Thiol Esters from Steroid 17β-Carboxylic Acids: Carboxylate Activation and Internal Participation by 17α-Acylates[1]

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The chemistry of the steroid 17β-carboxylic acids derived from 16,17α-disubstituted corticosteroids was investigated with respect to thiol ester formation. Major quantities of 17-spiro byproducts were observed in the reactions of 16-methyl-17α-acyloxy acids, and the degree of 17-ester participation leading to these structures was dependent on the carboxylate activating group used and stereochemistry at C-16. Diethyl phosphate mixed anhydrides of these acids reacted with mercaptide salts to give mixtures of thiol esters with 17-spiro acylthio ortho esters, which predominated and were particularly stable in the case of 16β-methyl substrates; in addition, considerable reversion of 16α-methyl phosphate intermediates to starting acid was experienced. The use of diphenyl chlorophosphate as the activating agent greatly improved yields of thiol esters. Methanolysis of the phosphate adducts derived from 17α-acyloxy acids gave 17-spiro acyl ortho esters as the exclusive products. The reactions of 17α-acetoxy acids with 2-fluoro-*N*-methylpyridinium tosylate (FMPT) gave the novel 17-spiro acyl fluoro ketals **32–35**, whereas similar treatment of 17-hydroxy acids led to products of dehydration or of 18-methyl migration, including the novel 13,17-β-lactones **39** and **41**. Activation with carbonyldiimidazole followed by addition of mercaptans allowed the preparation of thiol ester products from 17-hydroxy acids, but the method was restricted to use with these substrates. Neighboring-group participation was not possible for the 16,17-acetonide acid **10**, and activation with either chlorophosphate diesters or FMPT followed by reaction with methanethiolate gave high yields of methylthio ester **17**.

Introduction

Dermatologically useful antiinflammatory activity in corticosteroids is compatible with a variety of modifications to the normal 20-keto-21-hydroxy side chain, as exemplified by the 21-deoxy, 21-deoxy-21-chloro, and steroid 17β-carboxylate ester classes of topical agents.[2] In the course of our investigations of structure–activity relationships in this area, we required the synthesis of thiol esters of steroid 17β-carboxylic (etianic) acids bearing either the 16α,17α-acetonide functionality or a 16-methyl in combination with a 17α-acyloxy or -hydroxy group.[3] Although the thiol esters of 16-unsubstituted-17-desoxyetianic acids were known,[4,5] there was no precedent for synthesis of the analogous 16,17α-disubstituted derivatives. The system of interest is particularly hindered, the 17β-carboxyl being flanked by a quaternary carbon (C-13), a tertiary carbon (C-16), and a 17α-oxy substituent. These features had a profound influence on the chemistry of activation and further reactivity of the 17β-carboxylate, particularly through participation by the neighboring 17α-acyloxy and -hydroxy groups, and led to the isolation of a novel series of 17-spiro dioxolanones and 18-methyl migration products. The elaboration of these findings is reported here.

Carboxylic acid starting materials for the desired thiol esters were prepared from fluocinolone acetonide **1**, flumethasone **2**, betamethasone **3**, the $\Delta^{9,11}$-16β-methyl corticoid **4**, and the 9α,11β-dichloride **5** by oxidative cleavage of the corticoid side chain, usually followed by esterification of free 17α-alcohol groups (Scheme I). Thus, oxidation of the 17α-hydroxy substrates **2–5** with periodic acid[6] in aqueous methanol gave high yields of etianic acids **6–9**. The 16,17-acetonide **1** (and corticoid 17-esters) did not react under these conditions, showing an unexpected limitation to the use of periodic acid. A potassium carbonate catalyzed air oxidation was therefore developed based on reports by Velluz[7] and Herzig,[8] permitting cleavage of **1** to the 16,17-acetonide acid **10** in 75% yield. The 17α-hydroxyetianic acids **6**, **7**, and **9** were transformed into the corresponding acetates and propionates **11–15** in a one-pot procedure similar to that of Phillips et al.,[9,10] consisting of reaction with excess acetyl or propionyl chloride and triethylamine followed by the addition of diisopropylamine to cleave the resulting 17-acyloxy carboxylic acid mixed anhydrides. The mixed anhydrides of 16β-methyl acids were particularly stable, as demonstrated by the isolation of the dipropionyloxy compound **16**[9] in 72% yield from **7** when the use of diisopropylamine was eliminated. The ease with which 17-esters could be prepared from etianic acid substrates suggests that the free acid group was involved in the process,[11] probably through the initial formation of a mixed anhydride and transfer of the acyl group from the 17β-carboxylate to the 17α-alcohol.

Activation with Chlorophosphate Reagents. Thiol esters of 16,17-acetonide acid **10** were successfully prepared by forming diethyl phosphate intermediates[12] and treatment in situ with sodium mercaptide salts. Thus, reaction of **10** with diethyl chlorophosphate and triethylamine in THF followed by filtration of the amine hydrochloride salt

(1) Contribution No. 704 from the Institute of Organic Chemistry.
(2) (a) Wolff, M. E. In *Burger's Medicinal Chemistry*, 4th ed., Part III; Wolff, M. E., Ed.; Wiley-Interscience: New York, 1981; pp 1310–1311. (b) Phillips, G. H. In *Mechanisms of Topical Corticosteroid Activity*; Wilson, C.; Marks, R., Ed.; Churchill Livingstone: New York, 1976; pp 1–18.
(3) Edwards, J. A. U.S. Patent 4 188 835, 1980.
(4) Jeger, O.; Norymberski, J.; Szpilfogel, S.; Prelog, V. *Helv. Chim. Acta* **1946**, *29*, 684.
(5) Phillips, G. H.; Marshall, D. R. U.S. Patent 3 989 686, 1980.
(6) Reichstein, T.; Meystre, Ch.; von Euw, J. *Helv. Chim. Acta* **1939**, *22*, 1107.
(7) Velluz L.; Petit, A.; Pesez, M.; Berret, R. *Bull. Soc. Chim. Fr.* **1947**, 123; *Chem. Abstr.* **1947**, *41*, 5537.
(8) Herzig, P. Th.; Ehrenstein, M. *J. Org. Chem.* **1951**, *16*, 1050.
(9) Phillips, G. H.; Bain, B. M. U.S. Patent 4 093 721, 1978.
(10) Phillips, G. H.; May, J. M. U.S. Patent 3 828 080, 1974; *Chem. Abstr.* **1975**, *82*, 31453x.
(11) By contrast, the esterification of free 17-alcohols in etianic acid thiol esters required catalysis with DMAP at elevated temperatures, as in the preparations of **48** and **49** from **47** (vide infra). If an 11β-alcohol was present, it was also esterified under these conditions. Selective base hydrolysis of the 11-esters of the resulting 11,17-diesters was readily achieved with 16α-methyl substrates, but no distinction was possible in the presence of a 16β-methyl group: Alvarez, F.; Kertesz, D., unpublished results.
(12) (a) Masamune, S.; Kamata, S.; DiaKur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693. (b) For a review of thiol ester forming methods, see: Haslam, E. *Tetrahedron* **1980**, *36*, 2409.

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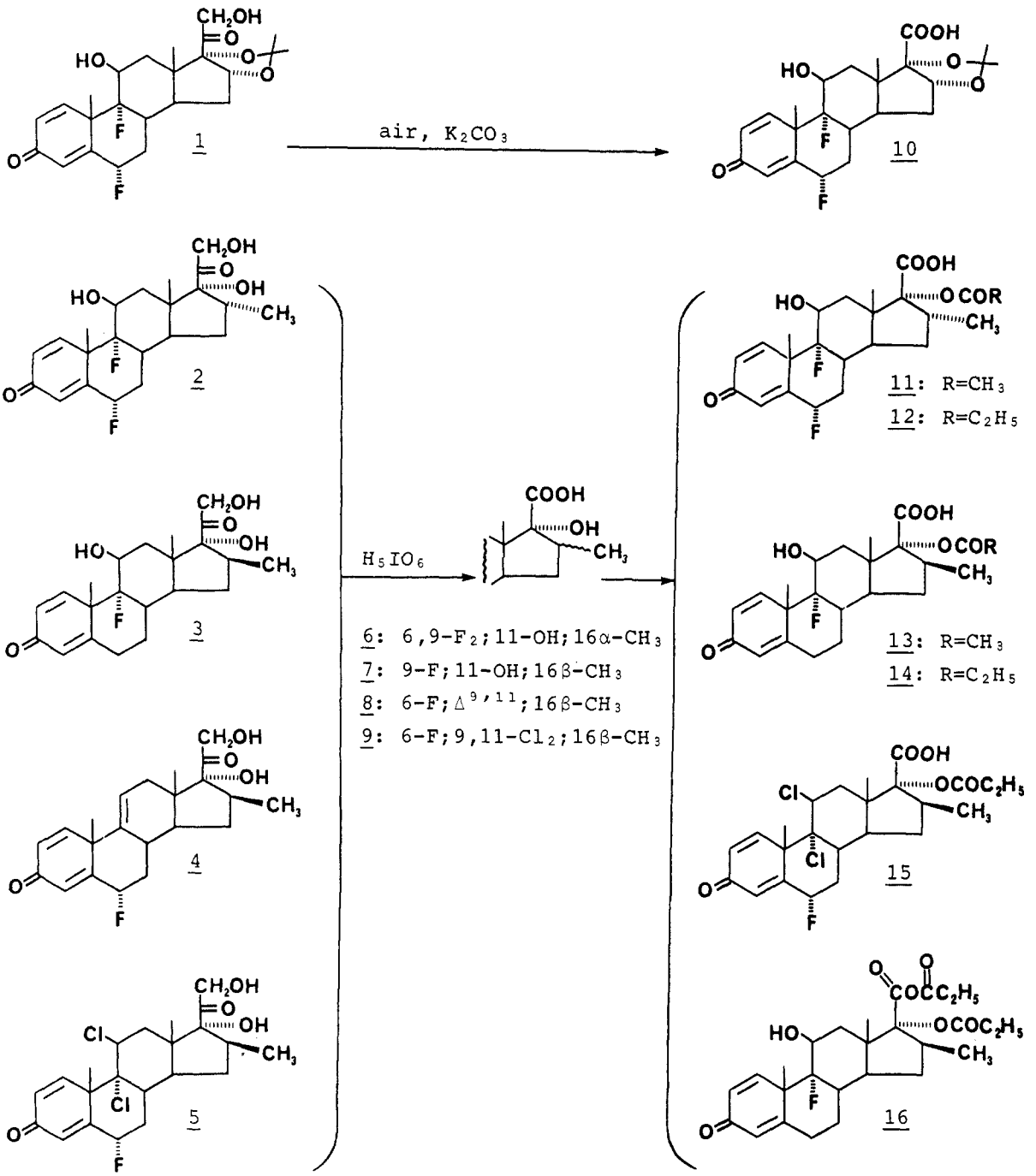
Scheme I. Preparation of Etianic Acids



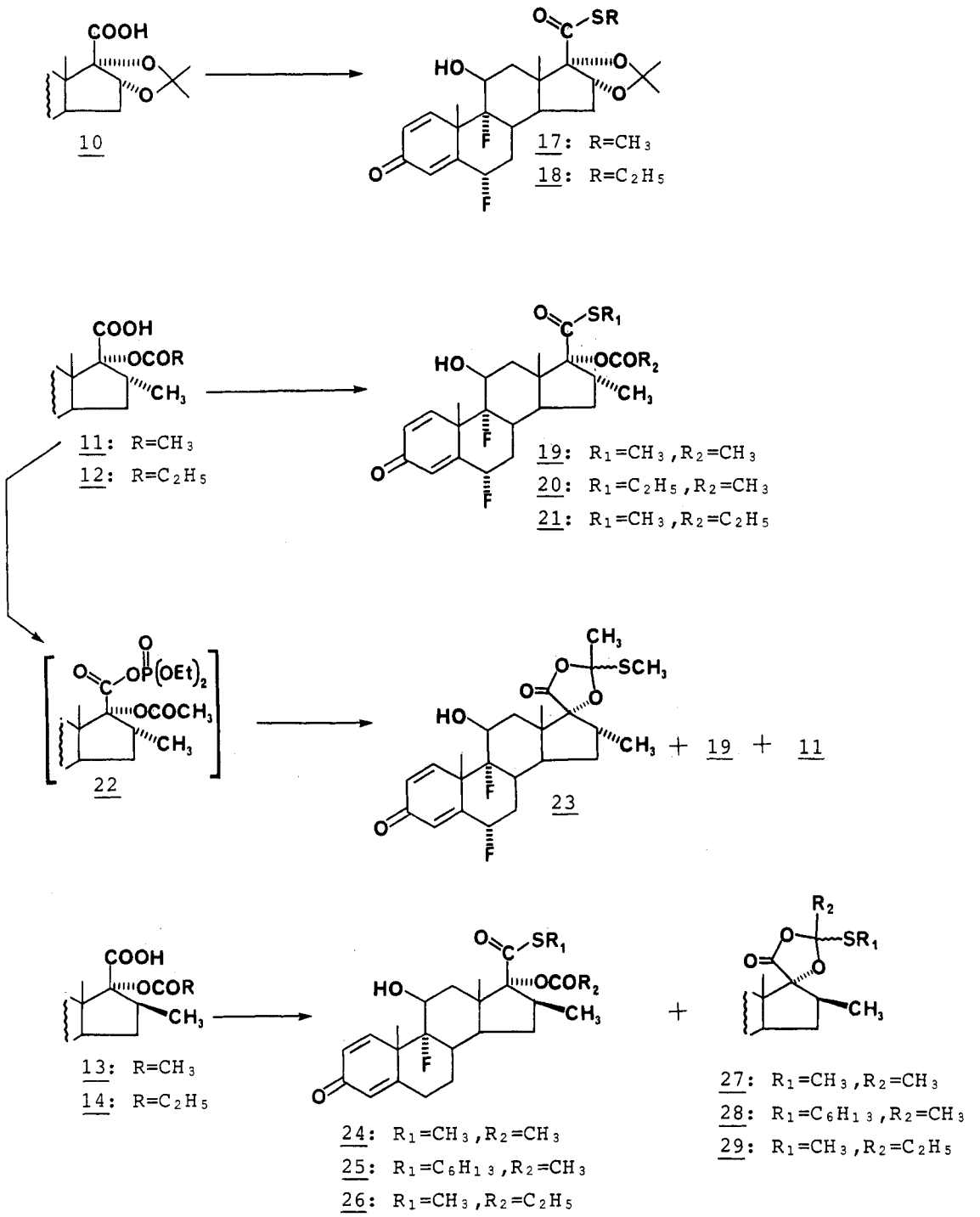
and addition of excess sodium methylthiolate in DMF gave 72% of methylthio ester **17** and 18% of unreacted **10**, whereas the use of sodium ethanethiolate gave 65% of **18** (Scheme II). However, application of this method to 16α-methyl-17α-acyloxy substrates gave uniformly low yields of the desired thiol esters accompanied by large quantities of recovered starting acids. For example, acetate **11** gave methylthio ester **19** (13%) and ethylthio ester **20** (26%) accompanied in each case by 46–48% of starting acid, while 17-propionate **12** afforded 33% of methylthio ester **21** and 25% of returned **12**.[13]

The reactions of etianic acids with chlorophosphate reagents produced single intermediates which could be observed by thin-layer chromatography (TLC), and when the intermediate formed from **11** (assumed to be phosphate **22**) was titrated to its disappearance with $NaSCH_3$, 12% of a new less polar material was formed in conjunction with 9% of thiol ester **19** and 34% of returned acid **11**. The new product showed a single absorption at 1790 cm^{-1} in the infrared in place of the 17-acylate and thiol ester peaks, and its identification as the novel 17-spiro acylthio orthoacetate **23** was supported by further spectral and analytical data. Although **23** was readily isomerized to **19** with excess thiolate and could be hydrolyzed to **11** with either acid or base, the isolated material was stable under neutral conditions. The formation of **23** by preferential attack of thiolate at the 17-acyloxy carbonyl has analogy in the chemistry of α-acetoxyisobutyryl chloride studied by Mattocks[14] and others,[15] and this form of neighboring-

(13) These results were representative of a series of reactions employing mercaptides as large as *n*-hexylthio in combination with 17-acylates as large as caproate.

