Oxidative Cyclization of Iodo Ketones. Synthesis of 6-Oxa-5α-pregnane-3,20-dione

Daniel Nicoletti, Alberto A. Ghini, and Gerardo Burton*,†

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, 1428 Buenos Aires, Argentina

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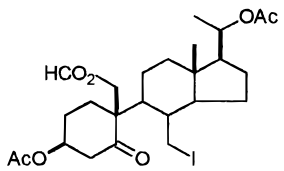
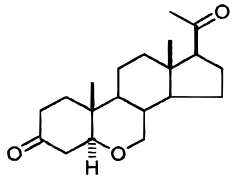
The steroidal δ- and γ-iodo ketones **1** and **9** were converted to the cyclic hemiketals **3** and **10**, by oxidation to the iodoso derivatives with *m*-CPBA. Spontaneous cyclization of the latter intermediates to the corresponding oxocarbenium ions, followed by stereoselective addition of water, rendered the hemiketals. Depending on the reaction conditions, the five-membered oxocarbenium ion derived from the γ-iodo ketone **9** may add H_2O or *m*-CPBA to give either the hemiketal or a Baeyer−Villiger type product **12**, while the oxocarbenium derived from **1** gives exclusively the hemiketal. When the reaction was carried out in dry methanol, methyl ketals were formed. Use of this methodology allowed us to synthesize 6-oxa-5α-pregnanes with and without functionalization at C-19.

The replacement of one or more carbon atoms of the steroid nucleus by heteroatoms gives rise to marked changes in the biological activity of steroidal derivatives.[1] Thus, numerous studies deal with total and partial syntheses of heterosteroids.[2] Recently, we described a synthetic approach to 6-oxa-5β-pregnanes in which the key step was the reductive cyclization of the δ-iodo ketone moiety in secosteroid **1**.[3] Formation of the less stable *cis* isomer at the A/B ring junction was due to the steric hindrance toward hydride attack from the α face in secosteroid **1**. In order to obtain the 6-oxapregnanes with *trans* configuration at the A/B ring junction (e.g., **2**), a different cyclization approach was required.



1

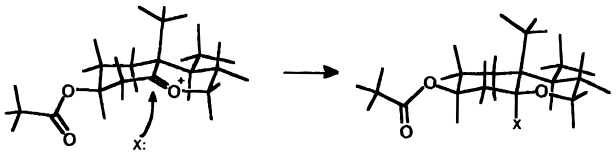


2

Kishi *et al.*[4] have shown that the stereochemical course of nucleophilic attack on a pyranosic oxocarbenium ion may be rationalized on the basis of stereoelectronics and steric effects. Thus, the oxocarbenium ion preferently accepts nucleophiles from the α (axial) side due to the anomeric effect of the ring oxygen. If a pyranosic oxocarbenium ion is formed in ring B of the steroid nucleus, nucleophiles (*e.g.*, H_2O, methanol, hydride, etc.) will attack at C-5 from the α face giving an A/B *trans* steroid (PM3-calculated structures are shown in Scheme 1); in this case, steric hindrance on the β face would favor stereoselectivity.

We initially focused our attention on the δ-iodo ketone moiety present in secosteroid **1** as a possible precursor

Scheme 1



of a steroidal oxocarbenium ion. Iodine in a higher oxidation state provides a better leaving group than univalent iodine,[5] and the highly labile iodoso intermediates have been postulated to be the initial products in the oxidation of alkyl iodides with *m*-CPBA.[6] Their fate depends on the type of substrate and the solvent, affording the product of R−I bond cleavage by elimination, substitution, α-carbon oxidation, or rearrangement.[7]

Results and Discussion

Cyclization of Secosteroid 1 to an A/B *Trans*-Fused Oxasteroid. We wondered if the oxygen in the carbonyl group at C-5 in secosteroid **1** could displace the C-7 iodine leaving group. In that case, a pyranosil oxocarbenium ion would be formed which, in the presence of water, would yield hemiketal **3** with the desired stereochemistry at C-5 (Scheme 2). Oxidation of iodine compounds with peroxyacids has been the subject of several studies,[6,7] but to our knowledge it has not been used for hemiketal formation. Hemiketal formation was also achieved by this procedure with the γ-iodo ketone moiety present in 18-iodo-20-keto steroids (see below). Table 1 summarizes the different conditions assayed for reaction of secosteroid **1** with *m*-CPBA. When 2 equiv of the peracid (more than the theoretical requirement for alkyl iodide oxidation[6]) was used in dichloromethane saturated with water (entry 1), 5α-hydroxy-6-oxasteroid **3** was isolated in 33% yield and unreacted compound **1** was recovered among other minor products. The best yield was obtained with 5 equiv of *m*-CPBA in Cl_2CH_2−H_2O at 0 °C (entry 5); changing the solvent to THF−H_2O

† Tel/Fax: 54 1 788-6915. e-mail: burton@quimor.qo.fcen.uba.ar

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(1) Suginome, H.; Yamada, S.; Wang, J. B. *J. Org. Chem.* **1990**, *55*, 2170.

(2) Huisman, H. O. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 240.

(3) Nicoletti, D.; Ghini, A. A.; Brachet-Cota, A. L.; Burton, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1089.

