Pergamon

Tetrahedron 55 (1999) 3355–3364

TETRAHEDRON

Unusual Hydroxy-γ-sultone Byproducts of Steroid 21-Methanesulfonylation. An efficient Synthesis of Mometasone 17-Furoate (Sch 32088)

Richard W. Draper,* Bin Hu, Andrew T. McPhail,† Mohindar S. Puar, Eugene J. Vater and Lois Weber

Chemical Process Research and Development Department, Schering-Plough Research Institute, Kenilworth, New Jersey, 07033 and †P. M. Gross Chemical Laboratory, Duke University, Durham, North Carolina, 27708.

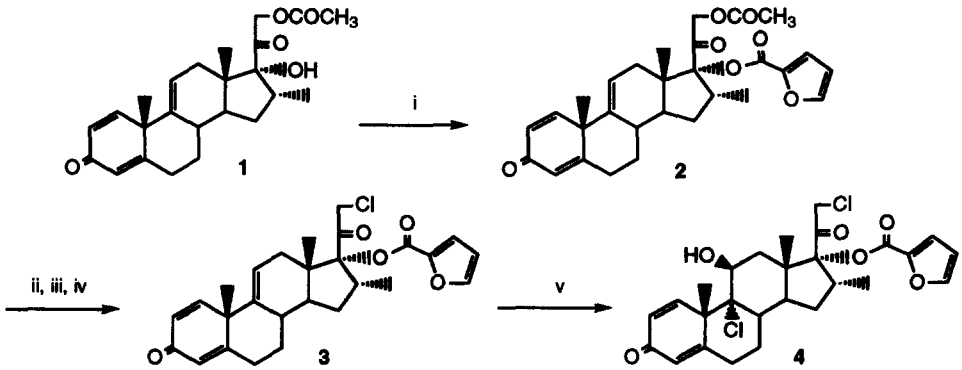
Received 17 June 1998; revised 31 August 1998; accepted 5 September 1998

Abstract: An efficient two stage synthesis of the steroid anti-inflammatory agent mometasone 17-furoate (Sch 32088) **4** from 17α,21-dihydroxy-16α-methyl-9β,11β-oxidopregna-1,4-diene-3,20-dione **6** is described and the structures of unusual δ-hydroxy-γ-sultone byproducts of 4-dimethylamino-pyridine catalyzed methanesulfonylation of 21-hydroxy-20-ketosteroids are deduced.

This paper is dedicated to the memory of Professor D. H. R. Barton whose teaching and creative ideas of steroid conformation theory allowed many who followed to better understand the chemistry of these beautiful molecules.

Introduction

Discovered in our laboratories, mometasone 17-furoate, 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione 17-(2'-furoate),[1] Sch 32088, Elocon,® **4** is a medium potency synthetic corticosteroid anti-inflammatory agent, indicated for the treatment of steroid responsive dermatoses, such as psoriasis[2] and dermatitis.[3] More recently, mometasone 17-furoate monohydrate, Nasonex,® has been approved for the prevention and relief of symptoms of seasonal allergic rhinitis.[4] The drug is characterized by its low potential for systemic activity as measured by its effect on the hypothalamic-pituitary-adrenal axis when applied topically.[5,6]



i furoyl chloride, 4-dimethylaminopyridine, CH_2Cl_2; ii 70% perchloric acid, methanol;
iii methanesulfonyl chloride, pyridine; iv lithium chloride, DMF;
v 1,3-dichloro-5,5-dimethylhydantoin, 70% perchloric acid, THF, water

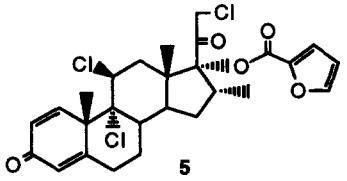
Scheme 1. Original synthesis of mometasone 21-furoate[7]

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01146-6

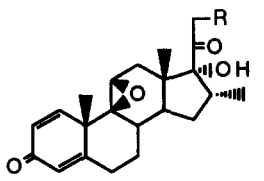
A synthesis of mometasone 17-furoate (Scheme 1) from commercially available intermediate **1** has been described by Shapiro et al.[7,8] Thus the free hydroxyl group of 17α,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione 21-acetate **1** was furoylated, followed by selective hydrolysis of the 21-ester and subsequent mesylation and chlorination to give the side chain functionalized triene **3**. Introduction of the vicinal chlorohydrin system to ring C was accomplished by reaction of the triene with 1,3-dichloro-5,5-dimethylhydantoin (DDH) in the presence of perchloric acid. The authors point out[7] that the formation of **4** is accompanied by a substantial quantity of the corresponding 9α,11β,21 trichloro analog **5** (ratio of **4** : **5** = 7 : 1), a normal byproduct for this method of halohydrin formation.[9] As **5** is an extremely insoluble compound in the usual solvents, crystallization of the crude material is not an effective method of purging this impurity. In this paper, we present the results of our efforts toward developing a more efficient and shorter process for the manufacture of mometasone furoate starting with the alternative commercially available 16α-methyl-9β,11β-epoxide[10] intermediate **6**. We also describe the formation, isolation and structure determination of hitherto unrecognized steroid 17β-(2,2-dioxido-4-hydroxy-1,2-oxathiolan-4-yl) byproducts arising during the methylsulfonylation of 21-hydroxy-20-ketosteroids.

Results and discussion

Scission of the oxide ring in **6** with hydrochloric acid would generate the C-ring 9α,11β-chlorohydrin system and simultaneously circumvent the impurity problem noted above. In addition, this process would utilize a less expensive source of chlorine. We also wished to improve the original 21-mesylation/chlorination procedure (mesyl chloride in pyridine followed by addition of lithium chloride) of the Shapiro synthesis, as material losses occur due to formation of the 21-pyridinium chloride salt **8**.