(14) Mattocks, A. R. *J. Chem. Soc.* **1964**, 1918.

Scheme II. Thiol Esters via Phosphoric Mixed Anhydrides



group participation was noted with increasing frequency in further work.

When we applied the diethyl phosphate method of thiol ester formation to 17-acyloxy substrates in the 16β-methyl series, we found 17-spiro thio ortho esters to be the major products; the desired thiol esters were produced in low yields and amounts of recovered starting acids were insignificant. Moreover, chromatographic separation of the normal thiol ester and 17-spiro products derived from lower alkyl thiolates was difficult or impossible. Thus, treatment of the phosphate intermediate derived from 17-acetate **13** with $NaSC_6H_{13}$ gave 43% of spiro hexylthio orthoacetate **28** and 13% of the readily separable thiol ester **25**, whereas the reaction of similarly activated 17-propionate **14** with a stoichiometric amount of $NaSCH_3$ yielded 64% of an unresolvable mixture judged by IR and NMR[16] to be 3:1 of orthopropionate **29** with ester **26**. The

(15) (a) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016. (b) Alkoxydioxolanones (cyclic acyl ortho esters) are formed in the reactions of α-acetoxyisobutyryl chloride with alcohols. Treatment of this reagent with ethanethiol gave a mixture absorbing at 1800 cm^{-1} in the infrared, implying the formation of an alkylthiodioxolanone similar to **23**, but the product could not be isolated: Rüchardt, Ch.; Brinkmann, H. *Chem. Ber.* **1975**, *108*, 3224.

(16) In the absence of adequate guidance from TLC, comparison of the intensity of the 1790 cm^{-1} peak with that of the 17-ester carbonyl at 1730 cm^{-1} was useful for judging the composition of ortho ester–thiol ester product mixtures. A large downfield shift of the 18-methyl resonance (0.30–0.35 ppm from that of the thiol ester) was the most dramatic feature of cyclic ortho ester NMR spectra, and other differences were used to calculate proportions in isomeric mixtures: see the Experimental Section.

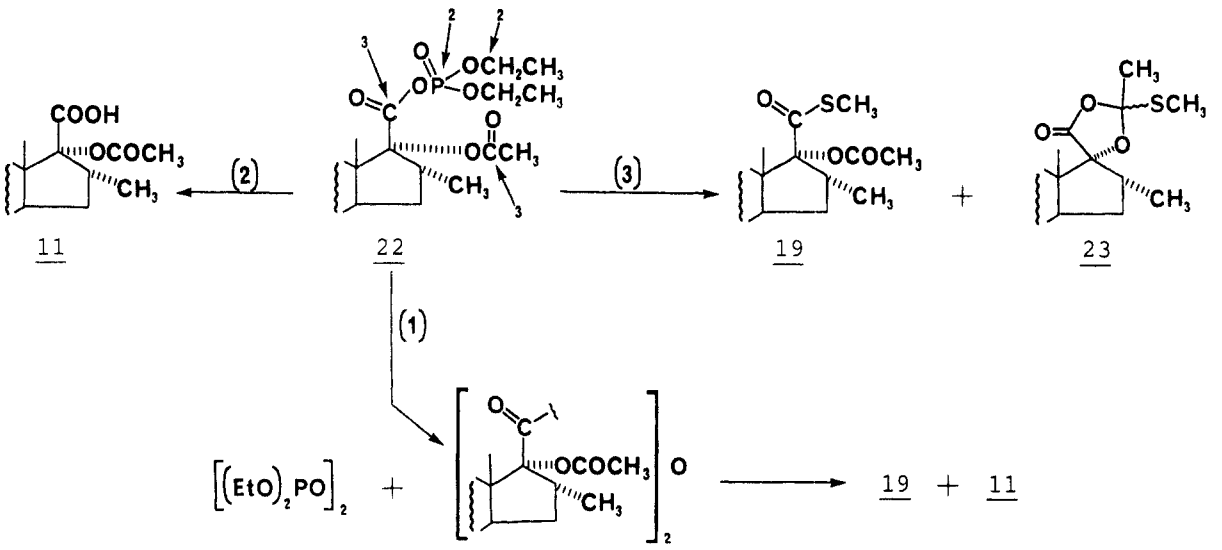


Figure 1.

conversion of ortho ester **29** to thiol ester **26** was completed by warming with an excess of $NaSCH_3$, as followed by disappearance of the 1790 cm^{-1} infrared absorption. Reaction of the diethyl phosphate adduct of acetate **13** with one equivalent of $NaSCH_3$ at 0 °C gave an estimated 9:1 mixture of cyclic orthoacetate **27** with thiol ester **24**, and a sample of pure **27** was obtained by painstaking chromatographic separation. The tendency of the 16β-methyl group to enhance the formation of 17-spiro thio ortho esters and increase their stability toward excess thiolate was a major feature of the chemistry of this series.[17]

Substitution of diphenyl chlorophosphate for the diethyl reagent markedly altered the course of subsequent reactions with thiolates; notably, reversion of intermediates derived from 16α-methyl acids to starting material did not occur and ortho ester formation was greatly reduced for 16β-methyl substrates, leading to increased yields of thiol esters in all cases. Thus, treatment of 16α-methyl propionate **12** with diphenyl chlorophosphate and TEA in dry THF for 1 h at 55 °C gave a single TLC visible intermediate, and subsequent addition of $NaSCH_3$ afforded an 89% isolated yield of **21**. Similarly, the reaction of the diphenyl phosphate adduct of 16β-methyl-17-propionate **14** with an equivalent of $NaSCH_3$ gave a mixture of more than 10:1 of thiol ester **26** with ortho ester **29**, and was readily driven on with excess thiolate and heat to give a 64% yield of pure **26**. Acetate **13** likewise gave 74% of **24**. The use of diphenyl chlorophosphate for activation of **10** gave a 75% of acetonide thiol ester **17**.

The thiol ester forming reactions of 16α-methyl acids activated with diethyl chlorophosphate were noteworthy for the considerable reversion to starting material experienced, and an attempt was made to relate this behavior to the nature of the actual intermediate. The similar quantities of thiol ester and returned acid obtained from reactions of thiolate with these diethyl phosphates could be rationalized in several ways (Figure 1). One possibility is that the true intermediates are symmetric anhydrides, resulting from a reported tendency of diethyl phosphate mixed anhydrides to "disproportionate"[12a] (path 1). Reversion of the mixed phosphate anhydride to carboxylic acid might also result from a partitioning of the intermediate by attack of thiolate on phosphorus[18] or the phosphate ethoxy α-carbons[21] (path 2) in preference to the 17β-carboxylate and 17α-acyloxy carbonyl carbons (path 3). Either the absence of alkoxy groups or a lower susceptibility of phosphorus to thiolate attack could then explain the superiority of diphenyl phosphate for thiol ester synthesis in this series. It was also considered possible that displacement of phosphate by chloride might occur during the activation procedure, with the resulting acid chlorides being the true intermediates in some of the phosphate-mediated chemistry. The possibility of acid chloride intermediates was discounted by investigation of the salt precipitates filtered from the intermediate-forming reactions, since formation of the presumed mixed anhydrides from **11** and **13** using either diethyl or diphenyl chlorophosphate was accompanied in each case by the virtual quantitative recovery (relative to carboxylic acid) of chloride ion as pure triethylammonium chloride. We found that acid chlorides could actually be formed and used without isolation,[24] and the reactions of **11** and **14** with thionyl chloride and TEA for 10 min at 0 °C followed by addition of $NaSCH_3$ thereby afforded 32 and 34% yields of respective methylthio esters **19** and **26**. Only small amounts of starting acids were recovered, and there were no detectable 17-spiro thio ortho ester products from these reactions.

An attempt was made to isolate and characterize a representative set of phosphate intermediates. Thus, reaction mixtures containing the 16α-methyl-17-acetoxy acid **11** and the 16β-methyl analogue **13** in combination with both diethyl and diphenyl chlorophosphate reagents were prepared as usual and subjected to aqueous workup pro-

(17) Facilitated access of thiolate to the 17α-acyloxy carbonyl and shielding of the resulting dioxolanone product carbonyl by the 16β,18-dimethyl system probably both contribute to this finding.

(18) Nucleophilic attack on phosphorus was suggested by Liu et al. to explain low yields of esters from the use of chlorophosphate diesters as activating agents (see ref 19). Low yields were also reported for thiol ester preparations using these reagents (see ref 20), but no difference between diethyl and diphenyl phosphate cases was noted in the cited work.

(19) Liu, H. J.; Chan, W. H.; Lee, S. P. *Tetrahedron Lett.* **1978**, 4461.

(20) Liu, H. J.; Sabesan, S. I. *Can. J. Chem.* **1980**, *58*, 2645.

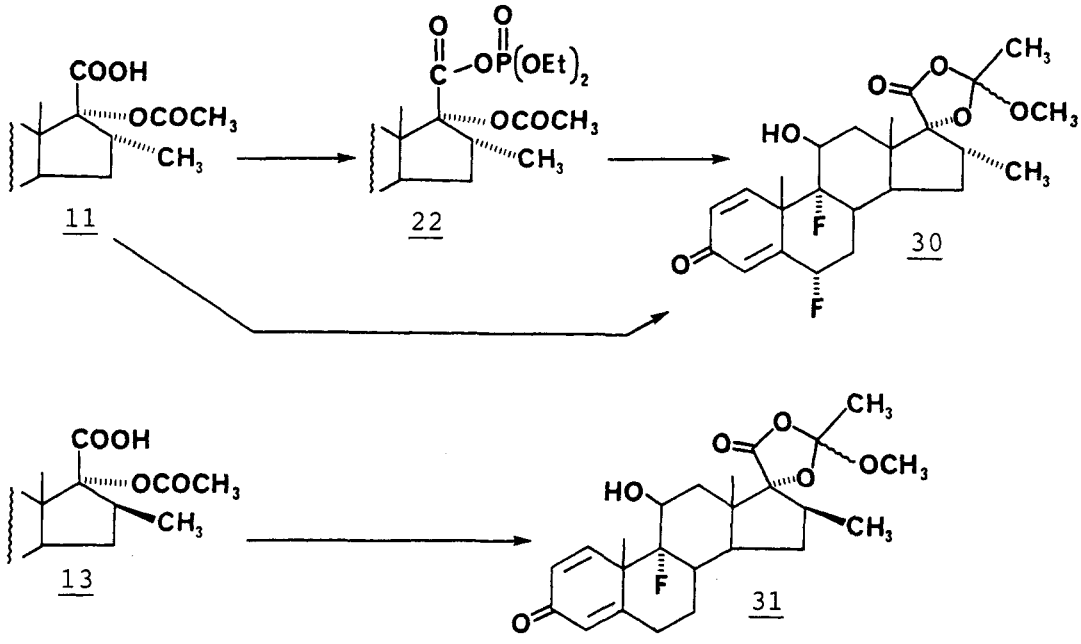
(21) Monodealkylation of the diethyl phosphate intermediate by sodium mercaptide (see ref 22) would give an anhydride salt, which could lead to free carboxylic acid by loss of metaphosphate or hydrolysis in the workup (see ref 23).

(22) Savignac, P.; Lavielle, G. *Bull. Chim. Soc. Fr.* **1974**, 1506.

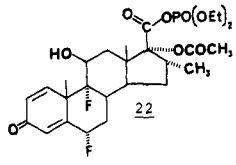
(23) Moon, M. W.; Khorana, H. G. *J. Am. Chem. Soc.* **1966**, *88*, 1798.

(24) The reactions of **11** and **14** with thionyl chloride gave TLC visible intermediates with very similar R_f's to those noted in reactions with diphenyl chlorophosphate, which at first suggested that acid chlorides might play a role in this chemistry.

Scheme III. Methanolysis of Phosphate-Activated 17α-Acetoxy Acids



cedures. Only the 16α-methyl diethyl chlorophosphate product **22** proved stable enough to be isolated in this



manner, with starting acid alone being isolated from the other reaction mixtures. Intermediate **22** was isolated in 84% yield; it survived purification by chromatography, and its identity was the desired diethyl phosphate mixed anhydride was confirmed by spectral and analytical data. To our surprise in a series of TLC experiments with mercaptide salts, the isolated phosphate **22** gave erratic yields of less than 10% of substitution products with $NaSCH_3$, these being roughly equal amounts of thiol ester **19** and spiro ortho ester **23**, and virtually no such products were obtained with $NaSC_2H_5$. In both cases the free acid **11** was the single major product. The inconsistent behavior of **22** toward thiolate before and after isolation is puzzling, but it is clear that reversion to free acid is a characteristic of the diethyl phosphate species itself, and is not a result of "disproportionation".

Although phosphate-activated etianic acids were found to be unreactive toward free mercaptans,[25] the solvolysis of these species with methanol proceeded with ease to give high yields of 17-spiro products. The products were those of 17-ester participation exclusively; no normal methyl ester products were detected. Thus, the 17-spiro acyl orthoacetate **30** was isolated in 71% yield from a solution of isolated phosphate **22** in methanol after heating at reflux for 1 h (Scheme III). Isolation of phosphate intermediates was not necessary to produce methoxydioxolanones, and the exchange of methanol for the THF in freshly filtered reaction mixtures containing either diethyl or diphenyl phosphate anhydrides and warming gave excellent yields of 17-spiro products in all cases. The 16α- and 16β-methyl orthoacetates **30** and **31** were prepared in this manner from **11** and **13** via the diethyl phosphates in 85% and 76% yields, respectively. Diethyl phosphates gave somewhat better yields than the diphenyl intermediates, and acid chloride preparations gave the same methanolysis products, but in poorer yields than phosphates.

The thiol esters of base-sensitive substrates and of free 17-hydroxy acids were inaccessable from phosphate intermediates. Thus, an attempted preparation of thiol ester **49** from **15** failed due to sensitivity of the 9,11-dichloride system to the required thiolate, and reactions of 17-hydroxy acids **6** and **7** with chlorophosphate reagents gave only polar materials presumed to be 17-phosphate esters.