(4) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976 and references cited therein. See also: (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983, pp 40−41.

(5) Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 822.

(6) Macdonald, T. L.; Narasimhan. N.; Burka, L. T. *J. Am. Chem. Soc.* **1980**, *102*, 7760 and references cited therein.

(7) Lee J.; Oh, J.; Jin, S.-j.; Choi, J.-R; Atwood, J. L.; Cha, J. K. *J. Org. Chem.* **1994**, *59*, 6955 and references cited therein.

S0022-3263(96)00108-9 CCC: $12.00

Scheme 2

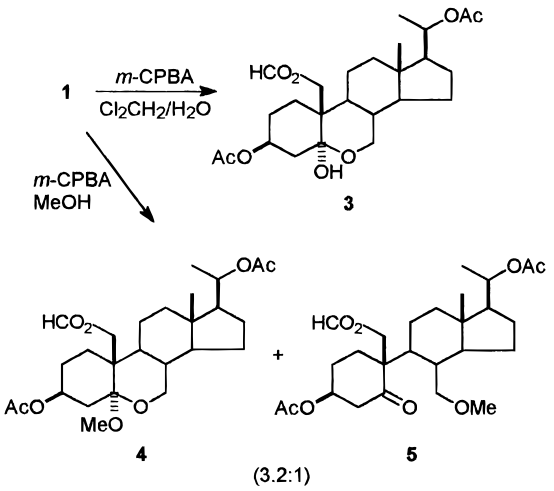


Table 1. Reaction of Iodo Ketones 1 and 9 with *m*-CPBA

entry	substrate	*m*-CPBA (equiv)	solvent[a]	time (h)	temp (°C)	product (yield, %)[b]
1	**1**	2	A	2	rt	**3** (33)
2	**1**	3	A	5	rt	**3** (38)
3	**1**	4	A	5	0	**3** (52)
4	**1**	4	B	5	0	**3** (52)
5	**1**	5	A	7	0	**3** (67)
6	**1**	8[c]	C	5	rt	**4** (59), **5** (18)
7	**9**	5	A	6	0	**12** (61)
8	**9**	5	B	4	rt	**12** (10), **10** (51)
9	**9**	5	B	3	rt	**10** (64)
10	**9**	6[c]	C	6	rt	**13** (97)[d]

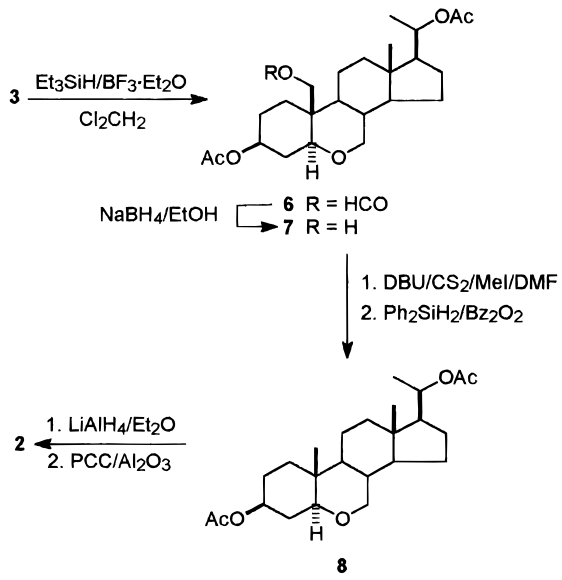
[a] A, Cl_2CH_2 saturated with H_2O; B, THF−H_2O (2:1); C, dry methanol. [b] Yields correspond to isolated products. [c] Dry *m*-CPBA was used. [d] This compound was partially hydrolyzed to **10** during chromatography. Yield corresponds to crude reaction product which was essentially pure by ^{1}H NMR.

(entry 4) did not improve the yield. When the reaction was carried out in methanol under anhydrous conditions (entry 6), the main product was methyl ketal **4**; the 7-methoxy derivative **5**, arising by direct nucleophilic attack of methanol at C-7 of the iodoso intermediate, was formed as a minor product. The latter results are consistent with the formation of the intermediate pyranosyl oxocarbenium ion postulated above, as the major reaction path.

The structures of hemiketal **3** and methyl ketal **4** and their stereochemistry at position 5 were confirmed by ^{1}H and ^{13}C NMR (proton decoupled and DEPT). The 3-H$^\alpha$ resonance (δ 5.05 for **3** and δ 4.78 for **4**) was especially diagnostic of the axial position of this hydrogen, indicative of the chair conformation of the A ring in an A/B *trans*-fused steroid. The carbon resonance at 97.3 ppm, which is typical of a hemiketal carbon assigned to C-5, confirmed the structure of compound **3**. This resonance was shifted to 99.7 ppm in methyl ketal **4**.

Stereoselective Reduction of Hemiketal 3. The conversion of hemiketal **3** to oxasteroid **6** with $ZnBH_4$/TMSCl in DME at 0 °C[8] occurred in low yield (30%). However a 75% yield was attained with $Et_3SiH/BF_3{\cdot}Et_2O$ (Cl_2CH_2, −15 °C, 1 h) (Scheme 3).[9] As above, the attack of the nucleophile on the oxocarbenium intermediate (in this case hydride) occurred from the less hindered α face with stereoselective formation of the 5α-H-6-oxasteroid **6**.