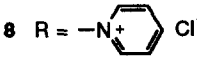


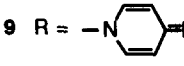
5

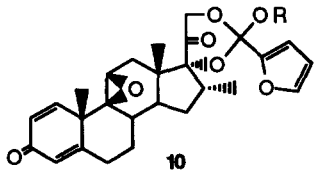


6 R = OH

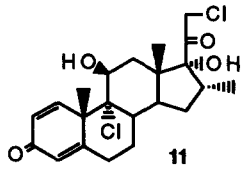
7 R = OSO_2CH_3

8 R =  Cl^-

9 R =  Cl^-



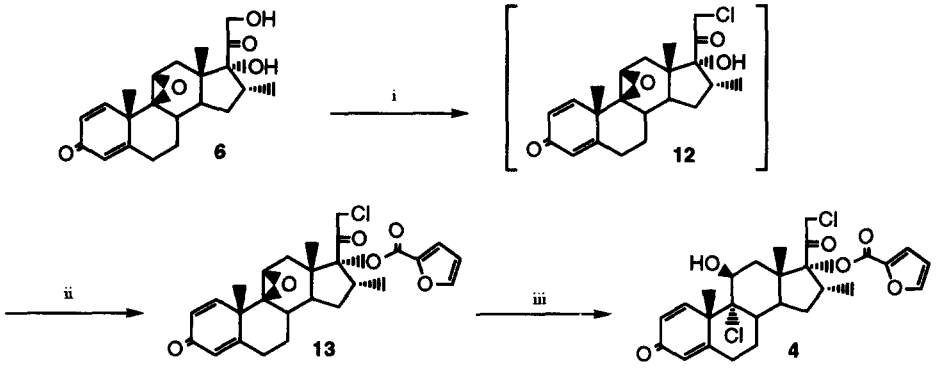
10



11

Several elegant methods for the simultaneous introduction of the 21-chloro-17-ester system into corticosteroids have been described, based on the opening of a 17,21-orthoester with chlorine from trimethylsilylchloride,[11] xanthene-9-carbonyl chloride[12] and triphenylmethylchloride.[13] To benefit from such an approach the synthesis of orthoester **10** is obligatory, which in turn necessitates the manufacture of a trialkylortho-2-furoate reagent.[14] Since these requirements would impose a significant burden to the cost structure, we favored a direct approach, *viz* 21-chlorination followed by 17-furoylation which we felt could be accomplished consecutively and without any isolation of intermediate **12**. Side chain modification must therefore be executed prior to C-ring functionalization as the hindered tertiary 17α-hydroxyl may not be selectively acylated in the presence of the secondary alcohol at the 11β position. Thus the route formulated in Scheme 2 suggests itself and was investigated.

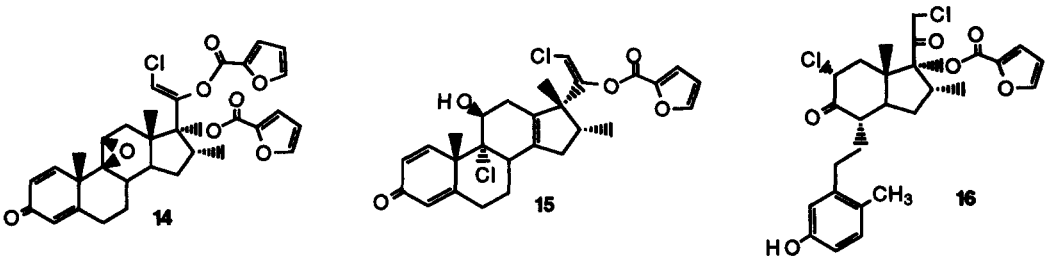
Most direct methods of converting hydroxyl to chloride involve expensive or toxic reagents, unsuitable for large scale manufacture (e.g. CCl_4/Ph_3P,[15] Mitsunobu,[16] etc.). One useful method for performing this transformation of steroid 21-alcohols to 21-chlorides is the Vilsmeier reagent [(chloromethylene)dimethylammonium chloride] in the presence of pyridine.[17] Alcohols in general have also been conveniently transformed into chlorides by means of a p-tosylchloride/4-dimethylaminopyridine (4-DMAP) system.[18] Not wishing to generate and handle the sensitive Vilsmeier salt, we chose to apply the latter method, selecting instead the cheaper and easier to handle reagent, mesyl chloride. In retrospect (*vide infra*) this was a poor decision from an impurity standpoint but nevertheless led to the discovery of some new steroid structures.



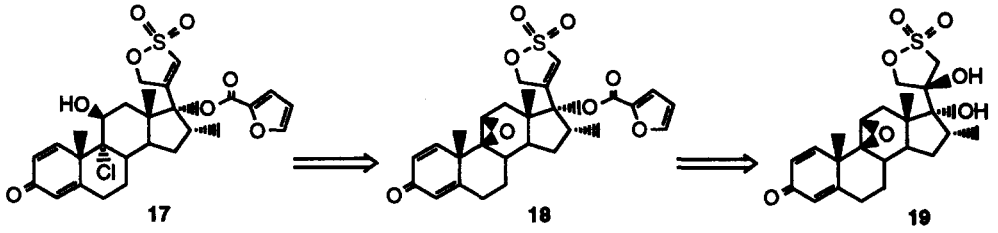
i methane (or p-toluene) sulfonyl chloride, 4-dimethylaminopyridine, CH_2Cl_2;
ii furoyl chloride, triethylamine, 4-dimethylaminopyridine, CH_2Cl_2; iii HCl, HOAc.

Scheme 2. New synthesis of mometasone 21 furoate

Treatment of epoxide **6** in methylene cloride at 0 °C with 4-DMAP (2.0 equivalents) and mesyl chloride (1.8 equivalents) followed by refluxing the suspension for 5 hours afforded completely the 21-chloro-9β,11β-epoxide **12**. About 1% of the 9α,21-dichloro-11β-hydrin **11** resulting from opening of the oxide ring by chloride ion was detected by hplc. The hplc retention time of this compound was identical to that of an authentic sample, prepared by reaction of the 21-chloro-9β,11β-epoxide **12** with hydrochloric acid in acetic acid.[19] Some 21-quaternary 4-dimethylaminopyridinium chloride salt corresponding to **9** was also observed by its characteristic aromatic NMR signals. No other byproduct was immediately detected in this reaction. Removal of base by washing with dilute HCl followed by crystallization from ethyl acetate afforded the chloride **12**. The tertiary hydroxyl group of this intermediate was esterified by contact with 2-furoyl chloride and Et_3N, catalyzed by 4-DMAP in methylene chloride, to give the 17α-(2-furoate) **13**. Furoylation at C_{17} is accompanied by the formation of the enol difuroate **14**,[20] the presence of which inhibits the crystallization of **13**, although this could be achieved after purification by careful chromatography on silica gel. The crude product was therefore converted by reaction with concentrated HCl in HOAc or hydrogen chloride gas in CH_2Cl_2 directly into mometasone 17-furoate **4**, comparable to material produced by Shapiro's route. Under these conditions the enol difuroate **14** is simultaneously hydrolyzed to **4**. To further improve efficiency in the synthesis of the 21-chloro-17-furoate **13**, 2-furoyl chloride and Et_3N could be added directly to the reaction solution of 21-chloride **12**, that is without any work-up or isolation of the latter intermediate.



The synthesis of mometasone furoate **4** through ring opening of epoxide **13** with HCl is accompanied by small amounts of two previously reported byproducts **15**[20] and **16**[21], both of which arise from carbonium ion mediated rearrangements. When this reaction was performed on **13** which had been produced from **6** without any intermediate purification, **4** was contaminated with a new, sulfur containing impurity. High resolution mass spectrometry for this compound gave a molecular formula of $C_{28}H_{31}ClO_8S$. The ^1H NMR spectrum of the new impurity, when compared to that for mometasone furoate, displayed all the expected chemical shifts with the exception of an additional methine proton at δ7.62. The C_{21} methylene signals had shifted downfield from its position centered at δ4.44 in mometasone furoate to δ5.21 in the impurity. In the ^{13}C NMR spectrum an additional carbon atom appeared at δ119.0, whereas the chemical shifts for C_{20} and C_{21} changed from δ197.0 and δ44.9 to δ151.1 and δ73.1, respectively. These spectral features coupled with IR data (for sulfonate ester) are accommodated by the dehydro-γ-sultone structure **17**. The double bond is assigned to the 4,5 rather than the 3,4-position of the sultone ring by the similarity of the chemical shifts for the C_{21} signals of compounds **17**,**18** and **19** (*vide infra*).