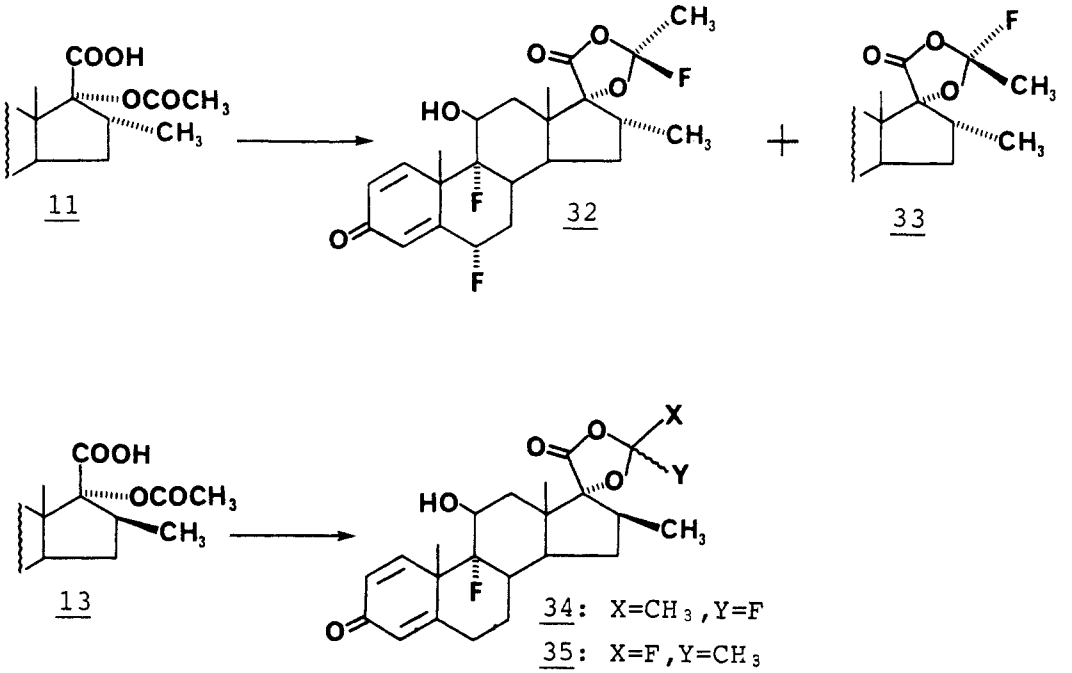
Reactions with 2-Fluoro-*N*-methylpyridinium Tosylate. In view of the limitations of chlorophosphate reagents, the use of 2-fluoro-*N*-methylpyridinium tosylate[26] (FMPT) for etianic acid activation was investigated. However, FMPT-derived intermediates did not react with free mercaptans, and neighboring group participation again dominated the chemistry. Thus, although the reaction of acetonide acid **10** with freshly prepared FMPT and TEA at −15 °C followed by addition of $NaSCH_3$ afforded a 92% yield of thiol ester **17**, the chemistry of substrates bearing 17α-acyloxy or -hydroxy groups was complex. Treatment of the 16α-methyl-17-acetoxyetianic acid **11** with FMPT and TEA gave complete conversion to a mixture of two compounds of similar R_f that were totally unreactive toward a large excess of $NaSCH_3$, even after 16 h at 110 °C. The products, isolated in a total yield of 64% by preparative TLC, were identified as the separate epimers **32** (34%) and **33** (30%) of a 17-spiro acylfluoro ketal (Scheme IV). Both cyclic ketals absorbed at 1805 cm^{-1} in the infrared and are related in structure and presumably in mechanism of formation to the previously noted acylorthoesters, but the complete incorporation of fluoride ion in this manner[27] and the stability of the resulting fluoroketal structures were quite unexpected. Proton NMR spectroscopy allowed the assignment of stereochemistry between the two fluoroketals, since the *S* epimer **32** showed splitting of the 16α-methyl by an adjacent fluorine,

(25) Carboxylate intermediates formed with phenyl dichlorophosphate are reported to be especially reactive toward free thiols (see ref 20), but the use of this reagent offered no advantage in the present work.

(26) (a) For a review, see: Mukaiyama, T. *Angew. Chem.* **1979**, *18*, 707. (b) For use of FMPT in thioester synthesis, see: Watanabe, Y.; Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1976**, 741.

(27) The participation of fluoride ion in the absence of other nucleophiles is the basis of a method for the synthesis of acyl fluorides using FMPT: Mukaiyama, T.; Tanaka, T. *Chem. Lett.* **1976**, 303.

Scheme IV. Reactions of 17α-Acetoxy Acids with FMPT



whereas the *R* epimer **33** did not.[28] The 16β-methyl-17-acetoxy acid **13** was similarly converted into epimeric fluoroketals **34** and **35**, but the relative stereochemistry of this pair could not be assigned by NMR, presumably since the 16β-methyl was too far from the ketal fluorine to show a coupling.

The standard FMPT/$NaSCH_3$ conditions were applied to 16β-methyl-17-hydroxy acid **9** in the hope that the lower reaction temperature would spare the 9,11-dichloride system. The dichloride system did indeed survive, but in this case the major product isolated in 34% yield was that of dehydration, the Δ^{16}-carboxylic acid **36** (Scheme V). The 9,11-fluorohydrin 16α-methyl acid **6** behaved quite differently when used in the same reaction sequence. In this case, the reaction mixture yielded 30% of normal thiol ester **37**, 18% of the 18-nor-$\Delta^{13,17}$-17-methyl rearrangement product **38**, and 12% of an unstable compound to which the 13,17-lactone-17β-methyl structure **39** has been assigned. This labile material absorbed at 1810 cm^{-1} in the infrared, and was transformed quantitatively into **38** with apparent loss of carbon dioxide while drying at 100 °C. The properties of **39** are compatible with the assigned structure as well as its possible role as an intermediate in the formation of olefin **38**. Mercaptide anion was not essential to the formation of these rearrangement products, and reaction of **6** with FMPT and TEA alone gave **38** (16%) and **39** (11%) along with some starting acid (7%) as the only isolable products. The 17-methyl olefin substrate exemplified by **38** is familiar among products of the Miescher–Kägi rearrangement[29] of androstane 17-alcohols and tosylates,[30] and the formation of β-lactone **39** appears related to a known rearrangement of steroid 17-spiro oxetanones.[31,32]

Stereochemistry at C-16 was suspected of influencing the choice of reaction path between products of 18-methyl migration and 16,17-olefin formation. Therefore, two additional 16β-methyletianic acids were subjected to the FMPT/TEA reaction conditions. The 9,11-fluorohydrin **7** gave 48% of 17-methyl-$\Delta^{13,17}$-olefin **40** and 8% of the labile β-lactone **41**, in results which parallel those for 16α-methyl fluorohydrin **6**. Addition of $NaSCH_3$ to the reaction mixture did not change yields or give thiol ester products. The $\Delta^{9,11}$-acid **8** behaved much the same as 9,11-dichloride **9** and gave 31% of dehydration product acid **42**. A 15% yield of corresponding thiol ester **43** accompanied **42** when $NaSCH_3$ was added to the reaction mixture, whereas the Δ^{16}-acyl fluoride **44** was isolated[27] in place of **43** when thiolate was not used. It was not possible to detect any overlap of product types in the reported reactions: each 17-hydroxyetianic acid appeared to give either 18-methyl migration or Δ^{16}-products exclusively.

Thus, the difference in reactions of 17-hydroxy acids with FMPT was associated with the 9,11-substitution pattern rather than C-16 stereochemistry. Both the 16α and the 16β-methyl fluorohydrins **6** and **7** gave 18-methyl migration products, whereas dichloride **5** and 9,11-olefin **4** experienced 17-alcohol dehydration.[33] The influence of the C-ring substitution pattern on the choice of reaction path was most likely due to its effect on overall molecular conformation,[36] probably in determining the nature and strain energy of the actual intermediate species. The

(28) The use of long range coupling effects to determine the stereochemistry of fluoride substituents is precedented by studies of the interaction between the steroid 6β-fluorine and the 19-angular methyl group: Bhacca, N. S.; Williams, K. H. *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day: San Francisco, 1964; pp 123–134, and references therein.

(29) (a) Kägi, H.; Miescher, K. *Helv. Chim. Acta* **1939**, *22*, 683. (b) Miescher, K.; Kägi, H. *Ibid* **1949**, *32*, 761.

(30) For reviews, see: (a) Wendler, N. L. In *Molecular Rearrangements Part 2*; de Mayo, P., Ed.; Wiley-Interscience: New York, 1964; pp 1020–1026. (b) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: New York, 1968; pp 269–272.

(31) (a) Herz, J. E.; Fried, J.; Grabowich, P.; Sabo, E. F. *J. Am. Chem. Soc.* **1956**, *78*, 4812. (b) Hirschmann, R.; Bailey, G. A.; Poos, G. I.; Walker, R.; Chemerda, J. M. *Ibid* **1956**, *78*, 4814.

(32) Rearrangement of 17,21-oxetanones to the isomeric 17β-methyl-13α,17α-keto oxides (see ref 31) is an example of 18-methyl migration with participation of a neighboring oxygen functionality (see ref 30a; also ref 30b, p 369).

(33) A similar divergence in reactivity reflecting C-ring substituent effects has been observed in acid-catalyzed reactions of 17α-hydroxy steroid 3,20-disemicarbazones, wherein 11-ketones gave Δ^{16}-products (see ref 34) and 11-alcohols underwent 18-methyl migration (see ref 35).

(34) Slates, H. L.; Wendler, N. L. *J. Org. Chem.* **1957**, *22*, 498.

(35) Taub, D.; Hoffsommer, R. D.; Wendler, N. L. *J. Org. Chem.* **1964**, *29*, 3486.

(36) The potential of C-ring substitution to markedly alter the preferred conformation of the steroid side chain was illustrated in a recent X-ray crystallographic study of a series of pregnanes: Duax, W. L.; Griffin, J. F.; Rohrer, D. C. *J. Am. Chem. Soc.* **1981**, *103*, 6705.

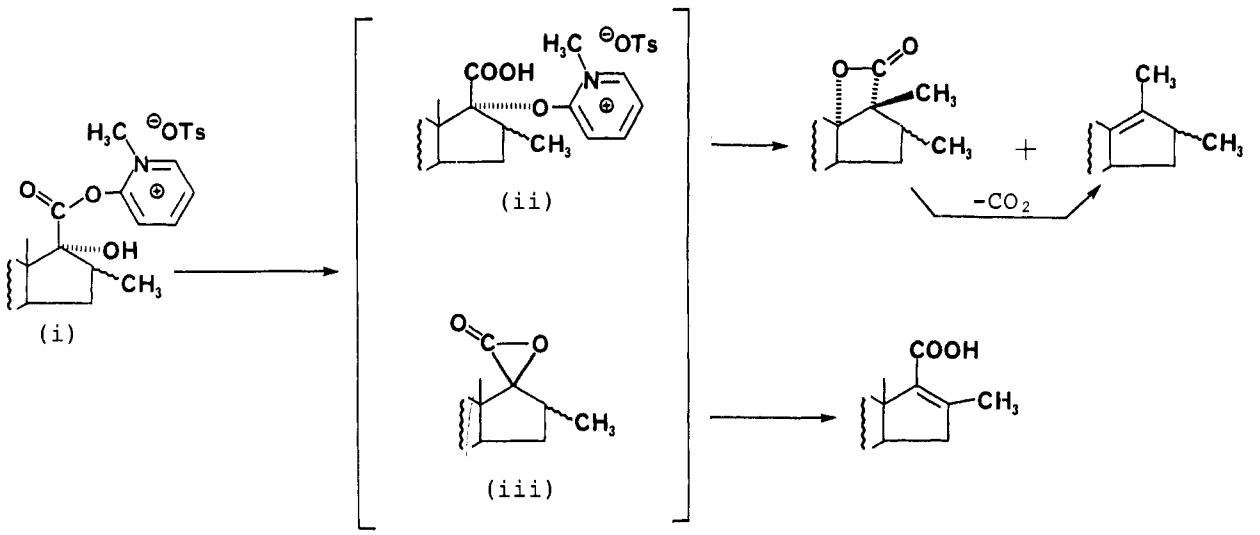
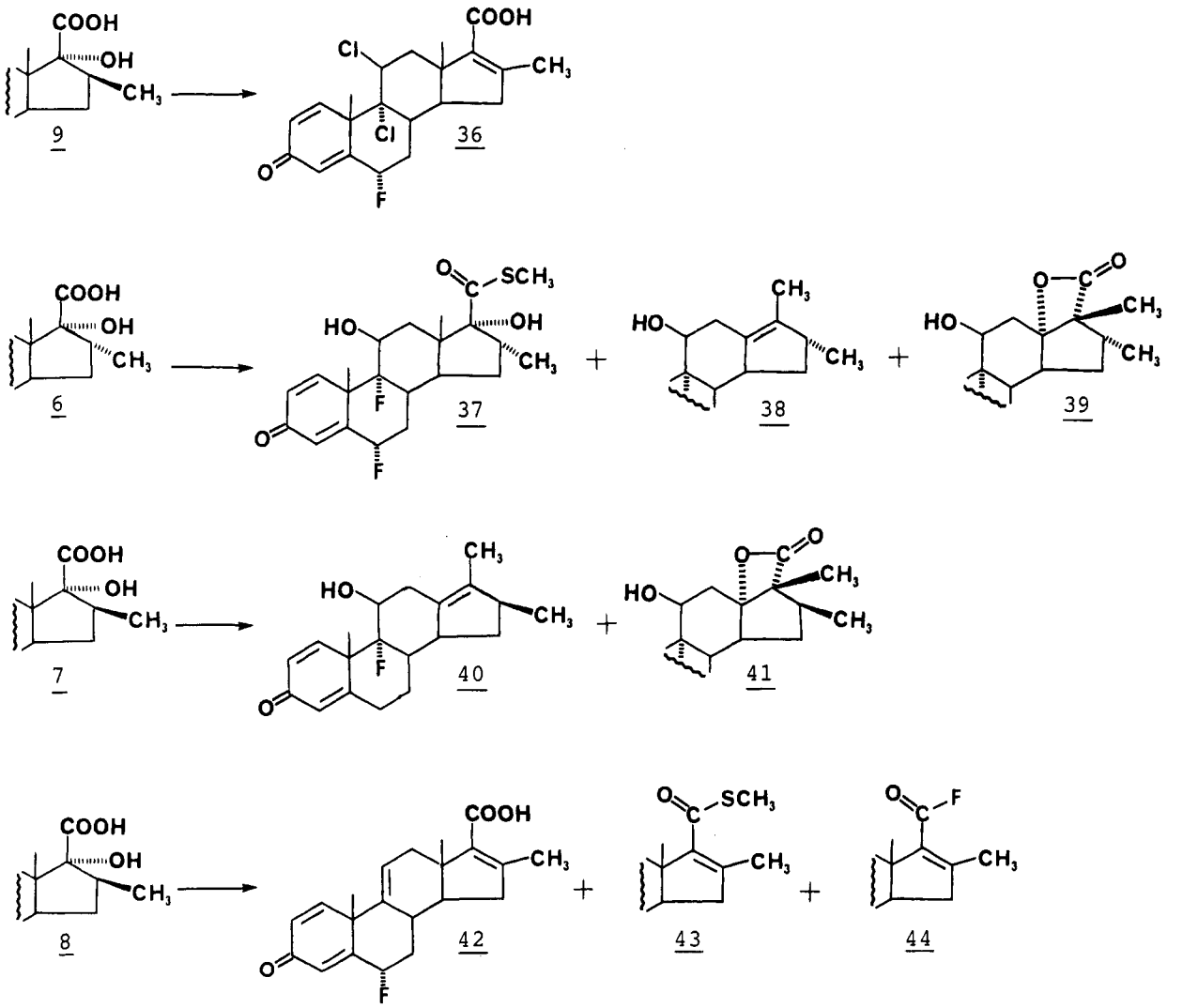


Figure 2.