Scheme 3



The structure of compound **6** was confirmed by ^{1}H and ^{13}C NMR spectroscopy; the stereochemistry at C-5 was evident from the *J* values in the ^{1}H NMR spectrum. Two resonances were of special diagnostic value: that at 3.10 ppm (dd, J = 12.8 and J = 3.6 Hz) was attributed to the 5-H$^\alpha$ and that at 4.76 ppm assigned to 3-H$^\alpha$. Final confirmation of the stereochemistry at C-5 was carried out at a later stage on compound **8** based on its NOESY spectrum, as all the oxapregnanes synthesized had identical configuration at this position (see below).

Synthesis of 6-Oxa-5α-pregnane 2. The regioselective deprotection of the 19-hydroxy group in compound **6** was attempted with different methods ranging from basic ($KHCO_3$ in methanol or methanol−water) to acidic conditions (TsOH in methanol). In all cases, mixtures of products with partial deprotection of the 3-hydroxy group resulted.[10] The desired product **7** was finally obtained in good yield (96%) by reduction with $NaBH_4$ at −10 °C; under this very mild and controlled condition, the 3-acetate was not affected even when a very large excess of reagent (*ca.* 15:1) was used.

As in the 5-β series,[3] deoxygenation of the primary hydroxyl group attached at C-19 was carried out using the Barton procedure, by reduction of the 19-dithiocarbonate with diphenylsilane which gave **8** in 80% yield (56% from **7**).[11] The NOESY spectrum of the latter compound gave us clear evidence of the *trans*-fusion of rings A and B, showing strong NOEs of 3-H$^\alpha$, 7-H$^\alpha$, and 9-H$^\alpha$ with 5-H$^\alpha$ and of the 10-methyl hydrogens with 4-H$^\beta$ and 8-H$^\beta$ (Figure 1). Deacetylation with $LiAlH_4$ to the diol, and oxidation with PCC on alumina,[12] yielded 6-oxa-5α-pregnane-3,20 dione (**2**) in 22% overall yield from **1**.

(8) Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *J. Org. Chem.* **1987**, *52*, 2594.

(9) The method used was essentially a hybrid of several reported ones. For related examples, see: Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417 and Lewis *et al.* in ref 4.

(10) With $KHCO_3$, diacetate **7** was obtained predominantly (*ca.* 70% yield), but with TsOH the 3,19-diol was the major product.

(11) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *47*, 8969 and references cited therein. In the 5β-series, tributyltin hydride was used for reduction of the dithiocarbonate to the analogous 6-oxa-5β-pregnane in 63% yield (ref 3). However, when diphenylsilane/benzoyl peroxide was used, the yield increased to 82%; thus the latter method was used in the present preparation.

(12) Cheng, Y.-S.; Liu, W.-L.; Chen, S.-h. *Synthesis* **1980**, 223.

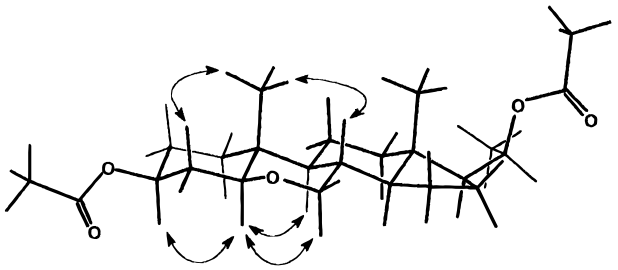


Figure 1. Most stable conformer (PM3, AMPAC 5.0) of oxasteroid **8**, showing relevant observed NOEs.

Oxidative Cyclization of 18-Iodo-20-ketopregnanes. To determine the scope of the oxidative cyclization of iodo ketones used above, we tried this reaction on steroids having a γ-iodo ketone moiety. Cyclization of 18-iodo-20-ketopregnanes to the corresponding hemiketals with silver acetate is a well-known procedure which constitutes a key step in the preparation of several steroids of biological significance.[13] As an alternative procedure and based on the results obtained above, we tried this cyclization with *m*-CPBA. It should be noted that silver ion promoted cyclization of secosteroid **1** ocurred in very low yields.

When 18-iodoprogesterone (**9**) was reacted with *m*-CPBA under the same conditions as those used for the preparation of **3** (Table 1, entry 7), a single product was obtained in 61% yield. This compound was identified as 18-acetoxytestosterone (**12**) on the basis of its ^{1}H and ^{13}C NMR spectra. It should be noted that the latter compound has structural features that make it a suitable precursor for naturally occurring steroids of biological importance.[14]

When the reaction was stopped after only 1 h, a transient species could be detected in the ^{1}H NMR spectra of the reaction mixture showing typical resonances for aromatic hydrogens of a *m*-CPBA ester and an 18-oxygenated steroid. Attempts to purify this compound by chromatography were unsuccessful, as it decomposed on contact with the adsorbent (compound **12** resulted from the attempted purification of this intermediate over silica gel). The structure of the intermediate was tentatively assigned as the peroxyester **11**, similar to those formed in the Baeyer−Villiger reaction.[15] A plausible mechanism for the formation of these compounds is depicted in Scheme 4 (path a) in which the peroxyacid attacks the furanosic oxocarbenium ion intermediate in a Baeyer−Villiger like reaction. The regioselective cleavage of the intermediate cyclic ion derived from **11** may be explained by assuming that the steric bulk of the electrophile H^+ is small and thus favors thermodynamic protonation of the oxygen on a secondary carbon.[16]

