each group, each weighing about 350 g) at 0 and 24 h, with the first dose being coadministered with saline and the second with Sephadex G200 (cross-linked dextran) (10 mg/mL) giving a final Sephadex concentration of 5 mg/mL; it dosing was carried out under halothane anesthesia (4% in oxygen, at 4 L/min for 3 min). At 48 h, the rats were killed, final body weight was recorded, and the lungs and thymus were removed and weighed. The doses reducing the Sephadex-induced edema and the thymus weight by 30% (ED_{50}) were calculated. Airway selectivity was defined as the ratio of thymus involution (ED_{50}) and inhibition of lung edema (ED_{50}).

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References

(1) Holgate, S. Mediator and cytokine mechanisms in asthma. *Thorax* **1993**, *48*, 103−109.
(2) Bousquet, J.; Chanez, P.; Lacoste, J. Y.; White, R.; Vic, P.; Godard, P.; Michel, F. B. Asthma: A disease remodelling the airways. *Allergy* **1992**, *47*, 3−11.
(3) Brattsand, R.; Selroos, O. Current drugs for respiratory diseases. Glucocorticoids. In *Drugs and the Lung*; Page, C. P., Metzger, W. J. Eds.; Raven Press: New York, 1994; pp 101−220.
(4) Check, W. A.; Kaliner, M. A. Pharmacology and Pharmacokinetics of Topical Corticosteroid Derivatives used for Asthma Therapy. *Am. Rev. Respir. Dis.* **1990**, *144*, S44−S51.
(5) Geddes, D. M. Inhaled corticosteroids: benefits and risks. *Thorax* **1992**, *47*, 404−407.
(6) Grahnen, A.; Eckernäs, S.-A.; Brundin, R. M.; Ling-Andersson, A. An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br. J. Clin. Pharmacol.* **1994**, *38*, 521−525.
(7) Dahlberg, E.; Thalén, A.; Brattstand, R.; Gustafsson, J.; Johansson, U.; Roempke, K.; Saartok, T. Correlation between Chemical Structure, Receptor Binding, and Biological Activity of Some Novel, Highly Active, 16α,17α-Acetal-Substituted Glucocorticoids. *Mol. Pharmacol.* **1984**, *25*, 70−78.

(8) Edsbäcker, S.; Andersson, P.; Lindberg, C.; Ryrfeldt, Å.; Thalén, A. Metabolic Acetal Splitting of Budesonide. *Drug. Metab. Dispos.* **1987**, *15*, 412−417.
(9) Foster, M.; Bottoms, S.; Jordan, R.; Wicks, S.; Webber, S.; Stuttle, K. A. J.; Newton, C. G.; Ashton, M. J.; Karlsson, J.-A. Effects of a Novel Airway Selective 17-Thiosteroid, RPR106541, on Biomarkers of Systemic Glucocorticoid Exposure Following 7 Day Oral Administration. *Am. Rev. Respir. Resources*, in press.
(10) Barton, D. H. R.; Crich, D.; Motherwell, W. B. New and Improved Methods for the Radical Decarboxylation of Acids. *J. Chem. Soc., Chem. Commun.* **1983**, 939−941.
(11) Brattsand, R. L.; Thalen, B. A. Novel androstane-17β-carboxylic acid esters, a process and intermediates for their preparation, compositions and method for the treatment of inflammatory conditions. *Eur. Pat. Application* 84850348.8, 1984 (to Aktiebolaget Draco).
(12) Kertesz, D. J.; Marx, M. Thiol Esters from Steroid 17β-Carboxylic Acids: Carboxylate Activation and Internal Participation by 17α-Acylates. *J. Org. Chem.* **1986**, *51*, 2315−2328.
(13) Barton, D. H. R.; Bridon, D.; Zard, S. Z. The Invention of New Radical Chain Reactions. Part XIII. High Yielding Decarboxylative Chalcogenation of Aliphatic and Alicyclic Acids. *Heterocycles* **1987**, *25*, 449−462.
(14) Lan, S. J.; Scanlan, L. M.; Weinstein, S. H.; Varma, R. K.; Warrack, B. M.; Unger, S. E.; Porubcan, M. A.; Migdalof, B. H. Biotransformation of Tipredane, A Novel Topical Steroid, in Mouse, Rat, and Human Liver Homogenates. *Drug. Metab. Dispos.* **1989**, *17*, 532−541.

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