Scheme V. Reactions of 17α-OH Acids with FMPT and $NaSCH_3$



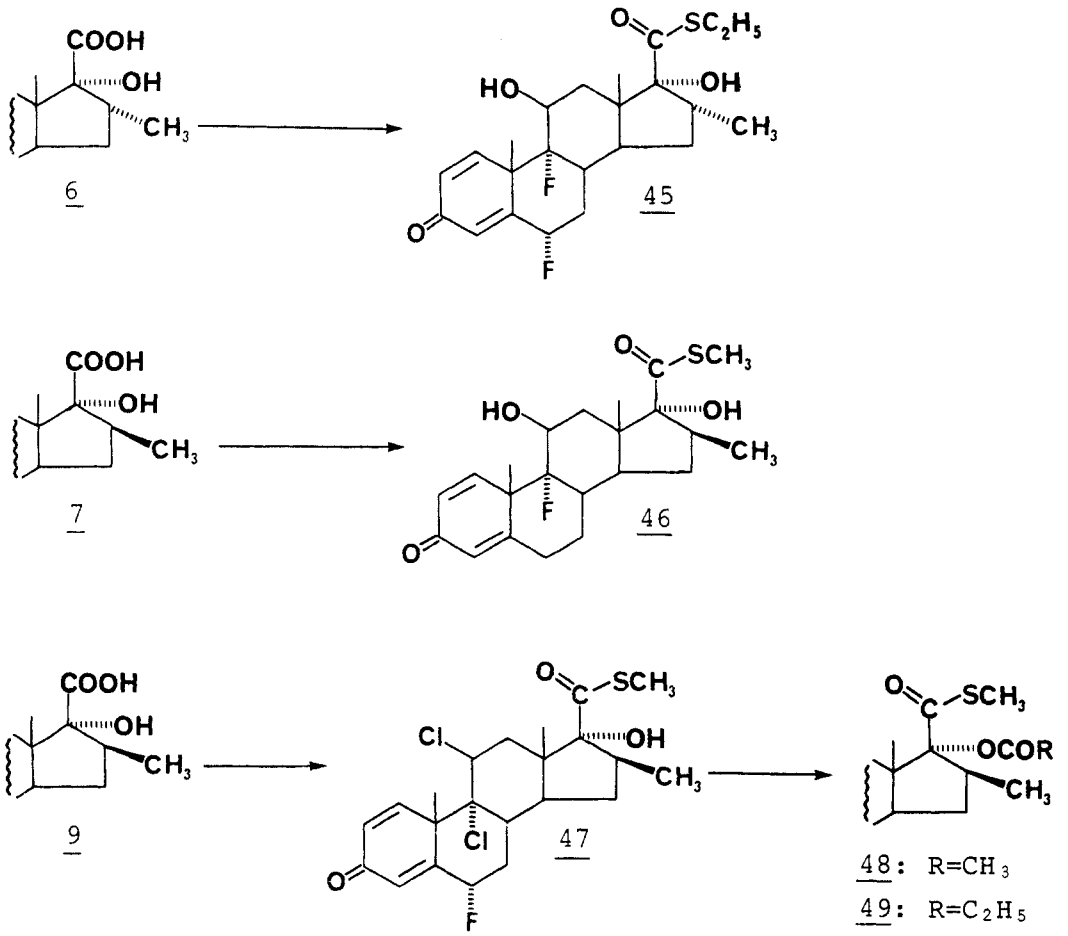
tendency of the resulting intermediate to rearrange would then depend on the degree of transcoplanarity between the 18-methyl and 17-leaving groups attained therein.[30] Both 17-oxo adduct (ii) and α-lactone[37] (iii) are potentially accessible from base-catalyzed transformations of initial pyridinium adduct (i), and either could serve as a transient intermediate in the subsequent reactions (Figure 2).

Activation with Carbonyldiimidazole. The use of carbonyldiimidazole[38] (CDI) as an activating agent pro-

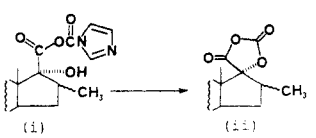
(37) Chapman, O. L.; Wotjkowski, P. W.; Adam, W.; Rodriguez, O.; Rucktäschel, R. *J. Am. Chem. Soc.* **1972**, *94*, 1365, and references therein.

(38) Gais, H. J. *Angew. Chem.* **1977**, *16*, 244.

Scheme VI. Thiol Esters of 17α-OH Acids via CDI



vided a solution to problems of thiol ester formation in the presence of both base-sensitive C-ring substituents and free 17-hydroxy groups. The intermediates formed in reactions of CDI with free 17-hydroxy acids comprised the only species encountered in the present work that was reactive toward free mercaptans. Thus, treatment of 16α-methyl-17-hydroxy acid **6** with CDI followed by addition of ethanethiol gave ethylthio ester **45** (40%), and 16β-methyl methylthio ester **46** (61%) was obtained by bubbling methyl mercaptan through the reaction mixture of CDI with 17-hydroxy acid **7** in DMF (Scheme VI). Syntheses of 9,11-dichloro-17-acetate methylthio ester **48** and propionate **49** were then accomplished by a similar preparation of 17-hydroxy thiol ester **47** from **9**, followed by dimethylaminopyridine (DMAP) catalyzed esterifications of the hindered 17-alcohol in mixtures of acetic or propionic anhydride with TEA at 80 °C. No reaction was observed when the 17-acetoxy acids **11** and **13** and the 16,17-acetonide **10** were treated with CDI followed by either mercaptan or mercaptide anion, presumably because reactive intermediates were not formed. The ability of CDI to activate 17-hydroxy acids towards thiol ester formation is remarkable in contrast to the failures with 17-derivatized substrates, and could result from steric factors alone or in combination with actual participation by the free 17-alcohol. In view of the ease with which 17-spirocyclic derivatives of the 17-hydroxy acids are formed, it seems reasonable to propose that the initial adduct (i) could give



the cyclic carbonate (ii) as the actual intermediate in these cases,[39] instead of an acylimidazolide.[38]

Many of the etianic acid thiol esters prepared in this work have proven to be extremely potent topical antiinflammatory agents, as measured in the rat[40] and in human vasoconstrictor[41] assays. A noteworthy separation between topical and systemic corticoid activity was also achieved, since most of the compounds were relatively inactive in the rat thymus involution and carrageenan-paw assays.[42] Thus, the 16α-methyl-17-propionyloxy methylthio ester **21** possessed topical activity in the order of fluocinolone acetonide (**1**) and the 16β-methyl 17-acetate **24** was approximately 1.3 times as potent, whereas both compounds demonstrated systemic activities of less than 5 times hydrocortisone.[45] A high ratio of topical to systemic activity such as that displayed by thiol esters **21** and **24** is of potential therapeutic value.[2b] All examples of 17-spiro acyl ortho esters and fluoro ketals were virtually inactive in both types of assay.

Experimental Section

General Methods. Melting points were obtained by using a Fisher-Johns apparatus and are uncorrected. Analytical TLC was

(39) We thank Dr. Arthur Kluge for this suggestion.
(40) Tonelli, G.; Thibault, L.; Ringler, I. *Endocrinology* **1965**, *77*, 625.
(41) Place, V. A.; Velasquez, J. G.; Burdick, K. H. *Arch. Dermatol.* **1970**, *101*, 531.
(42) Potencies were determined in intact rats using a combination of a two-day thymolytic assay (see ref 43) and a paw edema test (see ref 44).
(43) Dorfman, R. I.; Dorman, A. S.; Agnello, E. J.; Figdor, S. K.; Lauback, G. D. *Acta Endocrinol. (Copenhagen)* **1961**, *37*, 343.
(44) Winter, C. A.; Risley, E. A.; Nass, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
(45) The topical activity of hydrocortisone is approximately 0.001 times that of fluocinolone acetonide **1** when measured in our vasoconstrictor assays (see ref 41).

performed with Analtech 2.5 cm × 10 cm × 0.25 mm silica GF plates, and preparative TLC was done on Analtech silica GF 20 cm × 40 cm × 1 mm plates or with a Harrison Chromatotron centrifugal chromatography apparatus using 1 mm and 2 mm thick silica PF plates. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer, and frequencies are quoted to the nearest 5 cm^{-1}. Ultraviolet spectra were taken in methanol on a Cary 14 spectrophotometer. Proton NMR spectra were determined on Varian HA-100 (100 MHz), Bruker WH-90 (90 MHz), or Bruker WM-300 (300 MHz) instruments as solutions in hexadeuteriodimethyl sulfoxide (Me_2SO) or deuteriochloroform ($CDCl_3$) containing tetramethylsilane as an internal reference, and carbon-13 spectra were recorded on the Bruker WM-300 (75.5 MHz). Electron impact mass spectral data were obtained with Finnegan MAT CH-7 and 122-S direct inlet instruments at 70 eV, chemical ionization spectra were measured on the MAT 122-S at 90 eV, and high-resolution mass spectrometric measurements were made on a Finnigan MAT-311A. Elemental analyses were performed by the Syntex Analytical Services Group. All reactions were performed in heat-dried glassware under an atmosphere of nitrogen, unless otherwise noted, and sensitive reagents were introduced through septa by syringe.

Materials. Fluocinolone acetonide (**1**, 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide), flumethasone (**2**, 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione), and betamethasone (**3**, 9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione) are commercially available. The $\Delta^{9,11}$-corticoid **4** was kindly supplied by the Upjohn Company in the form of the 17,21-diacetate (17,21-dihydroxy-6α-fluoro-16β-methylpregna-1,4,9(11)-triene-3,20-dione 17,21-diacetate).[46] Chlorophosphate reagents, CDI, and DMAP were purchased from Aldrich; FMPT (prepared from 2-fluoropyridine,[27] Aldrich) is now commercially available. Tetrahydrofuran (THF) was purified by distillation from Na benzophenone. Standard solutions of $NaSCH_3$ (usually 0.83 N) were prepared by bubbling methyl mercaptan through a slurry of NaH (50% in oil, usually 2.0 g) in DMF (50 mL) until all solids dissolved, and solutions of other mercaptide salts were made similarly from liquid mercaptans and NaH in DMF or THF.

17,21-Dihydroxy-6α-fluoro-16β-methylpregna-1,4,9(11)-triene-3,20-dione (4). To a solution of 17,21-dihydroxy-6α-fluoro-16β-methylpregna-1,4,9(11)-triene-3,20-dione 17,21-diacetate[46] (1 g, 2.18 mmol) in MeOH (40 mL) was added K_2CO_3 (0.5 g) in water (5 mL), and the mixture was stirred at 20 °C for 1 h. The solution was acidified with 6 N HCl and diluted with ice water, after which the precipitate was filtered, washed, and dried to give 745 mg (91%) of crystalline **4**, mp 198–200 °C. A sample was recrystallized from acetone–hexane for analysis: mp 202–204 °C; UV 238 nm (ε 16400); IR (KBr) 1720 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.73 (s, 3 H, 18-CH_3), 1.03 (d, 2 H, J = 6.4 Hz, 16-CH_3), 1.37 (s, 3 H, 19-CH_3), 4.18 (d, 1 H, J = 19.5 Hz, 21-H), 4.38 (d, 1 H, J = 19.5 Hz, 21-H), 5.60 (d, 1 H, J = 4.6 Hz, 11-H), 5.71 (br dm, 1 H, J = 45 Hz, 6-H), 6.07 (s, 1 H, 4-H), 6.20 (dd, 1 H, J_1 = 10 Hz, J_2 = 2 Hz, 2-H), 7.39 (d, 1 H, J = 10 Hz, 1-H); MS, m/e 374 (M^+). Anal. Calcd for $C_{22}H_{27}O_4F$: C, 70.57; H, 7.27. Found: C, 70.56; H, 7.17.

9α,11β-Dichloro-17α,21-dihydroxy-6α-fluoro-16β-methylpregna-1,4-diene-3,20-dione (5). A solution of 17,21-dihydroxy-6α-fluoro-16β-methylpregna-1,4,9(11)-triene-3,20-dione 17,21-diacetate[46] (1 g, 2.18 mmol) in a mixture of CCl_4 (20 mL) and pyridine[47] (3 mL) was purged with nitrogen for 5 min, then treated with a gentle stream of chlorine for 15 min, and flushed with nitrogen again for 5 min. The resulting mixture was diluted with EtOAc, washed with dilute HCl, water, and brine, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized twice from acetone–hexane, giving 840 mg of the intermediate 9,11-dichloro-17,21-diacetate, which was then slurried in a mixture of MeOH (40 mL) and a solution of K_2CO_3 (300 mg) in water (4 mL) for 30 min. Ice water (30 mL) was added and the resulting precipitate was filtered, washed, and dried to give 590 mg (61%) of crystalline **5**: mp 215–217 °C; UV 236 nm (ε 15000); IR (KBr) 1710 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 1.07 (s, 3 H, 18-CH_3), 1.08 (d, 3 H, J = 6 Hz, 16-CH_3), 1.71 (s, 3 H, 19-CH_3), 4.15 (d, 1 H, J = 19 Hz, 21-H), 4.39 (d, 1 H, J = 19 Hz, 21-H), 4.96 (br m, 1 H, 11-H), 5.58 (br dm, J = 48 Hz, 6-H), 6.10 (s, 1 H, 4-H), 6.30 (dd, 1 H, J_1 = 10 Hz, J_2 = 2 Hz, 2-H), 7.24 (d, 1 H, J = 11 Hz, 1-H); MS, m/e 426, 428 ($M^+ - H_2O$). Anal. Calcd for $C_{22}H_{27}O_4Cl_2F$: C, 59.33; H, 6.11. Found: C, 59.32; H, 5.98.

Oxidations with Periodic Acid. 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (6). To a slurry of (**2**) (2 g, 5.11 mmol) in MeOH (40 mL) was added a solution of periodic acid (1.7 g, 7.46 mmol) in water (40 mL), and the mixture was stirred open to the air at 20 °C for 16 h. The volume was reduced to 60 mL by evaporation, ice water (80 mL) was added, and the precipitate was filtered, washed, and dried, giving 1.88 g (94.5%) of crystalline **6**, mp 285–289 °C. A sample was recrystallized from acetone–hexane for analysis:[48] mp 303–304 °C dec; UV 238 nm (ε 16300); IR (KBr) 1700 (COOH), 1660 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.87 (d, 3 H, J = 9 Hz, 16-CH_3), 1.00 (s, 3 H, 18-CH_3), 1.49 (s, 3 H, 19-CH_3), 4.15 (br d, 1 H, J = 10 Hz, 11-H), 5.64 (br dm, 1 H, J = 48 Hz, 6 H), 6.10 (s, 1 H, 4-H), 6.27 (dd, 1 H, J_1 = 10 Hz, J_2 = 2 Hz, 2-H), 7.26 (d, 1 H, J = 9.4 Hz, 1-H); MS, m/e 396 (M^+). Anal. Calcd for $C_{21}H_{26}O_5F_2$: C, 63.63; H, 6.61. Found: C, 63.69; H, 6.72.

