Antiandrogen. II. Oxygenated 2-Oxapregnane Steroids

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Oxygenated derivatives of 2-oxachlormadinone acetate (17-acetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione) at C_{11}, C_{15}, and C_{16} were prepared as potential antiandrogenic agents. Biological evaluation showed the 15β-hydroxyl compound to have a high potent antiandrogenic activity when tested in the castrated male rat.

Keywords antiandrogen; 2-oxachlormadinone acetate; 15-hydroxylation; ventral prostate; ozonolysis; structure–activity relationship

In the course of our studies aimed at the preparation of potent antiandrogenic agents, 2-oxachlormadinone acetate (17-acetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione) has been shown to have potent antiandrogenic activity.[1] The bioavailability[2] of 2-oxachlormadinone acetate is higher than that of chlormadinone acetate, possibly as a result of the difference in their hydrophilicity. From this point of view, we were interested in preparing other oxygenated 2-oxasteroids for examination of their antiandrogenic activities. Some results along this line are presented in this paper.

One of our target compounds, 17-acetoxy-6-chloro-2-oxapregna-4,6-diene-3,11,20-trione (**7**), is one of the main metabolites of 2-oxachlormadinone acetate in the dog.[3] The 11-oxo compound (**7**) was prepared from 11β,17-diacetoxypregna-1,4,6-triene-3,20-dione (**1**)[4] as shown in Chart 1.

Oxidation of **1** with *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform gave the epoxide (**2**, 82.2% yield)[5] as a main product, which was subjected to ozonolysis in pyridine to afford the lactol (**3**, 75.9% yield). The structural assignment of C_1 was achieved by NMR analysis; in particular, the chemical shift of the C_1 proton was observed at 5.34 ppm as a singlet similar to that reported in the previous paper.[1] The lactol (**3**) was reduced with sodium borohydride ($NaBH_4$) in methanol–tetrahydrofuran (THF) mixture containing sodium hydroxide and sodium acetate, and successively treated with hydrochloric acid to furnish the lactone (**4**) in 72.8% yield. After mesylation of **4** with methanesulfonyl chloride in pyridine, the mesylate obtained was treated with potassium acetate in dimethyl sulfoxide (DMSO) at room temperature to yield the dehydrated

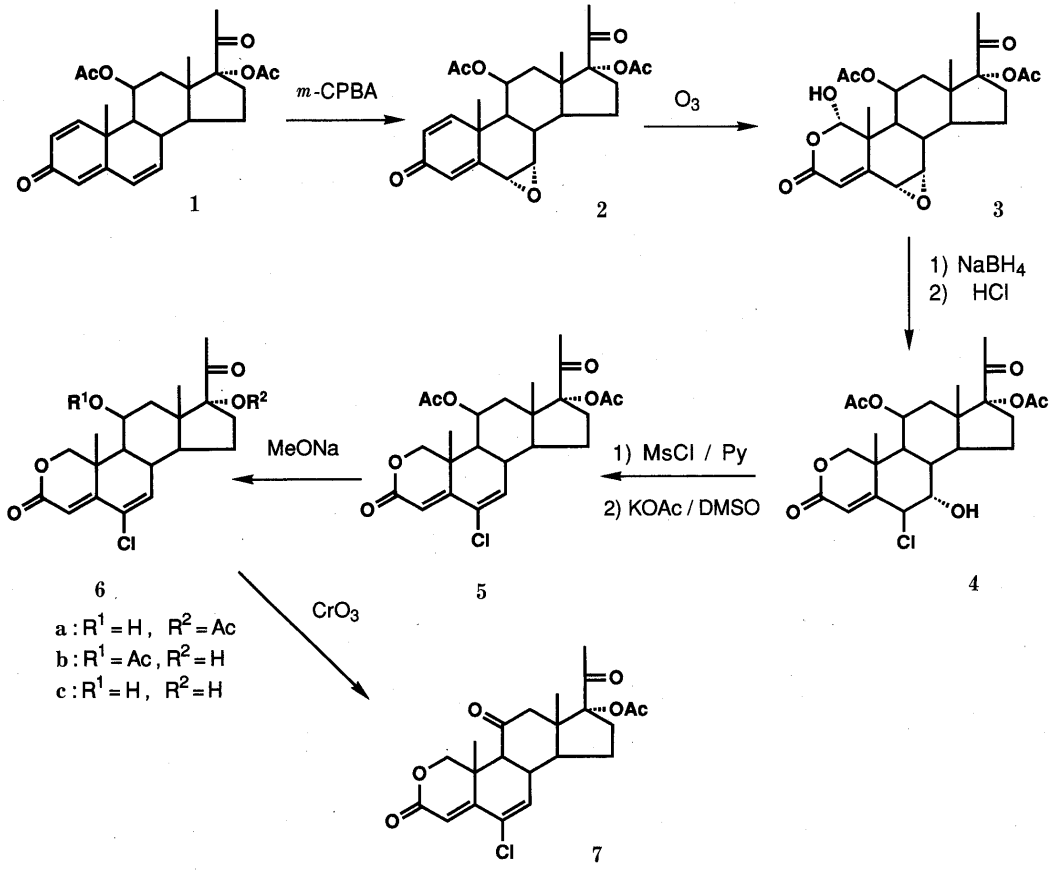

Chart 1

compound (**5**, 45.2% yield). Mild deacetylation of **5** with sodium methoxide in methanol–THF gave a mixture of monohydroxyl and dihydroxyl compounds, **6a**, **6b**, and **6c**, which was submitted to thin-layer chromatography (TLC) on silica gel to provide the pure compounds in 17.6%, 49.5%, and 17.1% yields, respectively. The 11β-hydroxyl compound (**6a**) was converted by the Jones oxidation method[6] into the 11-oxo compound (**7**) in 98.5% yield. The NMR, MS, and HPLC data for **7** corresponded with those of the main metabolite of 2-oxachlormadinone acetate in the dog.