From the above mechanism, it may be predicted that a high concentration of water would compete favorably with *m*-CPBA as a nucleophile in the addition to the intermediate oxocarbenium ion. The expected product of this reaction would be 18-hydroxyprogesterone **10** (Scheme 4, path b). Thus, when **9** was reacted with *m*-CPBA in THF−H_2O (2:1) for 4 h at rt[17] (Table 1, entry 8), a mixture of compounds **10** and **12** was obtained in a 5:1 ratio (according to the ^{1}H-NMR spectra). Adjusting the reaction time to 3 h (entry 9) allowed us to obtain **10** in 64% yield. In a similar way when the reaction was carried out in methanol under anhydrous conditions (entry 10) the methyl ketal **13** was obtained. No 18-methoxy derivatives were obtained in the latter case, as the neopentylic C-18 is highly hindered toward intermolecular nucleophilic attack.

Conclusions. Cyclic hemiketal formation from γ- and δ-iodo ketones has been achieved with the intermediacy of iodosyl species. The resulting oxocarbenium ions react with available nucleophiles (*e.g.*, H_2O, methanol, *m*-CPBA) to give hemiketals, ketals, or Baeyer−Villiger type products depending on reaction conditions, ring size, and/or steric hindrance. This new methodology allowed us to synthesize 6-oxa-5α-pregnanes with excellent stereoselectivity.

Experimental Section

Melting points are uncorrected. IR spectra were recorded in KBr pellets. ^{1}H and ^{13}C NMR spectra were measured at 200.13 and 50.32 MHz, respectively, in $CDCl_3$. Chemical shifts are downfield from TMS as internal standard, and *J* values are in hertz. NMR assignments, when given, are based on DEPT and 2D spectra (COSY-45, NOESY and HETCOSY). The electron impact mass spectra were obtained at 70 eV by direct inlet. Semiempirical calculations were performed with AMPAC 5.0 (Semichem). All solvents used were reagent grade. Solvents were evaporated at *ca.* 45 °C under vacuum. Dry *m*-CPBA was prepared by dissolving 80% *m*-CPBA in anhydrous Cl_2CH_2, drying with anhydrous Na_2SO_4 (4 h), evaporation of the solvent under a stream of N_2, and drying of the residue under vacuum (1 h, rt, 5×10^{-4} Torr). 3β,20β-Diacetoxy-19-(formyloxy)-7-iodo-6-nor-5,7-secopregnan-5-one (**1**) was prepared from pregnenolone acetate (3β-acetoxypregn-5-en-20-one) in 50% yield, as single product, using the procedure described previously[3] followed by chromatography on octadecyl-functionalized silica gel (Aldrich) with methanol−water as eluent. 18-Iodopregn-4-ene-3,20-dione (**9**) was prepared from 20β-hydroxypregn-4-en-3-one in 55% yield as described previously[18] and purified by chromatography on octadecyl-functionalized silica gel (Aldrich).

3β,20β-Diacetoxy-5α-hydroxy-19-(formyloxy)-6-oxapregnane (3). To a solution of 80% *m*-CPBA (1.00 g, containing 4.64 mmol) in Cl_2CH_2 (15 mL) and H_2O (0.1 mL) at 0 °C was added rapidly a solution of secosteroid **1** (0.527 g, 0.91 mmol) in Cl_2CH_2 (15 mL). The homogeneous solution was stirred at 0 °C for 7 h, diluted with ether, washed successively with 5% aqueous $Na_2S_2O_3$, a saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with ethyl acetate−hexane as eluent yielded hemiketal **3** (0.287 g, 67% from **1**); mp 148−150 °C (from acetone−hexane). IR (cm^{-1}): 3440, 1728, 1246, 1166, 1037. ^{1}H NMR (δ): 0.65 (3H, s), 1.14 (3H, d, J = 6.0), 2.00 (3H, s), 2.02 (3H, s), 3.51 (1H, dd, J = 5.0, 11.0), 3.72 (1H, t, J = 11.0), 4.56 (1H, d, J = 12.8), 4.63 (1H, d, J = 12.8), 4.83 (1H, m), 5.05 (1H, tt, J = 5.0, 11.0), 8.12 (1H, s). ^{13}C NMR (δ): 12.8 (CH_3), 19.9 (CH_3), 21.3 (CH_3), 21.4 (CH_3), 23.2 (CH_2), 25.0 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 29.7 (CH_2), 34.3 (CH), 39.3

(13) (a) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209. (b) Choay, P.; Monneret, C.; Khuong-Hun Q. *Bull. Soc. Chim. Fr.* **1973**, 1456. (c) Kirk, D. N.; Rajagopalan, M. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1860. (d) For a related approach via 18-nitrates, see: Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2252.

(14) For example, the neonatal metabolite 3β,16α,18-trihydroxy-5-androsten-17-one and related compounds. Das, R.; Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1821.