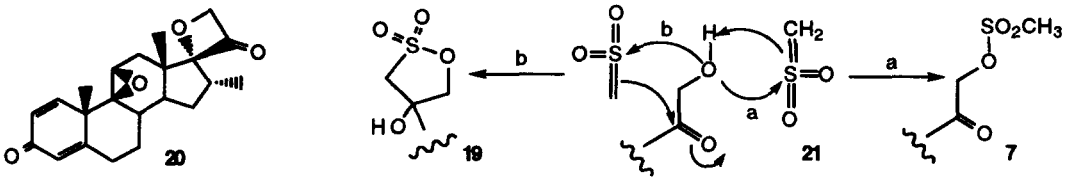
Scheme 3

A retrosynthetic analysis of the dehydro-γ-sultone **17** (Scheme 3) implies the genesis of this material occurs in the mesylation step. Closure of the chlorohydrin would lead to epoxide **18** which in turn could be derived from the δ-hydroxy-γ-sultone **19** by a simultaneous net dehydration in the sultone ring and furoylation at C_{17}. A reaction involving either attack of a 21-mesylate carbanion at C_{20} or a cycloaddition of sulfene would generate **19** in the mesylation step. With this hypothesis in mind, we sought to discover the putative δ-hydroxy-γ-sultone **19** in the crude product obtained from the mesylation of **6**. Careful examination of the mother liquors by tlc and hplc after crystallization of the 21-chloro 9,11-oxide **12** revealed an additional impurity which was isolated by preparative tlc (silica gel, CH_2Cl_2/EtOAc, 3 : 1). This indeed was the sought-after hydroxy-γ-sultone **19**. Support for the structure of **19** was derived from high resolution mass spectrometry which provided an elemental composition of $C_{23}H_{30}O_7S$. In the ^1H NMR spectrum the 20-OH proton (exchangeable with D_2O) appeared at

δ4.61 (1H s) and the C_{21} methylene protons were shifted from δ4.58 in **12** to δ4.41 in **19**. The protons attached to the additional methylene carbon were displayed as an AB quartet centered at δ3.55.

We are not aware of any cases in which simultaneous formation of byproduct hydroxy-γ-sultones occurs during mesylation of steroidal 21-hydroxy-20-ketones. This is not a new reaction however, there being at least two previous reports[22,23] in non steroid systems. There is also a related example[24] of a geminal mesyloxynitrile affording the 4-amino-1,2-oxathia-2,2-dioxide ring system on treatment with a non nucleophilic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The formation of this heterocycle was justified by abstraction of a proton from the mesylate carbon and subsequent attack on the adjacent nitrile group by the carbanion thus formed. Two mechanisms have been proposed to explain the formation of these δ-hydroxy-γ-sultones; namely formation and reaction of a mesylate carbanion on the α-carbonyl[22] or via a 1,3 cycloaddition reaction of the hydroxyketone with sulfene.[23] In this case we prefer the latter alternative, as abstraction of a proton from mesylate **7** should generate the 17-alkoxy anion rather than a mesylate carbanion. In addition, the amount of hydroxy-γ-sultone **19** was set at about 2% (by hplc area) in the first few minutes of reaction, that is during formation of the 21-mesylate **7**, and did not increase as conversion of the latter compound to the 21-chloride progressed. It should be noted in this context that tertiary amine catalyzed mesylations of alcohols and amines with mesyl chloride have been shown[25,26] to proceed through the intermediacy of sulfene.

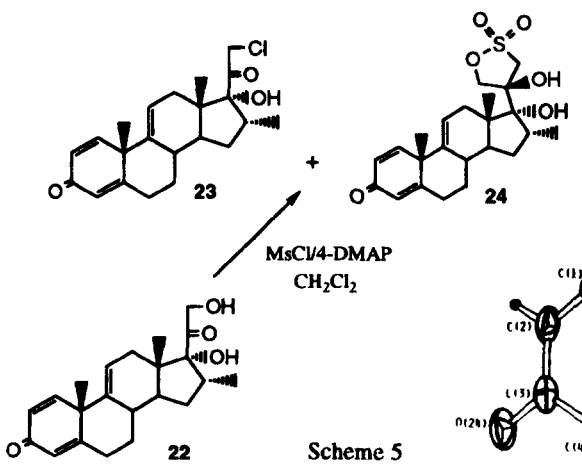
To distinguish between these two modes of reaction, we prepared the 21-mesylate **7** from epoxide **6** by treatment with mesyl chloride and triethylamine in THF for 3 hours at rt. After isolation and purification, the mesylate **7** was subjected to treatment with 4-DMAP. Only conversion to the 21-(4-dimethylaminopyridinium) mesylate salt **9** was observed, suggesting that formation of δ-hydroxy-γ-sultone **19** does not proceed through mesylate **7**. When the 21-mesylate **7** was reacted with DBU in CH_2Cl_2 at rt. only the spirooxacyclobutanone **20** was obtained, arising through an intramolecular substitution by the 17-alkoxide anion at C_{21}. This transformation of corticosteroid 21-mesylates to oxacyclobutanones with various bases is a well known reaction.[27] Sulfene **21** presumably reacts through a four centered transition state in which the hydroxyl proton is transferred to the sulfene carbon to generate the mesylate (major pathway, a in Scheme 4). Alternatively, instead of capturing a proton, the incipient negative charge forming on the sulfene carbon can attack the adjacent carbonyl group giving rise to the observed δ-hydroxy-γ-sultone (minor pathway, b in Scheme 4).



Scheme 4

NMR spectral data did not permit us to assign the absolute configuration at the new chiral center which arises in hydroxy-γ-sultone **19**. Study of a model of epoxide **6** suggests sulfene should approach the C_{20} carbonyl group on the side distal to the C_{18} angular methyl group. This could be either the pro-S or pro-R face depending on the conformation of the ketone. We attempted to forecast this by using the molecular modeling program, Sybyl,® (v. 6.4),[28] operating on a Silicon Graphics Indigo 2® system, to compute the minimum energy conformation of epoxide **6**. Similar energy minima were found for conformations in which the C_{16}-C_{17}-C_{20}-C_{21}

torsion angle was either about 170° or 350°, thus the model was not predictive of whether sulfene would likely approach the *si* or *re* face of the carbonyl group.