The other target compound, 17-acetoxy-6-chloro-15β-hydroxy-2-oxapregna-4,6-diene-3,20-dione (**15a**) is a main metabolite of 2-oxachlormadinone acetate in the rat and the human.[3] Such a hydroxylation at C_{15} has been observed in the metabolism[7] of cyproterone acetate, indicating a similar metabolic pathway of C-15 hydroxylation when the A-ring structure is resistant to metabolism.

The 17-hydroxy-2-oxa compound (**8**)[1] was chosen as a starting material, and converted to the 16-dehydro compound (**9**, 83.9% yield) by dehydration with phosphorus oxychloride in pyridine. Hydroxylation of **9** to the 15-dehydro compound (**10**), according to the method reported by Gardner *et al.*,[8] proceeded in a fair yield. Treatment of **9** in *tert*-butanol–dimethylformamide (DMF) mixture in the presence of sodium hydride at $-28\,^{\circ}C$ under an O_2 atmosphere (40 kg/cm^2) gave a crude mixture, which was submitted to preparative TLC to give the 15-dehydro compound (**10**) in 16.3% yield. Several attempts to increase the yield resulted in failure. Acetylation of **10** in the usual manner gave the 17-acetate (**11**) in 68.9% yield.

Treatment of **10** with *N*-bromoacetamide (NBA) in acetic acid in the presence of lithium acetate afforded the 15β-acetoxy-16α-bromo compound (**12**, 56.9% yield),[9] according to the reported method.[10] The compound (**12**) was refluxed with tributyltin hydride[11] and a catalytic amount of 2,2′-azobisisobutylonitrile in THF for 2 h to furnish the debrominated compound (**13**, 74.3% yield).[9]