17-Hydroxyetianic acids **7–9** were prepared by the same procedure.

11β,17α-Dihydroxy-9α-fluoro-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (7) was prepared from **3** in 97% yield: mp 247–251 °C. A sample was purified by dissolving in dilute Na_2CO_3, washing with EtOAc, acidifying the aqueous phase with dilute HCl, and cooling to ice. The precipitate was collected, washed, dried, and recrystallized from EtOAc:[50] mp 254–256 °C (lit.[10] mp 256–258 °C); UV 239 nm (ε 21450); IR (KBr) 1750, 1720 (COOH), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 1.07 (s, 3 H, 18-CH_3), 1.14 (d, 3 H, J = 9 Hz, 16-CH_3), 1.50 (s, 3 H, 19-CH_3), 4.14 (br d, 1 H, J = 12 Hz, 11-H), 6.01 (s, 1 H, 4-H), 6.21 (dd, 1 H, J_1 = 10 Hz, J_2 = 2 Hz, 2-H), 7.29 (d, 1 H, J = 10 Hz, 1-H); MS, m/e 378 (M^+). Anal. Calcd for $C_{21}H_{27}O_5F$: C, 66.65; H, 7.19. Found: C, 66.40; H, 7.47.

6α-Fluoro-17α-hydroxy-16β-methyl-3-oxoandrosta-1,4,9(11)-triene-17β-carboxylic acid (8) was prepared from **4** in 92% yield: mp 200–201 °C dec. Analytical sample from acetone–hexane: mp 197–199 °C dec; UV 238 nm (ε 16200); IR (KBr) 1740, 1710 (COOH), 1655 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.86 (s, 3 H, 18-CH_3), 1.13 (d, 3 H, J = 6.6 Hz, 16-CH_3), 1.38 (s, 3 H, 19-CH_3), 5.61 (d, 1 H, J = 5.2 Hz, 11-H), 5.72 (br dm, 1 H, J = 48 Hz, 6-H), 6.07 (s, 1 H, 4-H), 6.20 (dd, 1 H, J_1 = 10 Hz, J_2 = 1.4 Hz, 2-H), 7.40 (d, 1 H, J = 10 Hz, 1-H); MS, m/e 360 (M^+). Anal. Calcd for $C_{21}H_{25}O_4F$: C, 69.98; H, 6.99. Found: C, 69.99; H, 7.24.

9α,11β-Dichloro-6β-fluoro-17α-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (9) was prepared from **5** in 91% yield: mp 221–223 °C dec; UV 236 nm (ε 15200); IR (KBr) 1750, 1710 (COOH), 1665 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 1.14 (s, 3 H, 18-CH_3), 1.17 (d, 3 H, J = 8 Hz, 16-CH_3), 1.69 (s, 3 H, 19-CH_3), 4.96 (br m, 1 H, 11-H); MS, m/e 430, 432 (M^+). Anal. Calcd for $C_{21}H_{25}O_4Cl_2F$: C, 58.48; H, 5.84. Found: C, 58.59; H, 5.78.

Base-Catalyzed Air Oxidation. 6α,9α-Difluoro-11β,16α,17α-trihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 16,17-Acetonide (10). A stream of air was bubbled under the surface of a slurry of **1** (0.5 g, 1.10 mmol) in MeOH (25 mL) containing K_2CO_3 (0.5 g) for 10 min, after which the air flow was stopped and the mixture was stirred open to the air for another 16 h at 20 °C. The volume was reduced to 10 mL by evaporation, after which EtOAc (80 mL) was added and the mixture was extracted with water. The aqueous layer was acidified

(46) For preparation, see: Ayer, D. E.; Schlagel, C. A.; Flynn, G. L. *Ger. Patent* 2308731, 1973; *Chem. Abstr.* **1973**, *79*, 146739a.

(47) For a prior use of pyridine as a solvent for chlorination of steroids, see: Cutler, F. A., Jr.; Mandell, L.; Shew, D.; Chemerda. J. M. *J. Org. Chem.* **1959**, *24*, 1621.

(48) Full characterization was performed because the literature melting point of 333 °C (see ref 49) was unattainable.

(49) Anner, G.; Meystre, Ch., U.S. Patent 3636010, 1972.

(50) This compound has been reported, but spectral data were incomplete: cf. ref 10.

with dilute HCl and reextracted with EtOAc, the resulting organic layer being washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. Recrystallization from acetone–hexane gave 370 mg (75%) of **10**: mp 301–303 °C dec; UV 237 nm (ε 15 900); IR (KBr) 1725 (COOH), 1665 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.93 (s, 3 H, 18-CH_3), 1.14 and 1.29 (2 s, 6 H, $C(CH_3)_2$), 1.48 (s, 3 H, 19-CH_3), 4.15 (br d, 1 H, J = 10 Hz, 11-H), 4.96 (m, 1 H, 6-H); MS, m/e 438 (M^+). Anal. Calcd for $C_{23}H_{28}F_2O_5$: C, 63.00; H, 6.44. Found: C, 63.13; H, 6.24.

17α-Acetoxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (11). Acetyl chloride (2.5 mL) was added to an ice-cooled solution of **6** (1.5 g, 3.78 mmol) in CH_2Cl_2 (50 mL) and TEA (7.5 mL), and the mixture was stirred at 0 °C for 30 min, after which TLC (1% HOAc–35% acetone–hexane) indicated that starting material had been replaced by a mixture of **11** with a less polar material assumed to be the mixed anhydride of acetic acid with **11**. Diisopropylamine (7.5 mL) was added and the mixture was stirred for 2 h at 20 °C and then evaporated to dryness. The residue was dissolved in EtOAc and the solution washed with dilute HCl, water, and brine, dried (Na_2SO_4), and evaporated. The residue was triturated with hot CH_2Cl_2, affording 1.15 g (69%) of **11**. The analytical sample was recrystallized 4 times from acetone–hexane: mp 180–182 °C dec; UV 238 nm (ε 15 800); IR (KBr) 1735 (br, COOH, ester), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.86 (d, 3 H, J = 7 Hz, 16-CH_3), 1.02 (s, 3 H, 18-CH_3), 1.49 (s, 3 H, 19-CH_3), 2.01 (s, 3 H, $COCH_3$); MS, m/e 418 (M^+ – HF). Anal. Calcd for $C_{23}H_{28}O_6F_2$: C, 63.00; H, 6.44. Found: C, 62.87; H, 6.28.

6α,9α-Difluoro-11β-hydroxy-17α-(propionyloxy)-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (12) was prepared from **6** by using propionyl chloride in the above procedure. Recrystallization from acetone–hexane gave 94% of **12**, mp 217–218 °C; UV 238 nm (ε 16 825); IR (KBr) 1730 (ester), 1700 (COOH), 1665 (3-C=O) cm^{-1}; ^1H NMR (100 MHz Me_2SO) δ 0.83 (d, 3 H, J = 7 Hz, 16-CH_3), 0.98 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.99 (s, 3 H, 18-CH_3), 1.47 (s, 3 H, 19-CH_3), 2.26 (q, 2 H, J = 7 Hz, $COCH_2$); MS, m/e 350 (M^+ – COOH, COC_2H_5). Anal. Calcd for $C_{24}H_{30}O_6F_2$: C, 63.71; H, 6.68. Found: C, 63.74; H, 6.73.

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (13). Acetyl chloride (6 mL) was added to a solution of **7** (4.60 g, 12.2 mmol) in CH_2Cl_2 (200 mL) and TEA (4 mL), and the mixture was stirred at 0 °C for 30 min. Diisopropylamine (25 mL) was added and the solution was heated at reflux for 1 h, after which the procedure was completed as described for **11**. Crystallization from acetone–hexane gave 4.76 g (93%) of **13**, mp 196–198 °C. Analytical sample from acetone–hexane:[50] mp 218–220 °C (lit.[10] 212–214 °C); UV 239 nm (ε 17 900); IR (KBr) 1735 (br, COOH, ester), 1655 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.98 (s, 3 H, 18-CH_3), 1.31 (d, 3 H, J = 7 Hz, 16-CH_3), 1.50 (s, 3 H, 19-CH_3), 1.94 (s, 3 H, $COCH_3$); MS, m/e 361 (MH^+ – HOAc). Anal. Calcd for $C_{23}H_{29}O_6F$: C, 65.70; H, 6.95. Found: C, 65.73; H, 7.01.

9α-Fluoro-11β-hydroxy-17α-(propionyloxy)-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (14) and 9α-Fluoro-11β-hydroxy-17α-(propionyloxy)-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Propionic Anhydride (16). Propionate **14** was prepared in 84% yield from **7** by using propionyl chloride in the above procedure. The analytical sample was recrystallized three times from acetone–hexane:[50] mp 182–183 °C dec (lit.[10] mp 188–190 °C; UV 239 nm (ε 14 000); IR (KBr) 1735 (br, COOH, ester), 1655 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 1.06 (s, 3 H, 18-CH_3), 1.06 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.39 (d, 3 H, J = 7 Hz, 16-CH_3), 1.53 (s, 3 H, 19-CH_3), 2.25 (q, 2 H, J = 7 Hz, $COCH_2$); MS, m/e 435 (MH^+). Anal. Calcd for $C_{24}H_{31}O_6F$: C, 66.34; H, 7.19. Found: C, 66.15; H, 7.08. A second reaction using 75 mg (0.20 mmol) of **7** was worked up directly, without the diisopropylamine step, affording 80 mg (72%) of **16**, mp 170–173 °C. The analytical sample was recrystallized from acetone–hexane:[50] mp 177–178 °C dec (lit.[10] 180–182 °C); UV 239 nm (ε 16 240); IR (KBr) 1815 (anhydride), 1730 (br, anhydride ester), 1660 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.10, 1.14 (2 t, 6 H, J's = 7 Hz, CH_2CH_3's), 1.11 (s, 3 H, 18-CH_3), 1.42 (d, 3 H, J = 7 Hz, 16-CH_3), 1.55 (s, 3 H, 19-CH_3), 2.30, 2.43 (2 q, 4-H, J's = 7 Hz, $COCH_2$'s); MS, m/e 470 (M^+ – HF). Anal. Calcd for $C_{22}H_{35}O_7F$: C, 66.11; H, 7.19. Found: C, 66.09; H, 7.16.

9α,11β-Dichloro-6α-fluoro-17α-(propionyloxy)-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (15). Treatment of **9** (352 mg, 0.82 mmol) with propionyl chloride and TEA followed by diisopropylamine gave 229 mg (58%) of **15** (from acetone–hexane), mp 178–180 °C dec; UV 236 nm (ε 14 400); IR (KBr) 1740 (ester), 1710 (COOH), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 1.00 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 1.05 (s, 3 H, 18-CH_3), 1.35 (d, 3 H, J = 7 Hz, 16-CH_3), 1.72 (s, 3 H, 19-CH_3), 2.27 (q, 2 H, J = 7.5 Hz, $COCH_2$), 5.06 (d, 1 H, J = 2.5 Hz, 11-H); MS, m/e 487 (MH^+). Anal. Calcd for $C_{24}H_{29}O_5Cl_2$: C, 59.14; H, 6.00. Found: C, 59.11; H, 6.04.

General Methods for Synthesis of Thiol Esters from Acids 10–14. Preparation of 17β-[(Methylthio)carbonyl]-6α,9α-difluoro-11β,16α,17α-trihydroxyandrosta-1,4-dien-3-one 16,17-Acetonide (17). Method A. A slurry of **10** (351 mg, 0.80 mmol) in THF (10 mL) containing TEA (0.20 mL, 1.44 mm), was stirred at 20 °C for 30 min, during which time the acid dissolved and a precipitate assumed to be the triethylammonium salt was formed. Diethyl chlorophosphate (0.17 mL, 1.20 mmol) was added and stirring was continued, giving a new precipitate of triethylammonium chloride ($Et_3N{\cdot}HCl$). After 2 h, TLC (3% MeOH–CH_2Cl_2) of a sample of reaction mixture worked up between EtOAc and dilute aqueous HCl showed that conversion of **11** to a neutral intermediate was complete. Filtration into a fresh flask gave 118 mg (0.85 mmol) of pure $Et_3N{\cdot}HCl$ (elemental analysis) which was discarded. An 0.83 N solution of $NaSCH_3$ in DMF (2.2 mL, 1.83 mmol) was added to the filtrate, and the mixture was stirred at 20 °C for 16 h, after which it was diluted with EtOAc and extracted with dilute aqueous Na_2CO_3. The organic layer was washed, dried (Na_2SO_4), and evaporated to dryness, giving the crude thiol ester as a very poorly soluble solid. Recrystallization from 1:2 MeOH/CH_2Cl_2 by boiling off the CH_2Cl_2 and cooling in ice gave 255 mg (68%) of pure **17**, mp >300 °C; UV 238 nm (ε 20 415); IR (KBr) 1665 (br, 20-C=O, 3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.83 (s, 3 H, 18-CH_3), 1.13, 1.33 (2 s, 6 H, $C(CH_3)_2$), 1.46 (s, 3 H, 19-CH_3), 2.29 (s, 3 H, SCH_3); MS, m/e 453 (M^+ – CH_3). Anal. Calcd for $C_{24}H_{30}O_5FS$: C, 61.52; H, 6.45; S, 6.84. Found: C, 61.40; H, 6.56; S, 6.55. Acidification of the Na_2CO_3 extract, extraction with EtOAc, and recrystallization from acetone–hexane gave 64 mg (18%) of pure starting acid **10**.

Method B. Diphenyl chlorophosphate (116 μL, 0.5 mmol) was added to a solution of **10** (175 mg, 0.40 mmol) in THF (6 mL) and TEA (100 μL, 0.72 mmol), and the mixture was heated at 55 °C for 2 h, after which the TLC of a worked-up sample showed that formation of a neutral intermediate was complete. The mixture was cooled in ice, filtered to remove the $Et_3N{\cdot}HCl$ (52 mg, 0.38 mmol), and 0.83 N $NaSCH_3$/DMF (1.0 mL, 0.83 mm) was added. The mixture was stirred at 20 °C for 1 h and worked up as described in method A, affording (after recrystallization from MeOH–CH_2Cl_2) 141 mg (75%) of pure **17**, mp >300 °C.

Method C. To a slurry of FMPT (90 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) at −15 °C was added a separately prepared solution of **10** (110 mg, 0.25 mmol) in a mixture of CH_2Cl_2 (3 mL) and TEA (58 μL, 0.42 mmol). The conversion of **10** to a nonpolar intermediate was complete in 20 min (TLC, 1% HOAc–40% EtOAc–hexane), after which a solution of $NaSCH_3$ (0.83 N in DMF, 1.0 mL, 0.83 mmol) was added and the mixture was maintained at −15 °C in a freezer for 16 h. Standard acid–base workup and recrystallization from MeOH then afforded 109 mg (93%) of pure **17** in two crops, mp >300 °C.