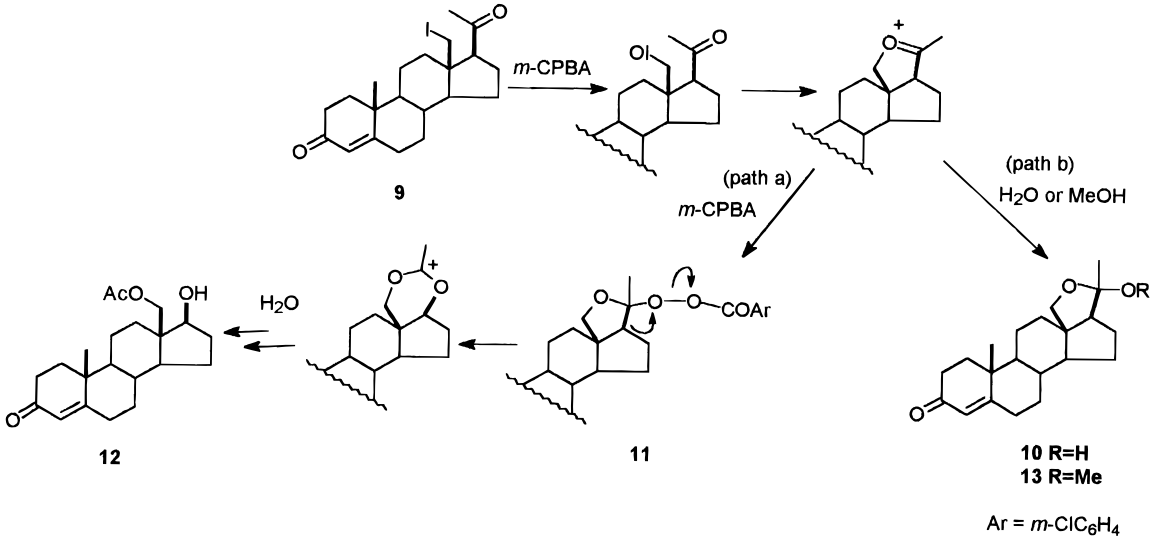
(15) March, J. *Advanced Organic Chemistry*, 4th Ed.; John Wiley & Sons: New York, 1992; pp 1098−1099.

(16) Compound **12** is not the thermodynamic product obtained by acyl transfer. On standing in Cl_2CH_2 in the presence of catalytic amounts of acid, **12** yields a 1:1 mixture of **12** and the 17-acetoxy-18-hydroxy isomer.

(17) The reaction was very slow at 0 °C.

(18) Benedetti, M. O. V.; Burton, G. *Org. Prep. Proced. Int.* **1992**, *24*, 701 and references cited therein.

Scheme 4



(CH_2), 39.5 (CH_2), 41.8 (C), 42.7 (CH), 42.8 (C), 51.7 (CH), 54.5 (CH), 62.7 (CH_2), 64.6 (CH_2), 70.6 (CH), 72.7 (CH), 97.3 (C), 160.8 (CH), 170.3 (C), 170.7 (C). MS (*m*/*z*, %): 388 (M − AcOH − H_2O, 40), 342 (388 − HCO_2H, 19). HRMS: calcd for $C_{23}H_{32}O_5$ (M − AcOH − H_2O) 388.2249, found 388.2248.

3*β*,20*β*-Diacetoxy-19-(formyloxy)-6-oxa-5α-pregnane (6). A solution of hemiketal **3** (0.277 g; 0.59 mmol), triethysilane (0.975 mL, 6.1 mmol), and $BF_3{\cdot}Et_2O$ (0.750 mL, 6.1 mmol) in dry Cl_2CH_2 (29 mL) was stirred at −15 °C under N_2 for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, the cooling bath was removed, and the reaction mixture was allowed to warm to rt with vigorous stirring. The solution was diluted with ether, washed successively with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with ethyl acetate−hexane as eluent yielded **6** (0.200 g, 75% from **3**) homogeneous by TLC; mp 165−167 °C (from acetone−hexane). IR (cm^{-1}): 1733, 1244, 1167, 1103, 1036. ^1H NMR (δ): 0.66 (3H, s), 1.15 (3H, d, J = 6.1) 2.00 (3H, s), 2.03 (3H, s), 3.10 (1H, dd, J = 3.6, 12.8), 3.12 (1H, t, J = 11.0), 3.91 (1H, dd, J = 5.0, 11.0), 4.52 (2H, AB q, J = 12.3), 4.76 (1H, m), 4.84 (1H, m), 8.11 (1H, s). ^{13}C NMR (δ): 12.7 (CH_3), 19.9 (CH_3), 21.2 (CH_3), 21.4 (CH_3), 21.6 (CH_2), 23.3 (CH_2), 25.6 (CH_2), 26.6 (CH_2), 27.3 (CH_2), 32.9 (CH_2), 35.5 (CH), 38.6 (C), 39.4 (CH_2), 42.7 (C), 51.6 (CH), 53.2 (CH), 54.5 (CH), 61.7 (CH_2), 70.8 (CH), 72.6 (CH), 73.7 (CH_2), 82.4 (CH), 160.9 (CH), 170.4 (C). MS (*m*/*z*, %): 450 (M^+, 0.6), 390 (M − AcOH, 10), 344 (390 − HCO_2H, 3), 330 (M − 2 AcOH, 11). HRMS: calcd for $C_{23}H_{34}O_5$ (M − AcOH) 390.2406, found 390.2407.