Scheme 5

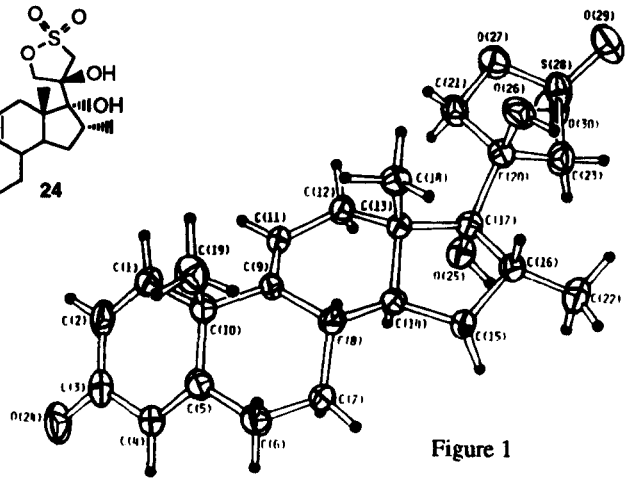


Figure 1

To unequivocally determine the configuration at the new chiral center in compound **19**, we ultimately resorted to X-ray crystallography. Unfortunately, usable crystals of the latter material could not be prepared, therefore the analogous hydroxy-γ-sultone **24** containing a 9,11 double bond was similarly prepared from **22** (Scheme 5). Suitable crystals of this compound were obtained from ethyl acetate and a single crystal X-ray structure elucidation (see experimental) established the absolute configuration at C_{20} as R. An ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom numbering scheme and the solid state conformation of **24** is illustrated in Figure 1.

When hydroxy-γ-sultone **19** was subjected to the usual furoylation conditions, the C_{20}-hydroxyl group was indeed eliminated with concomitant furoylation at C_{17} producing the epoxydehydro-γ-sultone **18**. Evidence of formation of the dehydro-γ-sultone ring came from the ^1H NMR spectrum in which the AB quartet for the methylene protons centered at δ3.55 had been replaced by a new signal for a vinyl proton at δ8.01 in addition to the three aromatic protons of the furan ring. Dehydro-γ-sultone **18**, upon epoxide opening with HCl in acetic acid, gave the corresponding 9α,11β-chlorohydrin dehydro-γ-sultone **17** identical to the impurity isolated from mometasone 17-furoate.

Finally, to produce mometasone 17-furoate free of hydroxy-γ-sultone byproduct **19**, we returned to the preparation of the 21-chloro-17-furoate **13**, using this time the original p-tosyl chloride/4-DMAP system of Wuts.[17] After refluxing for 5 hours, complete conversion to the 21-chloride **13** was observed with less than 0.1% of the 9α,11β-chlorohydrin **11** being formed (measured by HPLC area). The reaction mixture was cooled, triethylamine and furoyl chloride were added as before to afford the 21-chloride-17-furoate **13**. After washing the reaction mixture with dilute HCl and stirring with silica gel to remove base and traces of the chloride salt corresponding to **9**, respectively, the solution of **13** was treated with HCl in acetic acid to give mometasone furoate **4** crystallized from methanol in 72% overall yield from epoxide **6**. Adjusting the pH of the HCl washes to 12 with NaOH, followed by extraction with CH_2Cl_2 allowed a 90% recovery and reuse of the 4-DMAP.

Experimental

All reactions were carried out under nitrogen. Acid work-up comprised washing the organic solvent with 2N HCl and then brine and evaporation of the solvent under vacuum. Thick layer plates refer to Analtech silica gel, 20 cm x 20 cm x 1000μ. Melting points were determined with a Mel-temp melting point apparatus and are uncorrected. Retention times (R_t) refer to HPLC on a Supelcosil® LC-8 column (4.6 mm x 25 cm), mobile phase MeOH/H_2O (67 : 33), flow rate 1.5 mL/min, inj. vol. 10μL, conc ~0.5 mg/mL. IR spectra (cm^{-1}, in nujol unless noted otherwise) were recorded on a Mattson FTIR, model 6021. The ^{13}C-NMR spectra were recorded in DMSO-d_6 using either Varian Associates FT-80, XL-100, or XL-300 spectrometers operating at 20.0, 25.2, and 75.2 MHz respectively and internally locked to the deuterium frequency (15.4 MHz) of the solvent. ^1H-NMR spectra were similarly obtained using a Varian Associates XL-300 instrument. Chemical shifts are in ppm downfield from TMS. Optical rotations were measured at 20 °C as 0.5% solutions in $CHCl_3$ unless otherwise stated.

21-Chloro-17α-hydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione 12.[19] To a suspension of 17α,21-dihydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione **6** (3.725 g, 0.01 mole) and 4-DMAP (2.44 g, 0.02 mole) in CH_2Cl_2 (30 mL) at 0 °C was added dropwise CH_3SO_2Cl (1.4 mL, 0.018 mole). After addition, the mixture was refluxed for 4 hours then subjected to acid work-up affording a solid residue which was crystallized from ethyl acetate to yield **12**, 2.68 g (69%) m.p. 175-176 °C; $[\alpha]_D$ = + 51°; R_t = 6.7 min.; Anal. calcd for $C_{22}H_{27}ClO_4$: C, 67.60%; H, 6.96%; Cl, 9.07%. Found C, 67.67%; H, 6.96%; Cl 9.35%, ^1H NMR: 0.73 (3H, s, C_{13}-CH_3), 0.76 (3H, d, J = 6.5Hz, C_{16}-CH_3), 1.36 (3H, s, C_{10}-CH_3), 2.90 (1H, m, $H_{16\beta}$), 3.20 (1H, bt, $H_{11\alpha}$), 4.40 (1H, d, J = 17Hz, H_{21}), 4.75 (1H, d, J = 17Hz, H_{21}), 5.37 (1H, s, C_{17}-OH), 6.08 (1H, dd, $J_{1\text{-}2}$ = 10.0Hz, $J_{2\text{-}4}$ = 2Hz, H_2), 6.10 (1H, d, J = 2Hz, H_4), 6.62 (1H, d, J = 10Hz, H_1).

9β,11β-Epoxy-17α-hydroxy-17β-(4-(R)-hydroxy-2,2-dioxido-1,2-oxathiolan-4-yl)-16α-methyl-androsta-1,4-dien-3-one 19. The mother liquors from the above experiment were concentrated and chromatographed on thick layer plates (mobile phase, CH_2Cl_2/EtOAc 3 : 1). The most polar band was extracted with EtOAc which on evaporation gave the hydroxy-γ-sultone **19** as an amorphous solid, (51 mg, 1.1%). m.p. 100-115 °C (dec.); $[\alpha]_D$ = +5° (THF); R_t = 3.6 min.; HR-MS: calcd. for $C_{23}H_{31}O_7S$, $(M+H)^+$ 451.1791, found 451.1780; IR 3500, 3350 (OH), 1660, 1630, 1610 (C=O), 1460, 1150 cm^{-1} (OSO_2); ^1H NMR: 0.82 (3H, d, J = 6.5Hz, C_{16}-CH_3), 1.06 (3H, s, C_{13}-CH_3), 1.35 (3H, s, C_{10}-CH_3), 2.66 (1H, m, $H_{16\beta}$), 3.13 (1H, s, $H_{11\alpha}$), 3.35 (1H, d, J = 14Hz, CH_2SO_2), 3.90 (1H, d, J = 14Hz, CH_2SO_2), 4.36 (1H, d, J = 10Hz, H_{21}), 4.49 (1H, d, J = 10Hz, H_{21}), 4.61 (1H, s, C_{20}-OH), 5.87 (1H, bs, C_{17}-OH), 6.07 (1H, dd, $J_{1\text{-}2}$ = 10Hz, $J_{2\text{-}4}$ = 2Hz, H_2), 6.10 (1H, d, J = 2Hz, H_4), 6.61 (1H, d, J = 10Hz, H_1); ^{13}C NMR: δ15.9 C_{22}, 18.2 C_{18}, 23.5 C_{19}, 28.2 C_7, 28.8 C_6, 31.5 C_{15}, 32.2 C_8, 33.1 C_{16}, 34.3 C_{12}, 43.4 C_{10}, 45.9 C_{14}, 48.0 C_{13}, 62.4 C_{11}, 65.6 C_9, 55.9 $C_{CH_2SO_2}$, 76.1 C_{21}, 83.8 $C_{17/20}$, 83.9 $C_{20/17}$, 124.1 C_4, 127.0 C_2, 152.5 C_1, 165.7 C_5, 184.7 C_3.