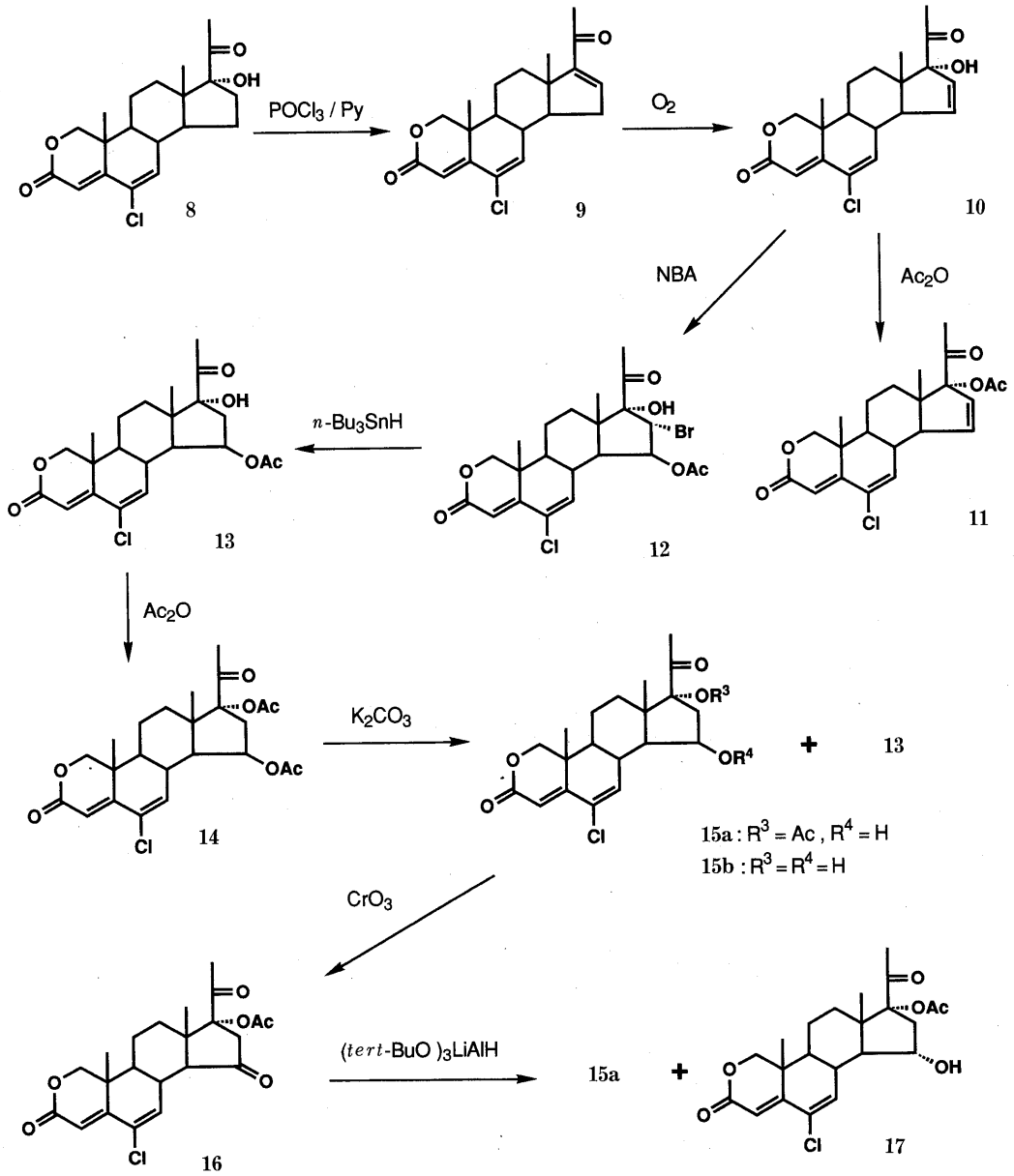

Chart 2

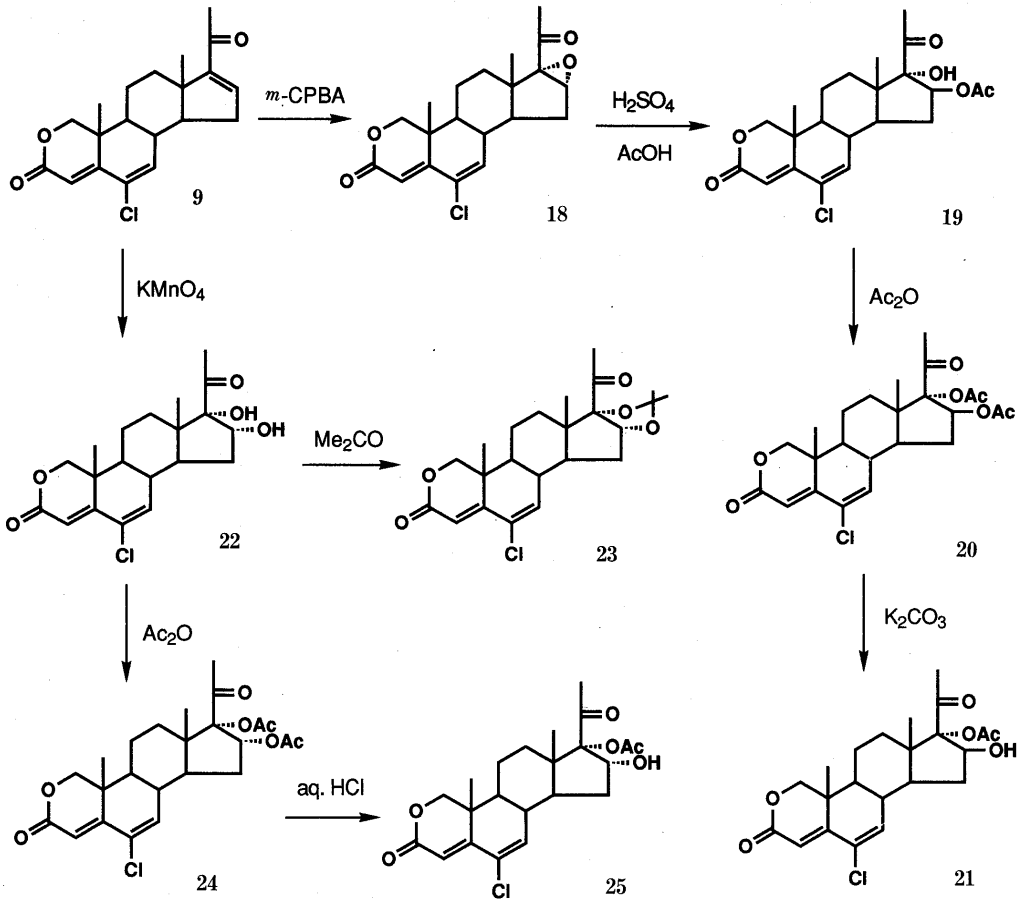

Chart 3

This compound (**13**) was led *via* usual acetylation to the diacetate (**14**, 84.9% yield).[9] Although mild deacetylation of the diacetate (**14**) is expected to give the 17-mono-acetate (**15a**) easily, the 15β-acetate (**13**) was obtained as a main product (35.0% yield) together with the 17-acetate (**15a**, 15.0% yield)[9] and the diol (**15b**, 11.1% yield)[9] as by-products, (see Experimental). The 17-acetate (**15a**) was oxidized with Jones' reagent in the usual manner to yield the trione (**16**, 81.2% yield) without isomerization at C_{14}. Reduction of the trione (**16**) with lithium tri-*tert*-butoxyaluminum hydride (Li(*tert*-BuO)$_3$AlH) in THF gave a mixture of 15β- and 15α-hydroxyl compounds in a ratio of 8 : 1, which was submitted to preparative TLC on silica gel to afford **15a** (79.6% yield) and **17** (10.9% yield)[9] in a pure state. The NMR, MS, and HPLC data for **15a** corresponded to those of the main metabolite of 2-oxachlormadinone acetate in the rat and the human.

Preparation of the 16α- and 16β-hydroxyl compounds was done *via* the route shown in Chart 3. The 16-dehydro compound (**9**) was oxidized with *m*-CPBA in dichloromethane to furnish the epoxide (**18**) in 90.3% yield. Treatment of **18** with a mixture of concentrated sulfuric acid and acetic acid[12] led to the 16β-acetoxyl compound (**19**, 42.9% yield), which was easily converted to the diacetate (**20**, 61.7% yield) in the usual manner. Selective deacetylation of **20** in a similar manner to that described for **14** gave the 16β-hydroxyl compound (**21**) in 30.2% yield.