3*β*,20*β*-Diacetoxy-19-hydroxy-6-oxa-5α-pregnane (7). A solution of **6** (0.190 g, 0.42 mmol) and $NaBH_4$ (0.122 g, 3.23 mmol) in absolute ethanol (30 mL) was stirred at −10 °C for 3 h, acidified (pH 5) with 1 M HCl, and then neutralized with a 10% aqueous $NaHCO_3$ solution. The solution was concentrated *in vacuo* to a volume of 10 mL, diluted with water, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with ethyl acetate−hexane as eluent yielded **7** (0.171 g, 96% from **6**) homogeneous by TLC; mp 179−181 °C (from acetone−hexane). IR (cm^{-1}): 3460, 1732, 1244, 1038. ^1H NMR (δ): 0.71 (3H, s), 1.15 (3H, d, J = 6.1), 2.01 (3H, s), 2.03 (3H, s), 3.15 (1H, dd, J = 4.7, 12.4), 3.16 (1H, t, J = 11.0), 3.78 (1H, d, J = 11.9), 3.92 (1H, dd, J = 5.0, 11.0), 4.12 (1H, d, J = 11.9), 4.72 (1H, m), 4.84 (1H, m). ^{13}C NMR (δ): 12.9 (CH_3), 19.8 (CH_3), 21.1 (CH_2), 21.2 (CH_3), 21.4 (CH_3), 23.2 (CH_2), 25.6 (CH_2), 26.9 (CH_2), 28.6 (CH_2), 32.9 (CH_2), 36.2 (CH), 38.7 (C), 39.3 (CH_2), 42.9 (C), 52.1 (CH), 53.5 (CH), 54.5 (CH), 62.0 (CH_2), 71.0 (CH), 72.7 (CH), 73.8 (CH_2), 83.7 (CH), 170.3 (C); FAB MS (3-nitrobenzyl alcohol + KCl) (*m*/*z*, %): 461 (M + K, 100). Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.2; H, 9.1. Found: C, 67.8; H, 8.7.

3*β*,20*β*-Diacetoxy-6-oxa-5α-pregnane (8). To a solution of 19-hydroxyoxasteroid **7** (0.161 g, 0.38 mmol), and DBU (0.23 mL, 1.55 mmol) in DMF (2.0 mL) was added CS_2 (2.1 mL, 34.8 mmol) and the reaction mixture was stirred for 45 min at rt. Methyl iodide (4.2 mL, 67.5 mmol) was added and the stirring continued for 45 min. The reaction mixture was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with ethyl acetate−hexane as eluent yielded the 19-dithiocarbonate (0.136 g, 70% from **7**). ^1H NMR (δ): 0.64 (3H, s), 1.15 (3H, d, J = 6.1); 2.01 (3H, s), 2.03 (3H, s), 2.57 (3H, s), 3.12 (1H, dd, J = 5.1, 12.1), 3.14 (1H, t, J = 11.2), 3.91 (1H, dd, J = 4.9, 11.2), 4.80 (2H, m), 4.85 (1H, d, J = 12.1), 5.03 (1H, d, J = 12.1). A solution of the dithiocarbonate (0.136 g, 0.27 mmol) in xylene (1.0 mL) was heated to 150 °C under N_2, and diphenylsilane (0.250 mL, 1.35 mmol) was added followed by 11 × 0.06 mL aliquots of a solution of benzoyl peroxide in xylene (0.129 g/mL, 1.8 equiv) at 20 min intervals. The solvent was evaporated, and the residue was chromatographed on silica gel with dichloromethane−hexane as eluent yielding **8** (0.086 g, 56% from **7**); mp 139−140 °C (from ethanol−water). IR (cm^{-1}): 1732, 1244, 1117, 1053, 1034. ^1H NMR (δ): 0.65 (3H, s, 13-Me), 0.92 (3H, s, 10-Me), 1.14 (3H, d, J = 6.1, 20-Me), 2.01 (3H, s, Ac), 2.03 (3H, s, Ac), 2.93 (1H, dd, $J_{5\alpha4\alpha}$ = 3.8, $J_{5\alpha4\beta}$ = 12.2, 5-H^α), 3.09 (1H, t, $J_{gem} \approx J_{7\alpha,8}$ = 11.0, 7-H^α), 3.86 (1H, dd, $J_{7\beta,8}$ = 4.7, J_{gem} = 11.0, 7-H^β), 4.69 (1H, m, 3-H), 4.83 (1H, m, 20-H). ^{13}C NMR (δ): 11.7 (CH_3, C-19), 12.7 (CH_3, C-18), 19.9 (CH_3, C-21), 20.4 (CH_2, C-11), 21.3 and 21.5 (CH_3, Ac), 23.4 (CH_2, C-1), 25.7 (CH_2, C-15), 26.8 (CH_2, C-16), 32.1 (CH_2, C-2), 32.8 (CH_2, C-4), 35.3 (CH, C-8), 35.9 (C, C-10), 39.1 (CH_2, C-12), 42.8 (C, C-13), 51.4 (CH, C-9), 53.2 (CH, C-14), 54.7 (CH, C-17), 71.5 (CH, C-3), 72.7 (CH, C-20), 73.6 (CH_2, C-7) 82.5 (CH, C-5), 170.4 (C, Ac). MS (*m*/*z*, %): 406 (M^+, 2), 346 (M − AcOH, 27). Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.9, H, 9.4. Found: C, 70.6; H, 9.2.