21-Chloro-17α-hydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) 13. (In one pot from **6**). To a suspension of 17α,21-dihydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione **6** (3.725 g, 0.01 mole) and 4-DMAP (2.44 g, 0.02 mole) in CH_2Cl_2 (30 mL) at 0 °C was added dropwise mesyl chloride (1.4 mL, 0.018 mole). After addition, the mixture was refluxed for 5 hours then cooled to 0 °C. Et_3N (1.5 ml, 0.011 mole) and 2-furoyl chloride (1.2 ml, 0.012 mole) were added and the mixture allowed to agitate at rt for 6 hours. Acid work-up afforded a gum which was chromatographed on a silica gel column. Elution with CH_2Cl_2/EtOAc (9 : 1) gave pure **13** which was crystallized from ether/hexane 3.44 g (71%); m.p. 182-184 °C; $[\alpha]_D$ = -14°; R_t = 8.1 min.; $C_{27}H_{29}ClO_6$ MW 484.97, Calc. C 66.87%, H 6.03%, Cl 7.31%; Found C 66.83%, H 6.01%, Cl 7.39%; ^1H NMR: 0.80 (3H, d, J = 6.5Hz, $C_{(16)}$-CH_3), 0.90 (3H, s, C_{13}-CH_3), 1.38 (3H, s, C_{10}-CH_3), 3.31 (1H, bs, $H_{11\alpha}$), 4.50 (2H, dd, J = 17Hz, center, H_{21}), 6.12 (1H, dd, J = 10, 2Hz, H_2), 6.14 (1H, d, J = 2Hz, H_4), 6.65 (1H, d, J = 10Hz, H_1), 6.73 (1H, dd, J = 1.5, 2Hz, $H_{4'}$), 7.52 (1H, d, J = 2Hz, $H_{3'}$), 8.05 (1H, d, J = 1.5Hz, $H_{5'}$).

9α,21-Dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) 4. To a solution of 21-chloro-17α-hydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) **13** (4.85 g, 0.01 mole) in HOAc (30 mL) at 5 °C was added dropwise conc. HCl (2.6 mL). After addition, the mixture was stirred at rt for 3 hours then poured slowly into $NaHCO_3$ solution (30 mL) with good agitation. The solid was filtered off, washed with H_2O, dried and crystallized from methanol to give to give **4**, 4.33 g (83%) m.p. 226-228 °C; $[\alpha]_D$ = +68°; R_t = 8.95 min.; IR 3390 (OH), 1720 (OC=O), 1650, 1610 cm^{-1} (C=O); $C_{27}H_{30}Cl_2O_6$ MW 521.43, Calc. C 62.19%, H 5.80%, Cl 13.60%; Found C 62.30%, H 5.82%, Cl 13.55%; ^1H NMR: 0.86 (3H, d, J = 6.5Hz, C_{16}-CH_3), 1.02 (3H, s, C_{13}-CH_3), 1.61 (3H, s, C_{10}-CH_3), 3.35 (1H, m, $H_{16\beta}$), 4.41 (1H, bs, $H_{11\alpha}$), 4.44 (1H, d, J = 15Hz, H_{21}), 4.60 (1H, d, J = 15Hz, H_{21}), 5.60 (1H, d, J = 4Hz, C_{11}-OH), 6.01 (1H, d, J = 2Hz, H_4), 6.25 (1H, dd, J = 10, 2Hz, H_2), 6.73 (1H, dd, J = 1.5, 2Hz, $H_{4'}$), 7.23 (1H, d, J = 2Hz, $H_{3'}$), 7.32 (1H, d, J = 10Hz, H_1), 8.04 (1H, d, J = 1.5Hz, $H_{5'}$). ^{13}C NMR: δ16.7 C_{22},

17.6 C_{18}, 24.5 C_{19}, 27.2 C_7, 30.6 C_6, 32.9 C_{15}, 34.5 C_8, 35.7 C_{16}, 36.5 C_{12}, 43.8 C_{14}, 44.9 C_{21}, 48.9 C_{13}, 50.0 C_{10}, 75.1 C_{11}, 82.9 C_9, 97.4 C_{17}, 112.3 $C_{3'}$, 119.7 $C_{4'}$, 125.1 C_4, 129.6 C_2, 142.9 $C_{2'}$, 147.8 $C_{5'}$, 152.0 C_1, 158.2 C_{OCO}, 165.8 C_5, 186.6 C_3, 196.9 C_{20}.

9α,21-Dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 11. To a solution of 21-chloro-17α-hydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione **12** (3.91 g, 0.01 mole) in HOAc (30 mL) at 5 °C was added dropwise with agitation conc. HCl (2.6 ml). After three hours at rt the solution was poured slowly into $NaHCO_3$ solution (30 mL) with good agitation. The solid was filtered off, washed with H_2O, dried and crystallized from ethyl acetate to give **11**, 3.55 g (83%), m.p. 245-245 °C (dec.); $[\alpha]_D$ = +127° (THF); R_t = 2.4 min.; IR 3500 (OH), 1720, 1660, 1600 cm^{-1} (C=O); $C_{22}H_{28}Cl_2O_4$ MW 427.37, Calc. C 61.83%, H 6.60%, Cl 16.59%; Found C 61.85%, H 6.88%, Cl 16.19%; ^1H NMR: 0.81 (3H, d, J = 6.5Hz, C_{16}-CH_3), 0.89 (3H, s, C_{13}-CH_3), 1.60 (3H, s, C_{10}-CH_3), 2.96 (1H, m, $H_{16\beta}$), 4.37 (1H, ddd, J = 1, 2, 4Hz, $H_{11\alpha}$), 4.40 (1H, d, J = 17Hz, H_{21}), 4.76 (1H, d, J = 17Hz, H_{21}), 5.32 (1H, s, C_{17}-OH), 5.48 (1H, d, J = 4Hz, C_{11}-OH), 5.99 (1H, d, J = 2Hz, H_4), 6.22 (1H, dd, J = 10, 2Hz, H_2), 7.30 (1H, d, J = 10Hz, H_1).