Incorporation of a hydroxyl function at $C_{16\alpha}$ was achieved by permanganese oxidation of the 16-dehydro compound (**9**) according to the method reported.[13] Thus, the 16α,17α-diol (**22**) was obtained (55.2% yield) and then converted to the diacetate (**24**, 56.4% yield) and the acetonide (**23**, 66.2% yield) in the usual manner. Again, the selective deacetylation of **24** was tried by the method described above (**14**→**15a** and **20**→**21**) but resulted in failure, indicating that the hydrolysis rate of the 17α-acetoxyl group was faster than that of the 16α-acetoxyl group in alkaline media. Acid hydrolysis has been found to be preferred over alkaline hydrolysis, and the treatment of the diacetate (**24**) with 0.1 N hydrochloric acid in methanol for 10 d gave the 16α-hydroxyl compound (**25**) in 12.1% yield after purification by preparative TLC.

Biological Activity

The antiandrogenic activity of the compounds prepared was determined in immature male castrated rats treated with testosterone propionate.[14] The ability of the compounds to antagonize the androgen-stimulated weight gain of the seminal vesicle and ventral prostate served as a measure of their activity. These data are shown in Table I. High antiandrogenic activities were exhibited by the 15β- and 11β-hydroxyl compounds (**15a** and **6a**) and the 11-oxo compound (**7**). On the other hand, the 15-oxo compound (**16**) was less active than the parent compound (chlormadinone acetate), and the 16-hydroxyl compounds (**21** and **25**) were inactive at the dose tested.

It is interesting that the main metabolites, **7** and **15a**, are more potent than 2-oxachlormadinone acetate. A pharma-

TABLE I. The Effect of Oxygenated 2-Oxapregnanes on Accessory Sex Organ Weights in Castrated Rat Given Testosterone Propionate (50 μg/rat, s.c.)

Compound	Dose[a] (mg/kg)	Organ weight[b] (mg/100 g body weight)	
		Ventral prostate	Seminal vesicle
6a	0.89	18.2±1.5[c]	32.7±1.6
6a	2.67	11.7±1.7[e]	17.7±3.0[e]
6a	8	8.4±0.9[e]	9.0±1.6[e]
7	0.89	14.4±1.2[e]	27.6±2.6[d]
7	2.67	11.9±1.2[e]	25.1±4.7[c]
7	8	8.0±0.4[e]	9.7±0.6[e]
15a	0.89	15.1±1.2[d]	27.0±1.5[e]
15a	2.67	10.0±1.1[e]	13.1±0.9[e]
15a	8	7.4±0.4[e]	8.5±0.4[e]
16	0.89	24.2±2.0	37.0±2.2
16	2.67	20.6±0.5	34.9±3.1
16	8	16.9±1.2[d]	25.5±2.6[d]
21	0.89	26.1±1.0	47.2±4.0
21	2.67	24.0±1.4	39.0±1.9
21	8	22.0±1.8	33.2±3.6
25	0.89	27.4±1.0	40.8±1.3
25	2.67	25.7±0.9	37.8±2.2
25	8	22.5±1.4	34.8±2.9
CMA[f]	5	16.9±1.0[d]	28.7±1.3[d]
CMA	15	14.6±0.7[e]	25.1±1.2[e]
CMA	45	8.3±0.3[e]	14.4±1.0[e]
2-oxaCMA[g]	0.67	18.1±1.6[c]	29.3±1.9[d]
2-oxaCMA	2	14.0±1.1[e]	22.2±1.4[e]
2-oxaCMA	6	11.0±0.7[e]	13.1±1.7[e]
Castrated control		6.0±0.3[e]	6.6±0.3[e]
T.P.[h] control		23.4±1.2	37.6±1.4

a) *per os*. *b*) Each value represents the mean±S.E. ($n=5$—10). *c*) Significantly different from the T.P. control ($p<0.05$). *d*) Significantly different from the T.P. control ($p<0.01$). *e*) Significantly different from the T.P. control ($p<0.001$). *f*) CMA: chlormadinone acetate. *g*) 2-oxaCMA: 2-oxachlormadinone acetate. *h*) T.P.: testosterone propionate.

cological study is in progress.

Experimental

Melting points were measured on a Mettler FPI melting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined on a Hitachi R-90H instrument in $CDCl_3$ solution using tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP1000 spectrometer. Elemental analysis was determined on a Hitachi 026 CHN analyzer. Preparative TLC was carried out on 20×20 cm plates with a 0.25 mm layer of Merck Silica gel 60 GF 254. Ozone was generated with a Nippon Ozone 0-10-2 instrument.

11β,17-Diacetoxy-6α,7α-epoxypregna-1,4-diene-3,20-dione (2) To a solution of **1** (0.68 g) in $CHCl_3$ (3.4 ml) was added slowly *m*-CPBA (1.08 g), and the mixture was stirred for 9 h at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 10% $NaHSO_3$, 4% NaOH and then water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give **2** (0.58 g, 82.2%). An analytical sample was obtained by recrystallization from Me_2CO–ether as colorless prisms. mp 227—230 °C. *Anal.* Calcd for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 67.95; H, 6.80. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s), 1.33 (3H, s), 2.02 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 3.51 (1H, m), 3.73 (1H, d, $J=3.5$ Hz), 5.44 (1H, dd, $J=3$, 6 Hz), 6.28 (1H, dd, $J=2$, 10 Hz), 6.46 (1H, d, $J=2$ Hz), 6.77 (1H, d, $J=10$ Hz). MS *m/z*: 442 (M^+), 399, 382, 357, 339, 297, 279.