17β-[(Ethylthio)carbonyl]-6α,9α-difluoro-11β,16α,17α-trihydroxyandrosta-1,4-dien-3-one 16,17-Acetonide (18). Prepared from **10** (350 mg, 0.80 mmol) according to method A, using $NaSC_2H_5$ [from ethanethiol (0.20 mL) and NaH (50% in oil, 68 mg, 1.42 mmol) in THF (3 mL)]. Recrystallization from acetone–hexane gave 240 mg (65%) of **18** in two crops: mp >300 °C; UV 239 nm (ε 20 145); IR (KBr) 1665 (br, 20-C=O, 3-C=O); ^1H NMR (100 MHz, Me_2SO) δ 0.85 (s, 3 H, 18-CH_3), 1.13, 1.32 (2 s, 6 H, $C(CH_3)_2$, 1.17 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.83 (q, 2 H, J = 7, SCH_2); MS, m/e 467 (M^+ – CH_3). Anal. Calcd for $C_{25}H_{32}O_5F_2S$: C, 62.22; H, 6.68. Found: C, 62.11; H, 6.75.

17α-Acetoxy-6α,9α-difluoro-11β-hydroxy-17β-[(methylthio)carbonyl]-16α-methylandrosta-1,4-dien-3-one (19) and 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-(methylthio))methylene Ketal (23). A solution of the in-

termediate prepared from **11** (420 mg, 0.96 mmol) according to method A was treated with 0.83 N $NaSCH_3$/DMF (4 mL, 3.32 mmol) and stirred at 20 °C for 16 h. Workup gave 200 mg (48%, after recrystallization) of pure starting acid **11** and a neutral fraction which was recrystallized from acetone–hexane, affording 58 mg (13%) of thiol ester **19**. Analytical sample of **19** (from acetone–hexane): mp >300 °C; UV 238 nm (ε 20100); IR (KBr) 1750 (ester), 1670 (20-C=O, 3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.91 (d, 3 H, J = 7 Hz, 16-CH_3), 0.97 (s, 3 H, 18-CH_3), 1.48 (s, 3 H, 19-CH_3), 2.01 (s, 3 H, $COCH_3$), 2.26 (s, 3 H, SCH_3); MS, m/e 469 (MH^+). Anal. Calcd for $C_{24}H_{30}O_5F_2S$: C, 61.52; H, 6.45. Found: C, 61.63; H, 6.38. The neutral mother liquor material consisted of a mixture of **19** with a slightly less polar material which was probably the spiro ortho ester **23**. In a separate experiment, a reaction mixture prepared from **11** (400 mg, 0.91 mmol), diethyl chlorophosphate (0.25 mL, 1.73 mmol) and TEA (0.20 mL, 1.43 mmol) in THF (10 mL) was treated with 0.4 mL increments of 0.83 N $NaSCH_3$/DMF at 15-min intervals until the TLC (3% MeOH–CH_2Cl_2, developed twice) of worked-up samples showed complete replacement of phosphate intermediate (R_f 0.34) by thiol ester **19** (R_f 0.47), ortho ester **23** (R_f 0.55), and acid **11** (R_f 0.0). A total of 2.8 mL (2.3 mmol) of $NaSCH_3$ solution was required. Acid–base workup gave 136 mg (34%) of acid **11**, and crystallization of the neutral residue from acetone–hexane gave mixtures **19** and **23** consisting of a first crop (113 mg) enriched in **19** and a second crop (98 mg) enriched in **23**. The mixtures were separated by preparative TLC (30% EtOAc–hexane, eluted twice), and recrystallizations (acetone–hexane) then gave 40 mg (9%) of **19** and 52 mg (12%) of **23**: mp 201–203 °C; UV 237 nm (ε 16670); IR ($CHCl_3$) 1790 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.95 (d, 3 H, J = 7 Hz, 16-CH_3), 1.26 (s, 3 H, 18-CH_3), 1.50 (s, 3 H, 19-CH_3), 1.92 (s, 3 H, 1′-CH_3), 2.22 (s, 3 H, SCH_3); MS, m/e 469 (MH^+). Anal. Calcd for $C_{24}H_{30}O_5F_2S$: C, 61.52; H, 6.45. Found: C, 61.50; H. 6.37. Addition of a 5-fold excess of $NaSCH_3$ to a solution of **23** in THF gave complete conversion to **19** in 2 h at 20 °C.

Thiol ester **19** was also prepared as follows: thionyl chloride (40 μL, 0.56 mmol) was added to solution of **11** (70 mg, 0.16 mmol) in THF (5 mL) containing TEA (0.10 mL, 0.72 mmol) at 0 °C, and the mixture was filtered into a fresh flask after 10 min. Addition of 0.83 N $NaSCH_3$/DMF (0.8 mL, 0.66 mmol) to the filtrate and workup after 1 h at 20 °C gave 24 mg (32%) of **19**, mp >300 °C, and 11 mg (16%) of **11**.

17α-Acetoxy-6α,9α-difluoro-17β-[(ethylthio)carbonyl]-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one (20). Preparation from **11** (200 mg, 0.46 mmol) and $NaSC_2H_5$ according to method A gave 58 mg (26%) of thiol ester **20** and 92 mg (46%) of returned **11**. The analytical sample was recrystallized twice from acetone–hexane: mp >300 °C; UV 238 nm (ε 19595); IR (KBr) 1745 (ester), 1665 (br, 20-C=O, 3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.90 (d, 3 H, J = 7 Hz, 16-CH_3), 0.98 (s, 3 H, 18-CH_3), 1.16 (t, 3H, J = 7 Hz, CH_2CH_3), 1.46 (s, 3 H, 19-CH_3), 1.98 (s, 3 H, $COCH_3$), 2.84 (q, 2 H, J = 7 Hz, SCH_2); MS, m/e 421 ($M^+ - SC_2H_5$). Anal. Calcd for $C_{25}H_{32}O_5F_2S$: C, 62.23; H, 6.68. Found: C, 62.50; H, 6.63.

6α,9α-Difluoro-11β-hydroxy-17β-[(methylthio)carbonyl]-17α-(propionyloxy)-16α-methylandrosta-1,4-dien-3-one (21). The reaction of **12** (1.5 g, 3.32 mmol) with $NaSCH_3$ according to method A gave 376 mg (25%) of returned **12** and 525 mg (33%) of thiol ester **21** in two crops. Analytical sample from acetone–hexane: mp 285–287 °C dec; UV 238 nm (ε 19565); IR (KBr) 1740 (ester), 1675 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.89 (d, 3 H, J = 7 Hz, 16-CH_3), 0.93 (s, 3 H, 18-CH_3), 1.00 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.46 (s, 3 H, 19-CH_3), 2.24 (s, 3 H, SCH_3), 2.29 (q, 2 H, J = 7 Hz, $COCH_2$); MS, m/e 482 (M^+). Anal. Calcd for $C_{25}H_{32}O_5F_2S$: C, 62.22; H, 6.68; S, 6.64. Found: C, 62.45; H, 6.82; S, 6.59. Method B proved superior for the preparation of **21**. Thus, the reaction of **12** (200 mg, 0.44 mmol) with diphenyl chlorophosphate (168 μL, 0.81 mmol) and TEA at 55 °C followed by treatment with $NaSCH_3$/DMF (0.83 mmol) gave 189 mg (89%) of **21**, mp 286–288 °C dec.

17α-Acetoxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Diethyl Phosphoric Anhydride (22). Diethyl chlorophosphate (120 μL, 0.83 mmol) was added to a solution of **11** (219 mg, 0.50 mmol) in THF (6 mL) containing TEA (125 μL, 0.9 mmol) and the mixture was warmed at 50 °C. After 1 h, TLC (0.5% HAc–35% acetone–hexane) showed that all but a trace of **11** had been converted to the intermediate (R_f 0.32) seen in preparations of **19** by method A. The mixture was cooled, diluted with EtOAc, washed with dilute Na_2CO_3 and water, dried (Na_2SO_4), and evaporated to dryness. The residue was partially purified by dissolving in acetone (2 mL) containing a drop of TEA, adding hexane (20 mL), and decanting the supernatant. Vacuum drying of the precipitate gave 242 mg (84%) of **22** as an amorphous solid judged >95% pure by TLC. An analytical sample was purified by centrifugal TLC (0.1% TEA–20% acetone–CH_2Cl_2) and precipitation as before, affording a semi-crystalline solid, mp 100–110 °C dec; UV 238 nm (ε 16100); IR ($CHCl_3$) 1780 (20-C=O), 1745 (ester), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz, 16-CH_3), 1.17 (s, 3 H, 18-CH_3), 1.36 (dt, 3 H, J_1 = 1 Hz, J_2 = 7 Hz, CH_2CH_3), 1.39 (dt, 3 H, J_1 = 1 Hz, J_2 = 7 Hz, CH_2CH_3), 1.54 (s, 3 H, 19-CH_3), 2.10 (s, 3 H, $COCH_3$), 4.21 (dq, 2 H, J_1 = 7 Hz, J_2 = 7 Hz, OCH_2), 4.35 (dq, 2 H, J_1 = 7 Hz, J_2 = 7 Hz, OCH_2); MS, m/e 575 (MH^+). Anal. Calcd for $C_{27}H_{37}O_9F_2P$: C, 56.44; H, 6.49. Found: C, 56.53; H, 6.57. Samples of **22** stored under argon at −20 °C remained 95–98% pure for 1–2 months, after which degradation (largely to **11**) was observed.

17α-Acetoxy-9α-fluoro-11β-hydroxy-17β-[(methylthio)carbonyl]-16β-methylandrosta-1,4-dien-3-one (24) and 11β,17α-Dihydroxy-9α-fluoro-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-(methylthio))methylene Ketal (27). The activation of **13** (168 mg, 0.40 mmol) by method B and reaction with $NaSCH_3$ (0.60 mmol) afforded (after recrystallization from acetone–hexane) 134 mg (74%) of **24**, mp 263–265 °C dec; UV 239 nm (ε 19600); IR (KBr) 1745 (ester), 1700 (20-C=O), 1660 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.86 (s, 3 H, 18-CH_3), 1.28 (d, 3 H, J = 7 Hz, 16-CH_3), 1.49 (s, 3 H, 19-CH_3), 1.98 (s, 3 H, $COCH_3$), 2.14 (s, 3 H, SCH_3); MS, m/e 403 ($M^+ - SCH_3$). Anal. Calcd for $C_{24}H_{31}O_5FS$: C, 63.98; H, 6.94; S, 7.11. Found: C, 63.73; H, 7.07; S, 7.41. The reaction of **13** (210 mg, 0.50 mmol) with diethyl chlorophosphate (0.70 mmol) and $NaSCH_3$ (0.70 mmol) according to method A gave 180 mg (80%) of a mixture, shown by TLC (0.25% TEA–55% ether–cyclohexane, developed three times) to be approximately 9:1 of ortho ester **27** (R_f 0.38) with **24** (R_f 0.44). The tendency of **27** to isomerize to **24** on silica gel during chromatography was partially overcome by inclusion of TEA in the eluent. Thus, a sample of **27** was purified for analysis by centrifugal TLC (0.4% TEA–65% ether–cyclohexane, developed 3 times) and recrystallization from ether–pentane: mp 202–203 °C dec; UV (ε 16000); IR (KBr) 1795 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) 1.15 (d, 3 H, J = 7 Hz, 16-CH_3), 1.17 (s, 3 H, 18-CH_3), 1.51 (s, 3 H, 19-CH_3), 1.83 (s, 3 H, 1′-CH_3), 2.19 (s, 3 H, SCH_3); MS, m/e 451 (MH^+). Anal. Calcd for $C_{24}H_{31}O_5FS$: C, 63.98; H, 6.94. Found: C, 63.86; H, 7.03.

17α-Acetoxy-9α-fluoro-17β-[(n-hexylthio)carbonyl]-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one (25) and 11β,17α-Dihydroxy-9α-fluoro-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-(n-hexylthio))methylene Ketal (28). The reaction of **13** (220 mg, 0.5 mmol) with diethyl chlorophosphate and $NaSC_6H_{13}$ according to method A and separation of the product mixture by preparative TLC (4% acetone–CH_2Cl_2, developed twice) afforded 35 mg (13%) of thiol ester **25** (R_f 0.38), mp 168–172 °C, and 111 mg (43%) of ortho thio ester **28** (R_f 0.33). A sample of **25** was recrystallized from EtOAc–hexane for analysis: mp 176–178 °C; UV 240 nm (ε 19025); IR (KBr) 1730 (ester), 1700 (20-C=O), 1660 (3-C=O) cm^{-1}; ^1H NMR (90 MHz, Me_2SO) δ 0.87 (br m, 6 H, 18-CH_3, CH_2CH_3), 1.28 (br m, 11 H, 16-CH_3, hexyl CH_2's), 1.49 (s, 3 H, 19-CH_3), 2.00 (s, 3 H, $COCH_3$); MS, m/e 403 ($M^+ - SC_6H_{13}$). Anal. Calcd for $C_{29}H_{41}O_5FS$: C, 66.89; H, 7.94. Found: C, 66.82; H, 8.07. The data for **28** (from acetone–hexane) were as follows: mp 129–131 °C; UV 237 nm (ε 16310); IR (KBr) 1795 (20-C=O), 1675 (3-C=O) cm^{-1}, ^1H NMR (90 MHz, Me_2SO) δ 0.85 (br t, 3 H, J = 5 Hz, CH_2CH_3), 1.14 (d, 3 H, J = 7 Hz, 16-CH_3), 1.16 (s, 3 H, 18-CH_3), 1.50 (s, 3 H, 19-CH_3), 1.84 (s, 3 H, 1′-CH_3); MS, m/e 403 ($M^+ - SC_6H_{13}$). Anal. Calcd for $C_{29}H_{41}O_5FS$: C, 66.89; H, 7.93. Found: C, 67.01; H, 8.00.