17α,21-Dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-methanesulfonate 7. To a stirred suspension of 17α,21-dihydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione **6** (2.96 g, 8 mmole) and Et_3N (2.24 mL, 16 mmole) in THF (40 mL) at 0 °C was added dropwise mesyl chloride (1.24 mL, 16 mmole). After addition was complete, the mixture was agitated for 4 hours at rt then diluted with H_2O and extracted with EtOAc. The extracts were washed with H_2O then evaporated to give a gum which was chromatographed on silica gel eluting with a CH_2Cl_2/EtOAc gradient, affording the title compound **7** as a glass, 3.02 g, (84%), m.p. 93-96 °C (dec.); $[\alpha]_D$ = +65°; R_t = 4.9 min.; IR 3440 (OH), 1720, 1650,1600 (C=O), 1460, 1170 cm^{-1} (OSO_2); HR-MS: calcd. for $C_{23}H_{31}O_7S$, $(M+H)^+$ 451.1791, found 451.1794; ^1H NMR: 0.78 (3H, d, J = 6.5Hz, C_{16}-CH_3), 0.78 (3H, s, C_{13}-CH_3), 1.36 (3H, s, C_{10}-CH_3), 2.86 (1H, m, $H_{16\beta}$), 3.20 (1H, bs, $H_{11\alpha}$), 3.25 (3H, s, CH_3S), 4.90 (1H, d, J = 18Hz, H_{21}), 5.24 (1H, d, J = 18Hz, H_{21}), 5.32 (1H, s, C_{17}-OH), 6.09 (1H, dd, J = 10, 2Hz, H_2), 6.10 (1H, d, J = 2Hz, H_4), 6.63 (1H, d, J = 10Hz, H_1).

17α,21-Dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-(4-dimethylaminopyridinium methanesulfonate) 9. To a stirred solution of 17α,21-dihydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione 21 methanesulfonate **7** (90 mg, 0.2 mmole) in CH_2Cl_2 (2 mL) at rt was added 4-DMAP (49 mg, 0.4 mmole). The mixture was refluxed for 3 hours, cooled and subjected to acid work-up affording **9** as a solid residue. 104 mg (91%). ^1H NMR: 0.78 (3H, s, C_{13}-CH_3), 0.80 (3H, d, J = 6.5Hz, C_{16}-CH_3), 1.37 (3H, s, C_{10}-CH_3), 2.79 (1H, m, $H_{16\beta}$), 3.20 (3H, s, CH_3S), 3.23 (1H, bs, $H_{11\alpha}$), 3.47 (2H, m, H_{21}), 5.68 (1H, s, C_{17}-OH), 5.74 (6H, s, NCH_3), 6.10 (1H, dd, J = 10, 2Hz, H_2), 6.10 (1H, d, J = 2Hz, H_4), 6.63 (1H, d, J = 10Hz, H_1), 7.03 (2H, d, J = 7Hz, $H_{3',5'}$), 8.09 (2H, d, J = 7Hz, $H_{2',6'}$).

9β,11β-epoxy-16α-methyl-17α,21-oxidopregna-1,4-diene-3,20-dione 20. To a solution of 17α,21-dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-methanesulfonate **7** (1.13 g, 2.5 mmole) in CH_2Cl_2 (25 mL) was added DBU (0.75 mL, 5 mmole) and the mixture refluxed for 2 hours. Acid work-up gave a gum which was chromatographed on silica gel eluting with a CH_2Cl_2/EtOAc gradient. Combination of the like fractions and evaporation of the solvent gave compound **20** (710 mg, 80%), crystallized from EtOAc, m.p. 191-192 °C; $[\alpha]_D$ = +80°; IR, 1810, 1660, 1630, 1610 cm^{-1} (C=O); HR-MS: calcd. for $C_{22}H_{27}O_4$, $(M+H)^+$ 355.1909, found 355.1919; ^1H NMR: 0.96 (3H, s, C_{13}-CH_3), 0.97 (3H, d, J = 4Hz, C_{16}-CH_3), 1.33 (3H, s, C_{10}-CH_3), 3.24 (1H, s, $H_{11\alpha}$), 4.95 (1H, d, J = 11Hz, H_{21}), 4.98 (1H, d, J = 11Hz, H_{21}), 6.07 (1H, d, J = 2Hz, H_4), 6.09 (1H, dd, J = 10, 2Hz, H_2), 6.62 (1H, d, J = 10Hz, H_1),

21-Chloro-17α-hydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione 23.[17] To a suspension of 17α,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione **22** (3.565 g, 0.01 mole) and 4-DMAP (2.44 g, 0.02 mole) in CH_2Cl_2 (30 mL) at 0 °C was added dropwise mesyl chloride (1.4 mL, 0.018 mole). After addition, the mixture was refluxed for 4 hours then subjected to acid work-up affording a solid residue which was crystallized from ethyl acetate to yield **23**, 2.58 g (69%), m.p. 209-210 °C; HR-MS: calcd. for $C_{22}H_{28}ClO_3$, $(M+H)^+$ 375.1717, found 375.1727.

17α-hydroxy-17β-(4-(R)-hydroxy-2,2-dioxido-1,2-oxathiolan-4-yl)-16α-methylandrosta-1,4,9(11)-triene-3-one 24. The mother liquors from the above experiment were concentrated and chromatographed on thick layer plates (mobile phase, CH_2Cl_2/EtOAc 4 : 1). The most polar band was extracted with EtOAc which on evaporation gave the hydroxy-γ-sultone **24**, (55 mg, 1.1%) crystallized from ethyl acetate. m.p. 130-140 °C (dec.); $[\alpha]_D$ = -32° (THF); HR-MS: calcd. for $C_{23}H_{31}O_6S$, (M+H)+ 435.1841, found 435.1840; IR 3500, 3350 (OH), 1670, 1620, 1610 (C=O), 1460, 1150 cm^{-1} (OSO_2); ^1H NMR: 0.86 (3H, d, J = 6.5Hz, C_{16}-

CH_3), 0.87 (3H, s, C_{13}-CH_3), 1.36 (3H, s, C_{10}-CH_3), 3.36 (1H, d, J = 14Hz, CH_2SO_2), 3.3.80 (1H, d, J = 14Hz, CH_2SO_2), 4.42 (2H, dd, center, J = 10Hz, H_{21}), 4.61 (1H, s, C_{20}-OH), 5.45 (1H, dd, J = 6Hz, H_{11}), 5.94 (1H, s, C_{17}-OH), 5.96 (1H, d, J = 2Hz, H_4), 6.16 (1H, dd, J_{1-2} = 10Hz, J_{2-4} = 2Hz, H_2), 7.38 (1H, d, J = 10Hz, H_1); ^{13}C NMR: δ15.4 C_{22}, 15.8 C_{18}, 26.4 C_{19}, 33.2 C_{16}, 35.5 C_8, 45.5 C_{10}, 47.6 C_{13}, 47.7 C_{14}, 55.8 $C_{CH_2SO_2}$, 76.1 C_{21}, 83.8 $C_{17/20}$, 83.9 $C_{20/17}$, 120.6 C_{11}, 122.8 C_4, 126.3 C_2, 141.9 C_9, 155.3 C_1, 167.7 C_5, 185.0 C_3, Unassigned, 31.3, 33.9, 34.3, 34.5, (C_6, C_7, C_{12}, C_{15}).

X-ray crystal structure analysis of 24.