11β,17-Diacetoxy-6α,7α-epoxy-1α-hydroxy-2-oxapregn-4-ene-3,20-dione (3) A solution of **2** (6.3 g) in pyridine (32 ml) was ozonized by passing a stream of ozone (0.1 mmol/min, 1 h) at −30 °C. The progress of the reaction was followed by TLC. The resulting mixture was stirred for 10 min at room temperature. After addition of 10% $NaHSO_3$ (3 ml), the resulting mixture was stirred for 1 h. The product was extracted with EtOAc, and the organic layer was washed with 10% H_2SO_4 and water, dried over anhydrous $MgSO_4$, and concentrated to give **3** (5.0 g, 75.9%). An analytical sample was obtained by recrystallization from Me_2CO–ether as colorless prisms. mp 202—205 °C. *Anal.* Calcd for $C_{24}H_{30}O_9$: C, 62.33; H, 6.54. Found: C, 62.26; H, 6.58. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s), 1.26 (3H, s), 2.02 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 3.49 (1H, d, $J=4$ Hz), 3.59 (1H, d, $J=4$ Hz), 5.34 (1H, s), 5.51 (1H, m), 6.16 (1H, s). MS *m/z*: 462 (M^+), 420, 377, 359, 342, 317.

11β,17-Diacetoxy-6β-chloro-7α-hydroxy-2-oxapregn-4-ene-3,20-dione (4) To a solution of **3** (5 g) in THF (25 ml) and MeOH (20 ml) were added a solution of NaOAc (2.5 g) in water (9.6 ml) and a solution of NaOH (0.45 g) in water (1 ml). After addition of $NaBH_4$ (0.36 g) and phenol (0.84 g), the mixture was stirred for 30 min at room temperature. Ice (15 g) and concentrated HCl (18 ml) were added, and then the reaction mixture was stirred for 25 min at room temperature and poured into water. The precipitate was collected by filtration, washed with water and dried to give **4** (3.8 g, 72.8%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 227—230 °C. *Anal.* Calcd for $C_{24}H_{31}ClO_8$: C, 59.69; H, 6.47. Found: C, 59.74; H, 6.58. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s), 1.49 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.11 (3H, s), 4.08 (1H, br s), 4.14 and 4.26 (2H, ABq, $J=10.5$ Hz), 4.48 (1H, d, $J=3$ Hz), 5.33 (1H, m), 5.96 (1H, s). MS *m/z*: 482 (M^+), 447, 440, 397, 361, 345.

11β,17-Diacetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione (5) To a solution of **4** (184 mg) in pyridine (2 ml) was added dropwise methanesulfonyl chloride (0.2 ml), and the mixture was stirred for 20 h at room temperature. After addition of 3% HCl, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to give a mesylate. A mixture of the mesylate (162 mg), potassium acetate (120 mg) and DMSO (1.2 ml) was stirred for 23 h at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 9 : 1) to give **5** (80 mg, 45.2%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 322—326 °C. *Anal.* Calcd for $C_{24}H_{29}ClO_7$: C, 62.00; H, 6.29. Found: C, 62.19; H, 6.20. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s), 1.31 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 4.20 (2H, s), 5.26 (1H, m), 6.17 (1H, s), 6.40 (1H, br d, $J=2$ Hz). MS *m/z*: 464 (M^+), 422, 421, 404, 379.

Hydrolysis of 5 To a solution of **5** (100 mg) in THF (12 ml) and MeOH (5 ml) was added 28% solution of sodium methoxide in MeOH (24 μl), and the mixture was stirred for 2 h at room temperature. After addition of 3% HCl, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 7 : 1) to give less polar **6b** (45 mg, 49.5%), more polar **6a** (16 mg, 17.6%) and most polar **6c** (14 mg, 17.1%).

11β-Acetoxy-6-chloro-17-hydroxy-2-oxapregna-4,6-diene-3,20-dione (**6b**): mp 263—265 °C (Me_2CO–hexane). *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.30; H, 6.46. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s), 1.29 (3H, s), 2.06 (3H, s), 2.26 (3H, s), 4.18 (2H, s), 5.23 (1H, m), 6.15 (1H, s), 6.41 (1H, d, $J=2$ Hz). MS *m/z*: 422 (M^+), 379, 369, 362, 336, 319, 301.

17-Acetoxy-6-chloro-11β-hydroxy-2-oxapregna-4,6-diene-3,20-dione (**6a**): mp 281—283 °C (Me_2CO–hexane). *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.32; H, 6.49. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s), 1.45 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 4.21 and 4.49 (2H, ABq, $J=10.8$ Hz), 4.23 (1H, m), 6.13 (1H, s), 6.41 (1H, br d, $J=2$ Hz). MS *m/z*: 422 (M^+), 380, 379, 362, 337, 319, 301, 271.

6-Chloro-11β,17-dihydroxy-2-oxapregna-4,6-diene-3,20-dione (**6c**): mp 316—320 °C (Me_2CO). *Anal.* Calcd for $C_{20}H_{25}ClO_5$: C, 63.07; H, 6.62. Found: C, 63.01; H, 6.67. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, s), 1.45 (3H, s), 2.29 (3H, s), 4.17 and 4.44 (2H, ABq, $J=10.6$ Hz), 4.22 (1H, m), 6.13 (1H, s), 6.40 (1H, br d, $J=2$ Hz). MS *m/z*: 380 (M^+), 362, 337, 327, 319, 301, 294.