6-Oxa-5α-pregnane-3,20-dione (2). A solution of diacetate **8** (0.076 g, 0.19 mmol) and $LiAlH_4$ (0.076 g, 2.0 mmol) in dry ether (7.5 mL) was stirred at rt for 3 h under N_2. The reaction mixture was treated successively with ethyl acetate and 10% aqueous HCl. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to dryness, yielding the 3,20-diol (0.060 g, 96% from **8**). ^1H NMR (δ): 0.77 (3H, s), 0.92 (3H, s), 1.13 (3H, d, J = 6.1), 2.89 (1H, dd, J = 3.8, 12.1), 3.09 (1H, t, J = 11.0), 3.61 (1H, m), 3.20 (1H, m), 3.87 (1H,dd, J = 4.7, 11.0). The crude diol (0.060 g, 0.18 mmol) in dry CH_2Cl_2 (4.0 mL) was stirred at rt with PCC on alumina (1.1 g, 1 mmol/g, 1.1 mmol), for 4 h under N_2. The resultant brown mixture was diluted with ether, percolated through Florisil, eluting with ether and Cl_2CH_2, and

evaporated to dryness. Chromatography on silica gel with ethyl acetate−hexane as eluent yielded **2** (0.048 g, 81% from **8**); mp 187−188 °C (from ethanol). IR (cm^{-1}): 1709, 1388, 1364, 1072, 1039. ^1H NMR (δ): 0.68 (3H, s, 13-Me), 1.09 (3H, s, 10-Me), 2.13 (3H, s, 20-Me), 3.19 (1H, t, $J_{gem} \approx J_{7\alpha,8} = 11.1$, 7-H$^{\alpha}$), 3.24 (1H, t, $J_{5\alpha,4\beta} \approx J_{5\alpha,4\alpha} = 9.5$, 5-H$^{\alpha}$), 3.93 (1H, dd, $J_{7\beta,8}$ 4.7, $J_{gem} = 11.1$, 7-H$^{\beta}$). ^{13}C NMR (δ): 11.0 (CH_3, C-18), 13.6 (CH_3, C-19), 20.7 (CH_2, C-11), 23.3 (CH_2, C-15), 23.6 (CH_2, C-16), 31.6 (CH_3, C-21), 32.1 (CH_2, C-1), 35.2 (CH, C-8), 35.9 (C, C-10), 37.5 (CH_2, C-2), 38.7 (CH_2, C-4), 44.1 (CH_2, C-12), 44.4 (C, C-13), 52.1 (CH, C-9), 52.7 (CH, C-14), 63.1 (CH, C-17), 73.2 (CH_2, C-7), 82.6 (CH, C-5), 209.0 (C, C-3 and C-20). MS (*m*/*z*, %): 318 (M^+, 7), 300 (M − H_2O, 7). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.8.