9α-Fluoro-11β-hydroxy-17β-[(methylthio)carbonyl]-17α-(propionyloxy)-16β-methylandrosta-1,4-dien-3-one (26) and

the Isomeric 17,20-(1′-Ethyl-1′-methylthio)methylene Ketal (29). The activation of acid **14** (113 mg, 0.26 mmol) with diethyl chlorophosphate (1 mmol) and treatment with $NaSCH_3$ (2.5 mmol) according to method A gave 133 mg of a neutral residue which was purified by preparative TLC (2% CH_3OH–CH_2Cl_2, developed twice). The product was 77 mg (64%) of a chromatographically homogeneous solid, estimated to be a 3:1 mixture of ketal **29** with thiol ester **26** by comparing the integrals of the methylthio group ^1H NMR resonances (2.12 ppm for **29**, 2.17 ppm for **26**) and intensities of the major infrared absorptions (1790 for 17β-carbonyl of **29**, 1740 cm^{-1} for acetate of **26**). A sample of the mixture (64 mg, 0.14 mmol) in THF (8 mL) was treated with additional $NaSCH_3$/DMF (1.65 mmol), and the mixture was heated at 45 °C for 6 h. Acid–base workup and recrystallization from acetone–hexane then afforded 30 mg (30% overall yield) of pure **26**: mp 223–224 °C; UV 239 nm (ε 18890); IR (KBr) 1740 (ester), 1700 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.88 (s, 3 H, 18-CH_3), 1.03 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.31 (d, 3 H, J = 7 Hz, 16-CH_3), 1.50 (s, 3 H, 19-CH_3), 2.17 (s, 3 H, SCH_3), 2.34 (q, 2 H, J = 7 Hz, $COCH_2$); MS, m/e 464 (M^+). Anal. Calcd for $C_{25}H_{33}O_5FS$: C, 64.63; H, 7.16; S, 6.90. Found: C, 64.38; H, 7.34; S, 6.87. Thiol ester **26** was also prepared by reaction of **14** (5.7 g, 13.26 mmol) with diphenyl chlorophosphate (19.3 mmol) and $NaSCH_3$ (20.8 mmol) according to method B. Analysis of the reaction mixture after 1 h at 20 °C, indicated the product to be **26** containing 5–10% of **29**. Extra $NaSCH_3$ (5 mmol) was added and the mixture was heated at 60 °C for 2 h, after which recovery and recrystallization of the product afforded 3.9 g (64%) of pure **26**, mp 223–224 °C. A third sample of **26** (34%) was prepared via activation of 14 with thionyl chloride, using the procedure described for **19**.

6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-methoxy)methylene Ketal (30). A solution of freshly prepared **22** (104 mg, 0.18 mmol) in MeOH (10 mL) was heated at reflux for 1 h, giving a 1:1 mixture of ketal isomers by TLC (R_f's 0.30, 0.37, 40% EtOAc–hexane). The solution was diluted with EtOAc, washed with dilute $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to dryness. Recrystallization from acetone–hexane afforded 58 mg (71%) of **30**, mp 200–202 °C dec; UV 238 nm (ε 16300); IR (KBr) 1795 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.99, 1.04 (2 d, 3 H, J's = 7 Hz, 16-CH_3's); 1.30, 1.32 (2 s, 3 H, 18-CH_3's), 1.54 (s, 3 H, 19-CH_3), 1.71, 1.72 (2 s, 3 H, 1′-CH_3's), 3.39, 3.42 (2 s, 3 H, OCH_3's); MS, m/e 452 (M^+). Anal. Calcd for $C_{24}H_{30}O_6F_2$: C, 63.71; H, 6.68. Found: C, 63.89; H, 6.64. A second sample of **30** was prepared from 11 (175 mg, 0.40 mmol) by reaction with diethyl chlorophosphate (0.56 mmol) and TEA (0.72 mmol) in THF according to method A followed by filtration of the mixture into a flask containing MeOH (5 mL). The THF was evaporated and the solution was stirred at 20 °C for 16 h and at 50 °C for 1 h, after which isolation as above afforded 154 mg (85%) of **30**, mp 198–200 °C.

11β,17α-Dihydroxy-9α-fluoro-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-methoxy)methylene Ketal (31). Following activation of acid **13** (168 mg, 0.40 mmol) with diethyl chlorophosphate (81 μL, 0.56 mmol) and TEA (100 μL, 0.72 mmol) and exchange of the THF solvent for MeOH as described above, the formation of **31** was complete in 16 h at 20 °C. The ketal isomers (R_f's 0.37) were not separable by TLC (40% EtOAc–hexane). Recovery and recrystallization of the product as described for **30** afforded 132 mg (76%) of **31**: mp 223–225 °C dec; UV 238 nm (ε 15400); IR (KBr) 1790, (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.20, 1.22 (2 d, 3 H, J's = 7.5 Hz, 16-CH_3's), 1.27, 1.31 (2 s, 3 H, 18-CH_3's), 1.57 (s, 3 H, 19-CH_3), 1.65, 1.66 (2 s, 3 H, 1′-CH_3's), 3.31, 3.32 (2 s, 3 H, OCH_3's); MS, m/e 435 (MH^+). Anal. Calcd for $C_{24}H_{31}O_6F$: C, 66.34; H, 7.19. Found: C, 66.42; H, 7.34.

Reactions of Acids 6–9, 11, and 13 with FMPT: Method D. Preparations were carried out in CH_2Cl_2 containing TEA as described in method C, except that thiolate was not added. Reactions were worked up after 30 min to 2 h at −15 °C.

6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-fluoro)-(*S*)-methylene Ketal (32) and Isomeric (*R*)-Methyl Ketal (33). The treatment of **11** (219 mg, 0.50 mmol) with FMPT at −15 °C (method D) resulted in conversion to two less polar products (R_f's 0.40, 0.57, 1% HOAc–35% EtOAc–hexane). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with dilute Na_2CO_3 and water, dried (Na_2SO_4), and evaporated to dryness, after which centrifugal TLC (45% EtOAc–hexane) and recrystallizations from acetone–hexane afforded 74 mg of ketal **32** (34%) and 66 mg of less polar isomer **33** (30%). The 13-Hz coupling of the 1′-methyl group in the ^1H NMR spectrum of each compound was consistent with the presence of a vicinal fluorine, and the additional 2-Hz coupling of the 16-CH_3 by a proximal fluorine was the basis for assignment of "*S*" stereochemistry to ketal **32**.[28] The data for **32** were as follows: mp 213–214 °C dec; UV 237 nm (ε 15770); IR (KBr) 1810 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.03 (dd, 3 H, J_1 = 7 Hz, J_2 = 2 Hz, 16-CH_3), 1.30 (s, 3 H, 18-CH_3), 1.52 (s, 3 H, 19-CH_3), 1.82 (d, 3 H, J = 13, 1′-CH_3); MS, m/e 440 (M^+). Anal. Calcd for $C_{23}H_{27}O_5F_3$: C, 62.72; H, 6.18. Found: C, 62.67; H, 6.19. The data for **33** were as follows: mp 210–211 °C dec; UV 236 nm (ε 15570); IR (KBr) 1805 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.95 (d, 3 H, J = 7 Hz, 16-CH_3), 1.31 (s, 3 H, 18-CH_3), 1.52 (s, 3 H, 19-CH_3), 1.90 (d, 3 H, J = 13, 1′-CH_3); MS, m/e 440 (M^+). Anal. Calcd for $C_{23}H_{27}O_5F_3$: C, 62.72; H, 6.18. Found: C, 62.53; H, 5.94. Attempts to convert fluoroketals **32** and **33** in a freshly prepared reaction mixture into thiol ester **19** failed. No reaction was observed following the addition of an excess of methanethiol in methylene chloride containing TEA, followed by addition of a 4-fold excess of 0.83 N $NaSCH_3$/DMF and warming at a reflux, followed by exchange of the solvent for toluene and heating at reflux for 16 h.

11β,17α-Dihydroxy-9α-fluoro-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid 17,20-(1′-Methyl-1′-fluoro)-methylene Ketal (34) and Isomeric Ketal (35). Treatment of **13** (210 mg, 0.50 mmol) with FMPT (method D) gave a 5:1 mixture of two neutral products (R_f's 0.42, 0.49, 40% EtOAc–hexane, developed twice). Workup and two recrystallizations of the crude product from acetone–hexane afforded 85 mg (40%) of less polar fluoroketal **34**, mp 185–186 °C dec; UV 238 nm (ε 15700); IR ($CHCl_3$) 1810 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, 3 H, J = 7.5 Hz, 16-CH_3), 1.26 (s, 3 H, 18-CH_3), 1.56 (s, 3 H, 19-CH_3), 1.80 (d, 3 H, J = 13 Hz, 1′-CH_3); MS, m/e 402 (M^+ − HF). Anal. Calcd for $C_{23}H_{28}O_5F_2$: C, 65.39; H, 6.68. Found: C, 65.53; H, 6.69. The mother liquor materials were recovered and purified by centrifugal TLC (0.2% TEA–40% EtOAc–hexane), and the separated products were recrystallized from acetone–hexane, which gave an additional 35 mg (17%) of pure **34** and 21 mg (10%) of more polar fluoro ketal **35**, mp 193–194 °C dec; UV 238 nm (ε 15300); IR ($CHCl_3$) 1810 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3 H, J = 7.5 Hz, 16-CH_3), 1.30 (s, 3 H, 18-CH_3), 1.56 (s, 3 H, 19-CH_3), 1.78 (d, 3 H, J = 13 Hz, 1′-CH_3); MS, m/e 402 (M^+ − HF). Anal. Calcd for $C_{23}H_{28}O_5F_2$: C, 65.39; H, 6.68. Found: C, 65.47; H, 6.40. Ketals **34** and **35** appeared more labile on silica gel than the 16α-methyl analogues, which necessitated the inclusion of TEA in the chromatographic eluent.

9α,11β-Dichloro-6α-fluoro-16-methyl-3-oxoandrosta-1,4,16-triene-17-carboxylic Acid (36). The preparation of thiol ester **47** from acid **9** (180 mg, 0.42 mmol) was attempted by method C. However, the major less polar product of reaction with FMPT (R_f 0.38, 1% HOAc–25% EtOAc–hexane, developed twice) remained unchanged after addition $NaSCH_3$/DMF (1.41 mmol) and warming to 20 °C, and workup then afforded 58 mg (34%) of Δ^{16}-acid **36** and a variety of minor neutral materials which were not further investigated. Analytical sample from acetone–hexane: mp 252–254 °C dec; UV 234 nm (ε 21040); IR (KBr) 1660 (br, COOH, 3-C=O) cm^{-1}; ^1H NMR (90 MHz, Me_2SO) δ 1.27 (s, 3 H, 18-CH_3), 1.74 (s, 3 H, 19-CH_3), 2.04 (s, 3 H, 16-CH_3), 4.98 (br m, 1 H, 11-H); MS, m/e 412, 414 (M^+). Anal. Calcd for $C_{21}H_{23}O_3Cl_2F$: C, 61.03; H, 5.61. Found: C, 61.12; H, 5.54.

6α,9α-Difluoro-11β,17α-dihydroxy-17β-[(methylthio)-carbonyl]-16α-methylandrosta-1,4-dien-3-one (37). The reaction of **6** (198 mg, 0.05 mmol) with FMPT and $NaSCH_3$ (method C) gave a mixture of three neutral products and 14 mg (7%) of returned **6**. Separation of the neutral components by centrifugal TLC (6% acetone–CH_2Cl_2) afforded 63 mg (30%) of **37** (R_f 0.25), along with 31 mg (18%) of triene **38** (R_f 0.40) and 22 mg (12%) of lactone **39** (R_f 0.15) (vide infra). Analytical sample of **37** from acetone–hexane: mp 275–277 °C dec; UV 239 nm (ε 19550); IR

(KBr) 1680 (20-C=O), 1665 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.83 (d, 3 H, J = 7 Hz, 16-CH_3), 0.92 (s, 3 H, 18-CH_3), 1.49 (s, 3 H, 19-CH_3), 2.17 (s, 3 H, SCH_3); MS, m/e 426 (M^+). Anal. Calcd for $C_{22}H_{28}O_4F_2S$: C, 61.95; H, 6.62. Found: C, 61.98; H, 6.74.

6α,9α-Difluoro-16α,17-dimethyl-11β-hydroxy-18-norandrosta-1,4,13(17)-trien-3-one (38) and 6α,9α-Difluoro-11β,13α-dihydroxy-16α,17β-dimethyl-3-oxo-18-norandrosta-1,4-diene-17α-carboxylic Acid 13-Lactone (39). The reaction of **6** (158 mg, 0.40 mmol) with FMPT according to method D followed by workup, preparative TLC, and recrystallizations from acetone–hexane gave 22 mg (16%) of **38** and 17 mg (11%) of **34** along with 11 mg (7%) of recovered **6** as the only isolable products. The data for **38** were as follows: mp 215–217 °C; UV 234 nm (ε 15 700); IR (KBr) 1670 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.92 (d, 3 H, J = 7 Hz, 16-CH_3), 1.39 (s, 3 H, 17-CH_3), 1.53 (s, 3 H, 19-CH_3); MS, m/e 334 (M^+). Anal. Calcd for $C_{20}H_{24}O_2F_2$: C, 71.83; H, 7.23. Found: C, 71.70; H, 7.05. The data for **39** were as follows: mp 154–156 °C dec; UV 236 nm (ε 15 800); IR ($CHCl_3$) 1815 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, trace CD_3OD) δ 1.14 (d, 3 H, J = 7.5 Hz, 16-CH_3), 1.36 (s, 3 H, 17-CH_3), 1.43 (s, 3 H, 19-CH_3); ^{13}C NMR ($CDCl_3$, trace CD_3OD) δ 13.15, 13.19 (16-CH_3, 17-CH_3), 23.73 (19-CH_3), 40.28 (C-16), 45.35 (C-14), 66.24 (C-17), 66.76 (d, J_{CF} = 0.40 Hz, C-11), 86.45 (d, J_{CF} = 2.45 Hz, C-6), 90.57 (C-13), 97.54 (d, J_{CF} = 2.39 Hz, C-9), 173.61 (17-C=O), 185.73 (C-3); MS, m/e 378 (M^+); HRMS, m/e calcd for $C_{21}H_{24}O_4F_2$ 378.1643, found 378.1640. A satisfactory elemental analysis could not be obtained. A sample of **39** which had been dried in vacuo at 100 °C for 16 h was completely transformed into the triene **38** (presumably by loss of CO_2), as confirmed by TLC, loss of the 1815 cm^{-1} absorption in the infrared, and the ^1H NMR spectrum. Samples of **39** were subsequently dried at ambient temperature and proved to be reasonably stable when stored at −20 °C for up to 2 months, after which significant degradation to **38** was observed.

16β,17-Dimethyl-9α-fluoro-11β-hydroxy-18-norandrosta-1,4,13(17)-trien-3-one (40) and 11β,13α-Dihydroxy-16β,17β-dimethyl-9α-fluoro-3-oxo-18-norandrosta-1,4-diene-17α-carboxylic Acid 13-Lactone (41). Reaction of **7** (151 mg, 0.40 mmol) with FMPT (method D) gave 107 mg of a neutral product which proved to be a mixture of triene **40** (R_f 0.44) and the lactone **41** (R_f 0.24) by TLC (7% acetone–CH_2Cl_2). Recrystallization from acetone–hexane gave 30 mg (24%) of pure **40**, and centrifugal TLC of the mother liquor materials (same system) followed by recrystallizations from acetone–hexane gave a further 31 mg (24%) of **40** and 12 mg (8%) of **41**. Products and yields were not altered by addition of $NaSCH_3$ to the reaction mixture in a separate experiment. Data for **40** were as follows: mp 256–258 °C; UV 236 nm (ε 20 070); IR (KBr) 1660 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 1.00 (d, 3 H, J = 7 Hz, 16-CH_3), 1.39 (s, 3 H, 17-CH_3), 1.51 (s, 3 H, 19-CH_3); MS, m/e 316 (M^+). Anal. Calcd for $C_{20}H_{25}O_2F$: C, 75.92; H, 7.96. Found: C, 75.77; H, 7.92. Lactone **41** was reasonably stable in solution, but dry samples were more labile than the 16α-methyl analogue **39** and rapidaly degraded to triene **40** on storage. The ^{13}C NMR resonances for the 16- and 17-methyls of **41** were shifted related to those of lactone **39**, and were consistent with the assigned cis-dimethyl system. Data for **41** were as follows: mp 258–260 °C dec (from CH_2Cl_2–hexane); UV 237 nm (ε 15 200); IR ($CHCl_3$) 1815 (20-C=O) 1670 cm^{-1} (3-C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, 3 H, J = 7.5 Hz, 16-CH_3), 1.34 (s, 3 H, 17-CH_3), 1.45 (s, 3 H, 19-CH_3); ^{13}C NMR ($CDCl_3$) δ 11.89, 17.97 (16-CH_3, 17-CH_3), 23.63 (19-CH_3), 28.95 (C-6), 37.89 (C-16), 45.79 (C-14), 65.82 (C-17), 67.97 (d, J_{CF} = 0.42 Hz, C-11), 91.55 (C-13), 98.19 (d, J_{CF} = 2.38 Hz, C-9), 175.59 (17-C=O), 185.99 (C-3); MS, m/e 340 (M^+ − HF); HRMS, m/e calcd for $C_{21}H_{24}O_4$ (M^+ − HF) 340.1675, found 340.1699, calcd for $C_{20}H_{25}O_2F$ (M^+ − CO_2) 316.1839, found 316.1826.