17-Acetoxy-6-chloro-2-oxapregna-4,6-diene-3,11,20-trione (7) A solution of **6a** (100 mg) in Me_2CO (8 ml) was treated with Jones' reagent (0.1 ml) at 0 °C, and the mixture was stirred for 7 min at 0 °C. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to give **7** (98 mg, 98.5%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 289—292 °C. *Anal.* Calcd for $C_{22}H_{25}ClO_6$: C, 62.78; H, 5.99. Found: C, 62.93; H, 5.90. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 1.36 (3H, s), 2.06 (3H, s), 2.13 (3H, s), 3.97 (1H, d, $J=11$ Hz), 5.02 (1H, d, $J=11$ Hz), 6.25 (1H, s), 6.35 (1H, br d, $J=1.5$ Hz). MS *m/z*: 420 (M^+), 402, 378, 335.

6-Chloro-2-oxapregna-4,6,16-triene-3,20-dione (9) To a solution of **8** (104.8 g) in pyridine (1.5 l) was added dropwise phosphorus oxychloride

(500 g) at 0 °C, and the mixture was stirred for 14 d at room temperature. The resulting mixture was poured into ice-water and the precipitate was collected by filtration, washed with water, and dried. The crude product was crystallized from MeOH to give **9** (83.6 g, 83.9%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 185—186 °C. *Anal.* Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.68. Found: C, 69.16; H, 6.75. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s), 1.23 (3H, s), 2.28 (3H, s), 4.06 and 4.24 (2H, ABq, J=11 Hz), 6.19 (1H, s), 6.36 (1H, d, J=2 Hz), 6.72 (1H, dd, J=2, 3 Hz). MS *m/z*: 346 (M^+), 331, 303, 175.

6-Chloro-17-hydroxy-2-oxapregna-4,6,15-triene-3,20-dione (10) To a mixture of sodium hydride (90 mg), *tert*-butyl alcohol (7.5 ml) and DMF (13 ml) was added a solution of **9** (500 mg) in DMF (13 ml) at −28 °C, and the mixture was stirred under 40 kg/cm^2 of oxygen pressure for 4 h at −28 °C. The reaction mixture was poured into 5% AcOH, and the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=9 : 1) to give **10** (85 mg, 16.3%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 261—264 °C. *Anal.* Calcd for $C_{20}H_{23}ClO_4$: C, 66.20; H, 6.39. Found: C, 66.44; H, 6.31. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, s), 1.23 (3H, s), 2.27 (3H, s), 4.08 and 4.24 (2H, ABq, J=11 Hz), 6.11 (1H, dd, J=3, 6 Hz), 6.21 (1H, s), 6.35 (1H, br d, J=6 Hz), 6.48 (1H, d, J=1.5 Hz). MS *m/z*: 362 (M^+), 319, 301.

17-Acetoxy-6-chloro-2-oxapregna-4,6,15-triene-3,20-dione (11) To a solution of **10** (320 mg) in acetic anhydride (4 ml) and pyridine (8 ml) was added 4-dimethylaminopyridine (80 mg), and the mixture was stirred for 3 h at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% HCl, 5% $NaHCO_3$, and then water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC (C_6H_6 : EtOAc=4 : 1) to give **11** (246 mg, 68.9%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 209—210 °C. *Anal.* Calcd for $C_{22}H_{25}ClO_5$: C, 65.26; H, 6.22. Found: C, 65.32; H, 6.18. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, s), 1.24 (3H, s), 2.04 (3H, s), 2.18 (3H, s), 4.09 and 4.25 (2H, ABq, J=11 Hz), 6.22 (1H, s), 6.32 (1H, br d, J=6 Hz), 6.43 (1H, dd, J=2.5, 6 Hz), 6.47 (1H, br s). MS *m/z*: 404 (M^+), 361, 319, 301.

15β-Acetoxy-6-chloro-17-hydroxy-2-oxapregna-4,6-diene-3,20-dione (13) To a solution of **10** (831 mg) in AcOH (54 ml) and EtOAc (18 ml) were added lithium acetate (5.4 g) and NBA (380 mg), and the mixture was stirred for 35 min at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was subjected to preparative TLC (C_6H_6 : EtOAc=4 : 1) to give the bromo compound (**12**, 654 mg, 56.9%); ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s), 1.23 (3H, s), 2.14 (3H, s), 2.24 (3H, s), 4.09 and 4.23 (2H, ABq, J=11 Hz), 5.10 (1H, d, J=2.5 Hz), 5.45 (1H, m), 6.14 (1H, br s), 6.21 (1H, s).

A mixture of **12** (270 mg), tributyltin hydride (2 ml), 2,2′-azobisisobutyronitrile (25 mg) and THF (15 ml) was refluxed for 2 h, and the solvent was evaporated off. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=19 : 1) to give **13** (169 mg, 74.3%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 119—123 °C. *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.56; H, 6.38. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s), 1.25 (3H, s), 2.10 (3H, s), 2.30 (3H, s), 4.09 and 4.23 (2H, ABq, J=11 Hz), 5.39 (1H, m), 6.21 (1H, s). MS *m/z*: 422 (M^+), 362, 344, 319, 301.