Crystal data : $C_{23}H_{30}O_6S$, *M* = 434.56, monoclinic, space group $P2_1(C_2^2)$ from the Laue symmetry, systematic absences (0*k*0 when $k \neq 2n$), and the fact that **24** is chiral, *a* = 11.724(1) Å, *b* = 14.800(2) Å, *c* = 6.130(1) Å, β = 91.69(1)°, *V* = 1063.2(4) Å^3, *Z* = 2, $D_{calcd.}$ = 1.357 g cm^{-3}, μ(Cu-*K*α radiation, λ = 1.5418 Å) = 16.3 cm^{-1}. ***Crystallographic measurements:*** Intensity data (±*h*,+*k*, +*l*; 2276 non-equivalent reflections, $\theta_{max.}$ = 75°), recorded at 298 K on an Enraf-Nonius CAD-4 diffractometer [Cu-*K*α radiation, graphite monochromator; ω-2θ scans, scanwidth (0.80 + 0.14tanθ)°] from a crystal of dimensions 0.04 x 0.14 x 0.54 mm, were corrected for the usual Lorentz and polarization effects; an empirical absorption correction [$T_{max.}$:$T_{min.(relative)}$ = 1.00:0.85], based on the φ-dependency of the intensities of several reflections with χ *ca.* 90°, was also applied. Unit-cell parameters were calculated from the diffractometer setting angles for 25 reflections (36°<θ<40°) widely separated in reciprocal space. ***Structure solution and refinement:*** The crystal structure was solved by direct methods. Atomic positional and thermal parameters (anisotropic C, N, O, S; isotropic H) were refined by means of several rounds of full-matrix least-squares calculations. An extinction correction (*g*) was included as a variable during the later iterations which converged (max. shift:esd = 0.03) at *R* = 0.042 [R_w = 0.052, GOF = 1.09, *g* = 2.6(5) x 10^{-6}] over 1663 reflections with $I > 2.0\sigma(I)$. A final difference Fourier synthesis contained no unusual features (Δρ: max. 0.22, min. -0.33 eA^{-3}). Crystallographic calculations were performed by use of the Enraf-Nonius Structure Determination Package (SDP 3.0). For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from the literature.[29] Tables of atomic positional and thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

17β-(2,2-Dioxido-3,4-dehydro-1,2-oxathiolan-4-yl)-9β,11β-epoxy-17α-hydroxy-16α-methylandrosta-1,4-dien-3-one 17-(2-furoate) 18. To a solution of 9β,11β-epoxy-17α-hydroxy-17β-(4-hydroxy-2,2-dioxido-1,2-oxathiolan-4-yl)-16α-methylandrosta-1,4-dien-3-one **19** (20 mg, 0.044 mmole) and 4-DMAP (18.3 mg, 0.15 mmole) in CH_2Cl_2 (2 mL) at rt was added triethylamine (28μL, 0.21 mmole) and 2-furoyl chloride (11.2 mg, 0.086 mmole). The mixture was kept at rt for 5 hours then purified by chromatography on one thick layer plate (mobile phase, CH_2Cl_2/EtOAc 17 : 3). A single band was extracted with EtOAc to give the title compound **18** as a gum (10 mg). MS calcd. for $C_{28}H_{31}O_8S$, $(M+H)^+$ 527, found 527; ^1H NMR: 0.90 (3H, d, J = 6.5Hz, C_{16}-CH_3), 0.93 (3H, s, C_{13}-CH_3), 1.39 (3H, s, C_{19}-CH_3), 3.28 (1H, s, $H_{11\alpha}$), 5.10 (1H, d, J = 15Hz, H_{21}), 5.29 (1H, d, J = 15Hz, H_{21}), 6.12 (1H, dd, J = 10, 2Hz, H_2), 6.13 (1H, d, J = 2Hz, H_4), 6.65 (1H, d, J = 10Hz, H_1), 6.70 (1H, d, J = 2Hz, $H_{4'}$), 7.38 (1H, d, J = 2Hz, $H_{3'}$), 7.52 (1H, s, H_{23}), 8.01 (1H, dd, J = 2, 1.5Hz, $H_{5'}$), ^{13}C NMR: δ17.1, 17.5, 24.0 (CH_3), 28.9, 28.9, 30.3, 30.6 (CH_2), 34.0, 37.7, 47.4 (CH), 43.6, 49.2 (*C), 62.4 C_{11}, 65.8 C_9, 73.2 C_{21}, 91.0 C_{17}, 112.6, 119.1, 119.5, 124.0, 127.5, 148.3, 152.5 (=CH), 143.2, 151.3, 156.8, (=C*), 165.8 (COO), 185.1 C_3.

9α-chloro-11β,17α-dihydroxy-17β-(2,2-dioxido-3,4-dehydro-1,2-oxathiolan-4-yl)-16α-methylandrosta-1,4-dien-3-one 17-(2-furoate) 17. To a solution of 9β,11β-epoxy-17α-hydroxy-17β-(4-hydroxy-2,2-dioxido-1,2-oxathiolan-4-yl)-16α-methylandrosta-1,4-dien-3-one **18** (15 mg, 0.029 mmole) in HOAc (1 mL) at 0 °C was added conc. HCl (0.3 mL). The mixture was kept at rt for 2 hours, diluted with CH_2Cl_2, washed with H_2O and $NaHCO_3$ solution and the solvent evaporated to afford **17** as a solid (14 mg, 87%). m.p. 163-167 °C (dec.); R_t = 5.2 min.; HR-MS: calcd. for $C_{28}H_{32}ClO_8S$, $(M+H)^+$ 563.1506, found 563.1531; ^1H NMR: 0.96 (3H, d, J = 6.5Hz, C_{16}-CH_3), 1.04 (3H, s, C_{13}-CH_3), 1.63 (3H, s, C_{10}-CH_3), 4.44 (1H, m, $H_{11\alpha}$), 5.18 (1H, d, J = 11Hz, H_{21}), 5.24 (1H, d, J = 11Hz, H_{21}), 5.65 (1H, d, J = 4Hz, C_{11}-OH), 6.02 (1H, d, J = 2Hz, H_4), 6.26 , (1H, dd, J = 10, 2Hz, H_2), 6.70 (1H, dd, J = 2, 1.5Hz, $H_{4'}$), 7.19 (1H, d, J = 2Hz, $H_{3'}$), 7.33 (1H, d, J = 10Hz, H_1), 7.59 (1H, s, H_{23}), 8.00 (1H, d, J = 1.5Hz, $H_{5'}$), ^{13}C NMR: δ16.7 C_{22}, 17.1 C_{18}, 24.2 C_{19}, 27.1 C_7, 29.7 C_6, 32.6 C_{15}, 34.0 C_8, 34.4 C_{12}, 37.5 C_{16}, 42.7 C_{14}, 49.43 C_{10}, 50.5 C_{13}, 73.1 C_{21}, 73.6 C_{11}, 85.6 C_9, 90.6 C_{17}, 83.9 C_{20}, 112.4 $C_{3'}$, 118.5 $C_{4'}$, 119.0 C_{CHSO_2}, 124.0 C_4, 128.6 C_2, 143.3 $C_{2'}$, 148.2 $C_{5'}$, 151.1 C_{20}, 152.5 C_1, 156.4 C_{OCO}, 166.3 C_5, 185.1 C_3.