6α-Fluoro-16-methyl-3-oxoandrosta-1,4,9(11),16-tetraene-17-carboxylic Acid (42) and 6α-Fluoro-17-[(methylthio)-carbonyl]-16-methylandrosta-1,4,9(11),16-tetraen-3-one (43). Reaction of **8** (170 mg, 0.47 mmol) with FMPT and $NaSCH_3$ (0.83 mmol) (method C) gave 77 mg of acidic material and 104 mg of neutral residue as an oil. Two crystallizations of the acid fraction from EtOAc–hexane gave 50 mg (30%) of **42**, mp 270–271 °C dec; UV 235 nm (ε 21 000); IR (KBr) 1715 (COOH), 1670 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.84 (s, 3 H, 18-CH_3), 1.36 (s, 3 H, 19-CH_3), 2.01 (s, 3 H, 16-CH_3), 5.57 (br d, 1 H, J = 4 Hz, 11-H); ^{13}C NMR ($CDCl_3$) δ 15.47 (18-CH_3), 17.48 (16-CH_3), 26.88 (19-CH_3), 38.27 (C-15), 40.12 (C-12), 40.35 (C-7), 45.85 (C-13), 50.93 (C-14), 87.31 (d, J_{CF} = 2.44 Hz, C-6), 119.66 (C-4), 122.74 (C-11), 127.75 (C-2), 135.67 (C-17), 141.23 (C-9), 158.79 (C-16), 161.89 (C-5), 170.19 (17-C=O), 185.39 (C-3); MS, m/e 342 (M^+). Anal. Calcd for $C_{21}H_{23}O_3F$: C, 73.66; H, 6.77. Found: C, 73.54; H, 6.67. A difficult purification of the neutral residue by preparative TLC (15% acetone–hexane, developed five times) and recrystallzation of the very soluble major component from pentane gave 26 mg (15%) of thiol ester **43**, mp 259–262 °C; UV 240 nm (ε 18 005); IR (KBr) 1700–1665 cm^{-1} (br, 20-C=O, 3-C=O); ^1H NMR (100 MHz, Me_2SO) δ 0.94 (s, 3 H, 18-CH_3), 1.37 (s, 3 H, 19-CH_3), 2.04 (s, 3 H, 16-CH_3), 2.25 (s, 3 H, SCH_3), 5.57 (br d, 1 H, J = 6, 11-H); MS, m/e 372 (M^+). Anal. Calcd for $C_{22}H_{25}O_2FS$: C, 70.94; H, 6.76. Found: C, 70.98; H, 6.50.

6α-Fluoro-16-methyl-3-oxoandrosta-1,4,9(11),16-tetraene-17-carbonyl Fluoride (44). The reaction of **8** (190 mg, 0.50 mmol) with FMPT alone (method D) gave 48 mg (28%) of acid **42** and 35 mg of a neutral fraction containing a single major product (R_f 0.58, 4% acetone–CH_2Cl_2). Centrifugal TLC (same system) of the labile neutral product and recrystallization from acetone–hexane gave 11 mg (8%) of **44**, mp 243–244 °C dec; UV 237 nm (ε 23 400); IR ($CHCl_3$) 1790 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3 H, 18-CH_3), 1.42 (s, 3 H, 19-CH_3), 2.19 (s, 3 H, 16-CH_3), 5.64 (d, 1 H, J = 6.6 Hz, 11-H); MS, m/e 344 (M^+); HRMS, m/e calcd for $C_{21}H_{22}O_2F_2$ 344.1588, found 344.1577. Anal. Calcd for $C_{21}H_{22}O_2F_2$: C, 73.24; H, 6.44. Found: C, 73.12; H, 6.50.

6α,9α-Difluoro-11β,17α-dihydroxy-17β-[(ethylthio)-carbonyl]-16α-methylandrosta-1,4-dien-3-one (45). To a solution of **6** (105 mg, 0.27 mmol) in DMF (7 mL) at −10 °C was added CDI (80 mg, 0.49 mmol) in DMF (3 mL) and the mixture was stored at −5 °C for 16 h, after which conversion to a slightly less polar material was complete (TLC, 0.25% HOAc–40% acetone–hexane). Ethyl mercaptan (0.2 mL, 2.7 mmol) was added, and the mixture was stirred at 20 °C for 16 h. The solution was evaporated to dryness, and the residue was purified by preparative TLC (10% acetone–benzene) to give 47 mg (40%) of **45**. Analytical sample, recrystallized 4 times from acetone–hexane: mp 253–256 °C dec; UV 238 nm (ε 19 730); IR (KBr) 1665 cm^{-1} (br, 20-C=O, 3-C=O); ^1H NMR (100 MHz, Me_2SO) δ 0.81 (d, 3 H, J = 7 Hz, 16-CH_3), 0.90 (s, 3 H, 18-CH_3), 1.14 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.46 (s, 3 H, 19-CH_3), 2.72 (q, 2 H, J = 7 Hz, SCH_2); MS, m/e 440 (M^+). Anal. Calcd for $C_{23}H_{30}O_4F_2S$: C, 62.71; H, 6.86. Found: C, 62.49; H, 7.08.

11β,17α-Dihydroxy-9α-fluoro-17β-[(methylthio)-carbonyl]-16β-methylandrosta-1,4-dien-3-one (46). An ice-cooled solution of **7** (100 mg, 0.26 mmol) and CDI (80 mg, 0.49 mmol) in DMF (8 mL) was stirred for 2 h, after which a gentle stream of CH_3SH gas was introduced below the surface of the mixture for 1 h. The mixture was purged with nitrogen and evaporated to dryness, and the product was purified by centrifugal TLC (3% MeOH–CH_2Cl_2) and recrystallization from acetone–hexane to give 66 mg (61%) of pure **46**, mp 242–244 °C dec; UV 239 nm (ε 19 400); IR (KBr) 1690 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (100 MHz, Me_2SO) δ 0.95 (s, 3 H, 18-CH_3), 1.02 (d, 3 H, J = 7 Hz, 16-CH_3), 1.47 (s, 3 H, 19-CH_3), 2.04 (s, 3 H, SCH_3); MS, m/e 388 (M^+ − HF). Anal. Calcd for $C_{22}H_{29}O_4FS$: C, 64.68; H, 7.16. Found: C, 64.69; H, 7.20.

9α,11β-Dichloro-6α-fluoro-17α-hydroxy-17β-[(methylthio)carbonyl]-16β-methylandrosta-1,4-dien-3-one (47). Reaction of **9** (200 mg, 0.46 mmol) with CDI and CH_3SH as described for the preparation of **46** and recrystallization of the product from acetone–hexane gave 180 mg (84%) of **47**, mp 232–233 °C dec; UV 237 nm (ε 19 850); IR (KBr) 1675 cm^{-1} (20-C=O, 3-C=O); ^1H NMR (90 MHz, Me_2SO) δ 1.03 (s, 3 H, 18-CH_3), 1.07 (d, 3 H, J = 7 Hz, 16-CH_3), 1.70 (s, 3 H, 19-CH_3), 2.10 (s, 3 H, SCH_3), 4.99 (br d, 1 H, J = 4 Hz, 11-H); MS, m/e 461–465 (MH^+). Anal. Calcd for $C_{22}H_{27}O_3Cl_2FS$: C, 57.27; H, 5.90; Cl, 15.37. Found: C, 57.34; H, 5.93; Cl, 15.33.

17α-Acetoxy-9α,11β-dichloro-6α-fluoro-17β-[(methylthio)carbonyl]-16β-methylandrosta-1,4-dien-3-one (48). A solution of **47** (110 mg, 0.24 mmol) and DMAP (15 mg, 0.12 mmol) in TEA (2 mL) and acetic anhydride (2 mL) was heated at 80 °C

for 1.5 h and then stirred at 20 °C for 16 h. The mixture was diluted with EtOAc, washed with water, and evaporated to dryness. The product was purified by preparative TLC (20% acetone–hexane, eluted 4 times) and crystallization from acetone–hexane, giving 57 mg (47%) of **48**, mp 250–251 °C dec; UV 235 nm (ε 19345); IR (KBr) 1750 (ester), 1700 (20-C=O), 1675 (3-C=O) cm^{-1}; ^1H NMR (90 MHz, Me_2SO) δ 0.95 (s, 3 H, 18-CH_3), 1.34 (d, 3 H, J = 7 Hz, 16-CH_3), 1.71 (s, 3 H, 19-CH_3), 2.05 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, SCH_3), 5.09 (br d, 1 H, J = 4 Hz, 11-H); MS, m/e 503–507 (MH^+). Anal. Calcd for $C_{24}H_{29}O_4Cl_2FS$: C, 57.26; H, 5.81. Found: C, 57.19; H, 5.85.

9α,11β-Dichloro-6α-fluoro-17β-[(methylthio)carbonyl]-17α-(propionyloxy)-16β-methylandrosta-1,4-dien-3-one (49). Freshly distilled propionic anhydride (0.3 mL, 2.34 mmol) was added to a solution of **47** (140 mg, 0.30 mmol) and DMAP (50 mg, 0.41 mmol) in TEA (3 mL), and the mixture was heated at 70 °C for 16 h. Purification of the product by centrifugal TLC (0.5% acetone–CH_2Cl_2) followed by crystallizations from MeOH and EtOAc–hexane gave 55 mg (35%) of **49**, mp 244–246 °C dec; UV 237 nm (ε 18995); IR (KBr) 1745 (ester), 1705 (20-C=O), 1670 (3-C=O) cm^{-1}; ^1H NMR (300 MHz, Me_2SO) δ 0.95 (s, 3 H, 18-CH_3), 1.05 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.33 (d, 3 H, J = 7 Hz, 16-CH_3), 1.71 (s, 3 H, 19-CH_3), 2.19 (s, 3 H, SCH_3), 2.33 (q, 2 H, J = 7 Hz, $COCH_2$); MS, m/e 468–472 ($M^+ - HSCH_3$). Anal. Calcd for $C_{25}H_{31}O_4Cl_2FS$: C, 58.03; H, 6.04; Cl, 13.70. Found: C, 57.98; H, 6.04; Cl, 13.68.

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Registry No. **1**, 67-73-2; **2**, 2135-17-3; **3**, 378-44-9; **4**, 101916-22-7; **4** diacetate, 50630-16-5; **5**, 101916-23-8; **5** diacetate, 101916-49-8; **6**, 28416-82-2; **7**, 37926-75-3; **8**, 101916-24-9; **9**, 101916-25-0; **10**, 65751-34-0; **11**, 101916-26-1; **12**, 65429-42-7; **13**, 37927-21-2; **14**, 37927-23-4; **15**, 101916-27-2; **16**, 37927-22-3; **17**, 74131-78-5; **18**, 101916-28-3; **19**, 101916-29-4; **20**, 74131-73-0; **21**, 73205-13-7; **22**, 101916-30-7; **23**, 101916-31-8; **24**, 79578-14-6; **25**, 74156-42-6; **26**, 79578-08-8; **27**, 101932-58-5; **28**, 101916-32-9; **29**, 101916-33-0; **30** (isomer 1), 101916-34-1; **30** (isomer 2), 101916-35-2; **31** (isomer 1), 101916-36-3; **31** (isomer 2), 101916-37-4; **32**, 101932-54-1; **33**, 101916-38-5; **34**, 101916-39-6; **35**, 101916-40-9; **36**, 101916-41-0; **37**, 74131-77-4; **38**, 101916-42-1; **39**, 101916-43-2; **40**, 101916-44-3; **41**, 101932-61-0; **42**, 101932-59-6; **43**, 101916-45-4; **44**, 101916-46-5; **45**, 74131-76-3; **46**, 87116-72-1; **47**, 101916-47-6; **48**, 101932-60-9; **49**, 101916-48-7; $NaSCH_3$, 5188-07-8; $NaSC_2H_5$, 811-51-8; $NaSC_6H_{13}$, 22487-02-1; CH_3SH, 74-93-1; acetyl chloride, 75-36-5; ethyl mercaptan, 75-08-1; propionyl chloride, 79-03-8.

(51) Deceased.

Organometallic Derivatives of Hormonal Steroids: 500-MHz One- and Two-Dimensional NMR Spectra of 17α-Propynylestra-1,3,5(10)-triene-3,17β-diol and Its $Co_2(CO)_6$ and $(C_5H_5)_2Mo_2(CO)_4$ Complexes

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Treatment of estrone with a propynyl Grignard reagent gives exclusively 17α-propynylestra-1,3,5(10)-triene-3,17β-diol. This 17α-alkynyl steroid reacts with $Co_2(CO)_8$ or $(C_5H_5)_2Mo_2(CO)_4$ to yield the cluster complexes $(RC{\equiv}CR')M_2$, where R = methyl, R′ is the steroidal moiety, and M = $Co(CO)_3$ or $(C_5H_5)Mo(CO)_2$. The cobalt complex of mestranol has likewise been prepared. The 500-MHz ^1H NMR spectra of these molecules are reported and are assigned by the two-dimensional COSY technique. The shifts of the 12α- and 14α-protons of the steroid are discussed in terms of the anisotropy in diamagnetic susceptibility of the alkyne linkage. ^{13}C spectra are also reported.

Introduction

The incorporation of organometallic moieties into biologically important molecules is a field of burgeoning importance. Typically, in steroid chemistry, $Fe(CO)_3$ fragments may be used as temporary protecting agents,[1] and allylpalladium[2] or $Cr(CO)_3$ units[3] have been exploited for synthetic purposes. Recently, advances in bioorganometallic chemistry have been directed toward immunology,[4] and we have described the use of steroidal hormones labeled with metal carbonyls to assay receptor sites.[5] This latter concept takes advantage of the strong infrared absorptions of metal carbonyls in the range 2100–1850 cm^{-1}—a window in which proteins do not absorb. Our goal is to monitor the hormone dependence of breast cancer while avoiding the use of radioactivity and its associated inconveniences.

In the particular case of estrogenic hormones, it has been reported that the 7α-, 11β-, and 17α-positions of estradiol (**I**) can tolerate substitution by bulky groups and still ex-

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