15β,17-Diacetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione (14) To a solution of **13** (15 mg) in acetic anhydride (0.25 ml) and dioxane (1 ml) was added 60% perchloric acid (1 μl), and the mixture was stirred for 20 min at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=19 : 1) to give **14** (14 mg, 84.9%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 126—130 °C. *Anal.* Calcd for $C_{24}H_{29}ClO_7$: C, 62.00; H, 6.29. Found: C, 62.14; H, 6.25. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, s), 1.26 (3H, s), 2.06 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 4.10 and 4.25 (2H, ABq, J=11 Hz), 5.34 (1H, m), 6.22 (1H, s), 6.27 (1H, d, J=2 Hz). MS *m/z*: 464 (M^+), 404, 379, 362, 344, 319, 301.

Hydrolysis of 14 To a solution of **14** (110 mg) in MeOH (10 ml) was added a solution of K_2CO_3 (40 mg) in water (5 ml), and the mixture was stirred for 100 min at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC (C_6H_6 : EtOAc=5 : 1) to give 17-acetoxy-6-chloro-15β-hydroxy-2-oxapregna-4,6-diene-3,20-dione (**15a**, 15 mg, 15.0%), 6-chloro-15β,17-dihydroxy-2-oxapregna-4,6-diene-3,20-dione (**15b**, 10 mg, 11.1%), and **13** (35 mg, 35.0%). **15a**: mp 285—288 °C (Me_2CO–hexane). *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.41; H, 6.49. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, s), 1.24 (3H, s), 2.08 (6H, s), 4.10 and 4.25 (2H, ABq, J=11 Hz), 4.49 (1H, m), 6.20 (1H, s), 6.56 (1H, d, J=2 Hz). MS *m/z*: 422 (M^+), 379, 362, 344, 337, 319, 301. **15b**: mp 112—115 °C (Me_2CO). *Anal.* Calcd for $C_{20}H_{25}ClO_5$: C, 63.07; H, 6.62. Found: C, 63.19; H, 6.60. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, s), 1.24 (3H, s), 2.32 (3H, s), 4.08 and 4.24 (2H, ABq, J=11 Hz), 4.62 (1H, m), 6.19 (1H, s), 6.58 (1H, d, J=2 Hz). MS *m/z*: 380 (M^+), 362, 337, 319, 301.

17-Acetoxy-6-chloro-2-oxapregna-4,6-diene-3,15,20-trione (16) This compound was prepared from **15a** in 81.2% yield as described for preparation of **7**. *Anal.* Calcd for $C_{22}H_{25}ClO_6$: C, 62.78; H, 5.99. Found: C, 62.92; H, 5.94. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, s), 1.22 (3H, s), 2.13 (3H, s), 2.17 (3H, s), 4.08 and 4.25 (2H, ABq, J=11 Hz), 6.22 (1H, s), 7.16 (1H, br s). MS *m/z*: 420 (M^+), 360, 335, 317, 299.

17-Acetoxy-6-chloro-15α-hydroxy-2-oxapregna-4,6-diene-3,20-dione (17) To a solution of **16** (100 mg) in THF (40 ml) was added Li(*tert*-BuO)$_3$AlH (40 mg), and the mixture was stirred for 35 min at room temperature. After addition of 3% HCl, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=9 : 1) to give less polar **15a** (80 mg, 79.6%) and more polar **17** (11 mg, 10.9%). **17**: *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.60; H, 6.37. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (3H, s), 1.22 (3H, s), 2.04 (3H, s), 2.14 (3H, s), 4.09 and 4.23 (2H, ABq, J=11 Hz), 4.31 (1H, m), 6.21 (1H, s), 6.97 (1H, d, J=2 Hz). MS *m/z*: 422 (M^+), 379, 362, 344, 337, 301.

6-Chloro-16α,17-epoxy-2-oxapregna-4,6-diene-3,20-dione (18) To a solution of **9** (3.6 g) in CH_2Cl_2 (40 ml) was added *m*-CPBA (4.6 g), and the mixture was stirred for 24 h at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $Na_2S_2O_3$, 5% Na_2CO_3, and then water, dried over anhydrous $MgSO_4$, and concentrated to give **18** (3.4 g, 90.3%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 217—221 °C. *Anal.* Calcd for $C_{20}H_{23}ClO_4$: C, 66.21; H, 6.39. Found: C, 66.40; H, 6.31. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, s), 1.20 (3H, s), 2.03 (3H, s), 3.76 (1H, s), 4.05 and 4.22 (2H, ABq, J=11 Hz), 6.17 (1H, s), 6.24 (1H, d, J=2 Hz). MS *m/z*: 362 (M^+), 346, 302, 267.

16β-Acetoxy-6-chloro-17-hydroxy-2-oxapregna-4,6-diene-3,20-dione (19) To a solution of **18** (100 mg) in AcOH (2 ml) at 15 °C was added slowly a cold solution of concentrated H_2SO_4 (0.2 ml) in AcOH (2 ml), and the mixture was stirred for 7 h at room temperature. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC (hexane : EtOAc=2 : 1) to give **19** (50 mg, 42.9%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 217—221 °C. *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.57; H, 6.39. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s), 1.22 (3H, s), 2.08 (3H, s), 2.24 (3H, s), 4.06 and 4.23 (2H, ABq, J=11 Hz), 4.85 (1H, dd, J=6, 8 Hz), 6.19 (1H, s), 6.30 (1H, d, J=2 Hz). MS *m/z*: 422 (M^+), 379, 362, 334, 301.