Reaction of Secosteroid 1 with *m*-CPBA/MeOH. 3β,20β-Diacetoxy-5α-methoxy-19-(formyloxy)-6-oxapregnane (4). To a solution of dry *m*-CPBA (from 0.275 g of *m*-CPBA 80%, containing 1.27 mmol) in dry MeOH (5 mL) at rt was added rapidly a solution of secosteroid **1** (0.09 g, 0.16 mmol) in dry methanol (5 mL). The homogeneous solution was stirred at rt for 5 h and the reaction stopped by addition of saturated aqueous $Na_2S_2O_3$ (2 mL). The resulting mixture was concentrated to 1/5 of the volume, extracted with Cl_2CH_2, washed successively with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel with ethyl acetate−hexane (1:9) as eluent yielded methyl ketal **4** (0.045 g, 59% from **1**); mp 94−95 °C (from acetone−hexane). IR (cm^{-1}): 1728, 1456, 1367, 1244, 1168, 1037. ^1H NMR (δ): 0.64 (3H, s), 1.14 (3H, d, $J = 6.1$), 2.00 (3H, s), 2.02 (3H, s), 2.22 (1H, ddd, $J = 1.1, 5.1, 13.7$), 3.23 (3H, s), 3,27 (1H, t, $J = 11.0$), 3.50 (1H, dd, $J = 5.1, 11.0$), 4.61 (2H, s), 4.78 (1H, m), 4.83 (1H, m), 8.12 (1H, s). ^{13}C NMR (δ): 12.8 (CH_3), 19.9 (CH_3), 21.2 (CH_3), 23.2 (CH_2), 24.8 (CH_2), 25.7 (CH_2), 26.3 (CH_2), 31.9 (CH_2), 34.2 (CH), 39.5 (CH_2), 42.3 (C), 42.5 (CH and CH_2), 42.8 (C), 47.0 (CH_3), 51.8 (CH), 54.4 (CH), 63.0 (CH_2), 65.0 (CH_2), 69.8 (CH), 72.7 (CH), 99.7 (C), 160.8 (CH), 170.3 (C), 170.5 (C). MS (*m*/*z*, %): 480 (M^+, 2), 434 (M − HCO_2H, 15), 420 (M − AcOH, 100), 388 (420 − MeOH, 13). Anal. Calcd for $C_{26}H_{40}O_8$: C, 65.0; H, 8.4. Found: C, 64.8; H, 8.6. Further elution with ethyl acetate−hexane (2:8) yielded methoxy derivative **5** (0.014 g, 18% from **1**). IR (cm^{-1}): 1730, 1373, 1247, 1169, 1118. ^1H NMR (δ): 0.63 (3H, s), 1.15 (3H, d, $J = 6.1$), 2.01 (3H, s), 2.03 (3H, s), 2.45 (1H, dt, $J = 14.8, 2.0$), 3.06 (3H, s), 3,06 (1H, m), 3.25 (1H, dd, $J = 2.4, 10.0$), 3.34 (1H, dd, $J = 4.4, 14.8$), 4.31 (1H, d, $J = 11.7$), 4.56 (1H, d, $J = 11.7$), 4.85 (1H, m), 5.38 (1H, br s, $W_{1/2} = 9$), 8.11 (1H, s). ^{13}C NMR (δ): 12.1 (CH_3), 19.8 (CH_3), 21.2 (CH_3), 21.4 (CH_3), 23.1 (CH_2), 24.4 (CH_2), 24.7 (CH_2), 25.1 (CH_2), 28.1 (CH_2), 39.0 (CH), 39.5 (CH and CH_2), 42.2 (C), 42.9 (CH_2), 51.5 (CH), 53.7 (C), 55.1 (CH), 57.6 (CH_3), 64.7 (CH_2), 70.4 (CH_2), 72.7 (CH), 72.8 (CH), 160.9 (CH), 170.3 (C), 211.3 (C). MS (*m*/*z*, %): 480 (M^+, 3), 420 (M − AcOH, 15), 388 (420 − MeOH, 100), 328 (388 − AcOH, 40). HRMS: calcd for $C_{26}H_{40}O_8$ 480.2723, found 480.2725.

Reaction of 18-Iodopregn-4-ene-3,20-dione (9) with *m*-CPBA/THF−H_2O. 18-Hydroxypregn-4-ene-3,20-dione (10). A solution of **9** (0.044 g, 0.1 mmol) in THF (2.0 mL) was added rapidly to a solution of 80% *m*-CPBA (0.108 g, containing 0.5 mmol) in THF (2.0 mL) and water (2.0 mL) and stirred for 3 h at rt. Workup as above, followed by chromatography on Florisil with ethyl acetate−hexane as eluent, yielded 18-hydroxyprogesterone (**10**) (0.021 g, 64% from **9**); mp 157−159 °C (from acetone) (lit.[18] mp 157−159 °C); ^1H and ^{13}C NMR spectra are identical to those of an authentic standard.

Reaction of 18-Iodopregn-4-ene-3,20-dione (9) with *m*-CPBA/Cl_2CH_2−H_2O. 18-Acetoxytestosterone (12). A solution of **9** (0.044 g, 0.1 mmol) in Cl_2CH_2 (2.0 mL) was added rapidly to a solution of 80% *m*-CPBA (0.108 g, containing 0.5 mmol) in Cl_2CH_2 (2.0 mL) and water (0.010 mL) at 0 °C and stirred for 6 h at 0 °C. Workup as for **3** followed by chromatography on silica gel with ethyl acetate−hexane as eluent yielded **12** (0.021 g, 61% from **9**); mp 169−172 °C (from diethyl ether) (lit.[19] mp 170−173 °C). ^1H NMR (δ): 1.21 (3H, s), 2.10 (3H, s), 3.79 (1H, t, $J = 8.5$), 4.22 (1H, d, $J = 11.8$), 4.38 (1H,d, $J = 11.8$) and 5.73 (1H, s). ^{13}C NMR (δ): 17.4 (CH_3), 20.5 (CH_2), 21.2 (CH_3), 23.4 (CH_2), 30.9 (CH_2), 31.7 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 33.9 (CH_2), 35.6 (CH), 35.8 (CH_2), 38.6 (C), 45.3 (C), 50.4 (CH), 53.9 (CH), 62.1 (CH_2), 82.0 (CH), 124.1 (CH), 171.0 (C), 199.4 (C).

Reaction of 18-Iodopregn-4-ene-3,20-dione (9) with *m*-CPBA/MeOH. 20-Methoxy-18,20-oxidopregn-4-en-3-one (13). A solution of **9** (0.04 g, 0.091 mmol) in dry MeOH (2.0 mL) was added rapidly to a solution of dry *m*-CPBA (from 0.125 g of *m*-CPBA 80%, containing 0.58 mmol) in dry MeOH (2.0 mL) and stirred for 6 h at rt. Workup as for compound **4** afforded crude methyl ketal **13** (0.03 g, 97% from **9**). An analytical sample purified by column chromatography on silica gel had ^1H and ^{13}C NMR spectra identical to those of an authentic standard prepared from 18-hydroxyprogesterone.[20]

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **3**, **5**, and **6** and NMR peak assignments for compounds **3**, **4**, **5**, **6**, **7**, and **12** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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