9α,21-Dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) 4 (From epoxide **6** using mesyl chloride, with no isolation of intermediates). To a stirred suspension of 17α,21-dihydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione **6** (37.25 g, 0.1 mole) and 4-DMAP (21.96 g,

0.18 mole) in CH_2Cl_2 (300 mL) at 0 °C was added dropwise mesyl chloride (14 mL, 0.18 mole). The mixture was refluxed for 5.5 hours then cooled to 0 °C. Et_3N (15.4 ml, 0.11 mole) and 2-furoyl chloride (12.37 ml, 0.125 mole) were added and the mixture allowed to agitate at rt for 6 hours. After washing with 2N HCl and brine, the reaction solution was stirred with silica gel (81 g), filtered and the solids washed with CH_2Cl_2 (2 x 300 mL). The filtrate and washings were combined and concentrated to 300 mL, HOAc (50 ml) and conc. HCl (26 mL) were added and the mixture stirred overnight. The organic solution was washed with H_2O and $NaHCO_3$ solution then evaporated under vacuum to a solid residue which was crystallized from methanol (100 mL) with charcoal treatment to yield **4**, (37.43 g, 72% overall from **6**)

9α,21-Dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) 4 (From epoxide **6** using p-tosyl chloride, with no isolation of intermediates). To a stirred suspension of 17α,21-dihydroxy-9β,11β-oxido-16α-methylpregna-1,4-diene-3,20-dione **6** (37.25 g, 0.1 mole) and 4-DMAP (16.47 g, 0.135 mole) in CH_2Cl_2 (200 mL) at 0 °C was added dropwise a filtered solution of p-tosyl chloride (23.83 g, 0.125 mole) in CH_2Cl_2 (100 mL). The mixture was refluxed for 5 hours then cooled to 0 °C. Et_3N (32.9 ml, 0.235 mole) and 2-furoyl chloride (12.37 ml, 0.125 mole) were added and the mixture allowed to agitate at rt for 5 hours. After washing with 2N HCl and brine, the reaction solution was stirred with silica gel (81 g) filtered and the solids washed with CH_2Cl_2 (2 x 300 mL). The filtrate and washings were combined and evaporated to low volume and the residue dissolved in HOAc (290 ml). The stirred solution was cooled to 5 °C and conc. HCl (26 ml) was added slowly. After 3 hours the mixture was diluted with H_2O extracted with CH_2Cl_2, and the extracts washed with H_2O and $NaHCO_3$ solution. The organic solution was evaporated under vacuum to a solid residue which was crystallized from methanol (100 mL) with charcoal treatment to yield **4**, (37.98 g, 72.5% overall from **6**). The pH of the HCl washes from above was adjusted to 12 by the addition of NaOH and then extracted with CH_2Cl_2 (2 x 100 ml). Evaporation of the solvent gave 4-DMAP (14.9 g, 90%).

References

1. Shapiro, E. L. U. S. Patent 4,472,393, issued Sept. 18, 1985. *Chem. Abstr.* **1985**, *102*, P 95905k.
2. Rosenthal, D.; Duke, E. *Curr. Ther. Res.* **1988**, *44*, 790.
3. Viglioglia, P.; Jones, M. L.; Peets, E. A. *J. Int. Med. Res.* **1990**, *18*, 460.
4. Herbert, J. R.; Nolop, K.; Lutsky, B. *Allergy* **1996**, *51*, 569.
5. Medansky, R. S.; Bressinck, R.; Cole, G. W. *Cutis* **1988**, *42*, 480.
6. Bressinck, R.; Williams, J.; Peets, E. A. *Todays Ther. Trends* **1988**, *5*, 25.
7. Shapiro, E. L.; Gentles, M. J.; Tiberi, R. L.; Popper, T. L.; Berkenkopf, J.; Lutsky, B. L.; Watnick, A. S. *J. Med. Chem.* **1987**, *30*, 1581.
8. Popper, T. L.; Gentles, M. J.; Kung, T.T.; Berkenkopf, J.; Lutsky, B. L.; Watnick, A. S.; Shapiro, E.L. *J. Steroid Biochem.* **1987**, *27*, 837.
9. Dalton, D. R.; Smith, Jr., R. C.; Jones, D. G. *Tetrahedron*, **1970**, *26*, 575.
10. Oliveto, E. P.; Rausser, R.; Weber, L.; Nussbaum, A. L.; Gebert, W.; Coniglio, C. T.; Herschberg, E. B.; Tolksdorf, F.; Eisler, M.; Perlman, P. L.; Pechet, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 4431.
11. Green, M. J. U. S. Patent. 3,992,422, issued Nov. 16, 1976, *Chem. Abstr.* **1977**, *87*, P 39737s.
12. Sugai, S.; Okazaki, t.; Akaboshi, S. *Synthesis* **1982**, 1023.
13. Cimarusti, C. M.; Chao, S. T.; Brannick, L. J. *J. Med. Chem.* **1976**, *19*, 721.
14. Gardi, R.; Vitali, R.; Ercoli, A. *Gazz. Chim. Ital.* **1963**, *93*, 413.
15. Berkoz, B. M. U.S. Patent 3,644,340, issued Feb. 22, 1972, *Chem. Abstr.* **1972**, *76*, P 141207d.
16. Loibner, H.; Zbiral, E. *Helv. Chem. Acta* **1976**, *59*, 2100.
17. Wuts, P. G. M.; Cabaj, J. E.; Maisto, K. D. *Synthetic Commun.* **1993**, *23*, 2199.
18. Hwang, C. K.; Li, W. S.; Nicolaou, K.C. *Tetrahedron Letters* **1984**, *25*, 2295.
19. Terasawa, T.; Okada, T. *Synthetic Commun.* **1991**, *21*, 307
20. Puar, M. S.; Thompson, P. A.; Ruggeri, M.; Beiner, D.; McPhail, A.T. *Steroids* **1995**, *60*, 612.
21. Draper, R. W.; Puar, M. S.; Vater, E. J.; McPhail, A. T. *Steroids* **1998**, *63*, 135.
22. Barbee, T. R.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 6764.
23. Patonay, T.; Patonay-Peli, E.; Litkei, G.; Szilagyi, L.; Batta, G.; Dinya, Z. *J. Heterocycl. Chem.* **1988**, *25*, 343.
24. Calvo-Mateo, A.; Camarasa, M-J.; Diaz-Ortiz, A.; de las Heras, F. G. *J. Chem. Soc., Chem. Commun.* **1988**, 1114.
25. King, J. F.; Lee, T. W. S. *J. Amer. Chem. Soc.* **1969**, *91*, 6524.
26. Opitz, G. *Angew. Chem, Int. Edit.* **1967**, 6, 107.
27. Pons, M.; Simons, S. S. *J. Org. Chem.* **1981**, *46*, 3262.
28. Tripos Associates Inc.
29. Ibers, J. A.; Hamilton , W. C. Eds., *International Tables for X-Ray Crystallography, vol. IV* pp. 99, 149, The Kynoch Press, Birmingham, U.K. **1974**.