16β,17-Diacetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione (20) Acetylation of **19** was carried out as described for the preparation of **14**. An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. 61.7% yield. mp 266—269 °C. *Anal.* Calcd for $C_{24}H_{29}ClO_7$: C, 62.00; H, 6.29. Found: C, 61.86; H, 6.35. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, s), 1.22 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 2.19 (3H, s), 4.07 and 4.24 (2H, ABq, J=11 Hz), 5.25 (1H, dd, J=5, 8 Hz), 6.19 (1H, s), 6.28 (1H, d, J=2 Hz). MS *m/z*: 464 (M^+), 422, 404, 379, 362, 320, 301.

17-Acetoxy-6-chloro-16β-hydroxy-2-oxapregna-4,6-diene-3,20-dione (21) To a solution of **20** (273 mg) in THF (20 ml) and MeOH (10 ml) was added a solution of K_2CO_3 (44 mg) in water (3.7 ml), and the mixture was stirred for 25 min at room temperature. After addition of 3% HCl, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=9 : 1) to give **21** (75 mg, 30.2%). An analytical sample

was obtained by recrystallization from Me_2CO–hexane as pale yellow prisms. mp 219—223 °C. *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.57; H, 6.38. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s), 1.23 (3H, s), 2.07 (3H, s), 2.14 (3H, s), 4.08 and 4.25 (2H, ABq, J=11 Hz), 4.31 (1H, dd, J=5, 8 Hz), 6.21 (1H, s), 6.31 (1H, d, J=2 Hz). MS *m/z*: 422 (M^+), 380, 362, 337, 301.

6-Chloro-16α,17-dihydroxy-2-oxapregna-4,6-diene-3,20-dione (22) To a cold solution of **9** (300 mg) in Me_2CO (10 ml) and AcOH (0.1 ml) was added slowly a solution of potassium permanganate (144 mg) in Me_2CO (6 ml) and water (1 ml), and the mixture was stirred for 3 min at 0 °C. After addition of 10% $NaHSO_3$, the precipitate was filtered off and the filtrate was concentrated to dryness. The product was extracted with EtOAc, and the organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and then concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=4 : 1) to give ***22*** (182 mg, 55.2%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. mp 210—213 °C. *Anal.* Calcd for $C_{20}H_{25}ClO_5$: C, 63.07; H, 6.62. Found: C, 62.86; H, 6.67. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (3H, s), 1.20 (3H, s), 2.24 (3H, s), 4.07 and 4.23 (2H, ABq, J=11 Hz), 5.08 (1H, dd, J=3, 8 Hz), 6.18 (1H, s), 6.26 (1H, br s). MS *m/z*: 380 (M^+), 362, 337, 319.

6-Chloro-16α,17-isopropylidenedioxy-2-oxapregna-4,6-diene-3,20-dione (23) To a solution of **22** (67 mg) in Me_2CO (3 ml) was added a solution of phosphomolybdic acid (94 mg) in Me_2CO (14 ml), and the mixture was stirred for 30 min at room temperature. The reaction mixture was poured into 10% NH_4OH, and the product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=19 : 1) to give **23** (49 mg, 66.2%). An analytical sample was obtained by recrystallization from ether as pale yellow prisms. mp 257—259 °C. *Anal.* Calcd for $C_{23}H_{29}ClO_5$: C, 65.63; H, 6.94. Found: C, 65.76; H, 6.88. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s), 1.18 (3H, s), 1.20 (3H, s), 1.48 (3H, s), 2.22 (3H, s), 4.09 and 4.25 (2H, ABq, J=11 Hz), 5.05 (1H, d, J=4.8 Hz), 6.20 (1H, s), 6.31 (1H, d, J=2 Hz). MS *m/z*: 420 (M^+), 377, 319, 317.

16α,17-Diacetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione (24) Acetylation of **22** was carried out as described for the preparation of **14**. An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms. 56.4% yield. mp 243—244 °C. *Anal.* Calcd for $C_{24}H_{29}ClO_7$: C, 62.00; H, 6.29. Found: C, 61.85; H, 6.36. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, s), 1.21 (3H, s), 1.95 (3H, s), 2.09 (3H, s), 2.16 (3H, s), 4.09 and 4.25 (2H, ABq, J=11 Hz), 6.21 (1H, s), 6.25 (1H, br s), 6.30 (1H, m). MS *m/z*: 464 (M^+), 422, 404, 379, 362, 320, 301.

Hydrolysis of 24 To a solution of **24** (100 mg) in MeOH (10 ml) was added 0.1% HCl (0.5 ml), and the mixture was allowed to stand at room temperature for 10 d. After addition of water, the product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO=9 : 1) to give **25** (11 mg, 12.1%), **22** (30 mg, 36.6%) and the 16-acetate (42 mg, 46.2%) of **22** in a pure state. **25**: mp 252—256 °C. *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.66; H, 6.35. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, s), 1.21 (3H, s), 2.04 (3H, s), 2.14 (3H, s), 4.10 and 4.25 (2H, ABq, J=11 Hz), 5.35 (1H, m), 6.21 (1H, s), 6.31 (1H, d, J=2 Hz). MS *m/z*: 422 (M^+), 380, 362, 337, 301.

Antiandrogenic Assay Wistar strain male rats weighing 160—180 g were castrated at about 4 weeks of age. After two weeks, testosterone propionate (50 μg/rat) was administered daily by the subcutaneous route in 0.1 ml of sesame oil to all groups except controls. The test compounds were given by the *per os* route daily for 5 d. On day 6, the animals were sacrificed, and seminal vesicles and ventral prostates were secured and weighed.

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