Synthesis of Triamcinolone Acetonide from 9-Hydroxy-3-methoxy-17-(2-methoxy-3-oxazolin-4-yl)androsta-3,5,16-triene[1]

Daan van Leusen and Albert M. van Leusen*

Department of Organic and Molecular Inorganic Chemistry, Groningen Center for Catalysis and Synthesis, Groningen University, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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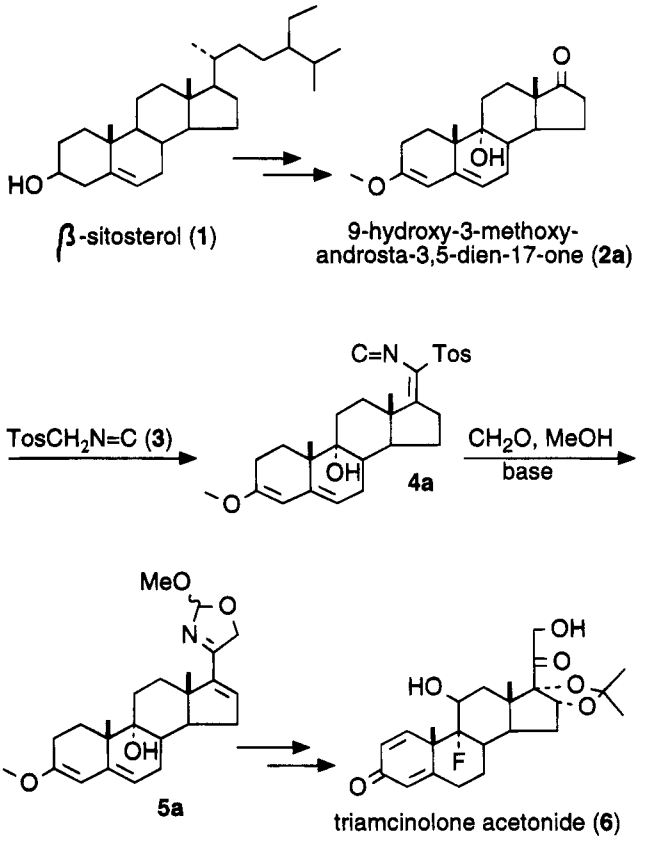
In a series of papers[2,3] we and others have shown that 17-(isocyano-tosylmethylene)-steroids **4** are useful precursors in the synthesis of 20-oxosteroids at large,[2a–c] and 17-(hydroxyacetyl)steroids in particular.[2d,3] 17–(Hydroxyacetyl) side chains – typical of corticosteroids – are conveniently build up in three reaction steps (Scheme 1), starting with 17-oxosteroids such as 9-hydroxy-3-methoxyandrosta-3,5-dien-17-one (**2a**).[2,4] Compound **2a** is available from 9-hydroxyandrost-4-ene-3,17-dione,[5] which is an intermediate of increasing importance, obtained by fermentation of plant sterols, like β-sitosterol (**1**), from soybeans.[6]

This paper describes a new synthesis of triamcinolone acetonide (**6**), which is a widely used anti-inflammatory drug.[7] The present discussion starts with (2'-*R*,*S*)-9-hydroxy-3-methoxy-17-(2-methoxy-3-oxazolin-4-yl)-androsta-3,5,16-triene (**5a**).[2d] The two carbons – C20 and C21 – of the intended 17-(hydroxyacetyl) group (of **6**) are already present in compound **5a**. They have been introduced previously in two steps. First, a formal Knoevenagel-type condensation of tosylmethyl isocyanide (TosMIC, **3**) with the 17-oxo group of **2a** gives **4a**, in which the TosMIC-methylene group provides C20.[2c] Next, the C21 carbon is introduced by reaction of **4a** with formaldehyde and MeOH to give **5a**. The conversion of **4a** to **5a** takes place with concomitant formation of the C16,C17 double bond through allylic deprotonation of **4a**.[2a,d] This double bond is nicely set up for the bis-hydroxylation that eventually leads to triamcinolone acetonide **6**. In fact, it is the purpose of this paper to demonstrate, through the synthesis of **6**, the versatility of the 16-dehydro-17-(2-methoxy-3-oxazolin-4-yl) moiety of compounds **5** in three ways: (1) as a precursor, as well as a protective group, of 17-(hydroxyacetyl) side chains; (2) as a precursor of *formyl* protected 17-(hydroxyacetyl) side chains; and, (3) as a handle for the introduction of the C16,C17 oxygen functions in compounds like **6**. The original synthesis of triamcinolone acetonide (**6**) by Bernstein *et al.* is based on cortisol-21-acetate, in which C20 and C21 are present from the beginning, and which uses a C11β-OH, rather than the C9α-OH as in **2a-5a**, for the introduction of the fluoride function at C9.[8]

Scheme 1



Complete hydrolysis (4 N H_2SO_4, rt, 18 h, Scheme 2) of 2-methoxy-3-oxazolines **5** was previously shown to give 17-(hydroxyacetyl)steroids **8**, whereas *partial* hydrolysis (60% aqueous HCOOH, rt, 45 min) gave C21-formates **7**.[2d] Bis-hydroxylation ($KMnO_4$) of the C16,C17 double bond to form compounds of type **10 - 12**, as well as the introduction of the 9α-fluoro and 11β-hydroxy substituents in the ultimate product **6**, requires protection of the C21-hydroxy group. Normally the acetyl group is used for these purposes.[9] A case in point, due to Bernstein *et al.*,[8] is the conversion ($KMnO_4$ or OsO_4) of 3,20-dioxopregna-4,9(11),16-trien-21-yl acetate to the corresponding 16α,17α-dihydroxy derivative. Potentially, the 2-methoxy-3-oxazolinyl group of compounds **5** could serve the same goal, *i.e.* the application as a protected 17-(hydroxyacetyl) group in similar bis-hydroxylations. Although we have previously been able to epoxidize the C16,C17 double bond of methoxyoxazolinyl compound **5c** (X = H),[10] it turned out that the dienol ether group of **5a** is affected by the conditions of bis-hydroxylation ($KMnO_4$

(1) Chemistry of Sulfonylmethyl Isocyanides Part 41; For Part 40 see: ref. 2d.

(2) (a) van Leusen, D.; van Echten, E.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 469. (b) van Leusen, D.; van Leusen, A. M. *Synthesis* **1991**, 531. (c) van Leusen, D.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 393. (d) van Leusen, D.; Batist, J. N. M.; Lei, J.; van Echten, E.; Brouwer, A. C.; van Leusen, A. M. *J. Org. Chem.* **1994**, *59*, 5650.

(3) Kochanny, M. J.; VanBrocklin, H. F.; Kym, P. R.; Carlson, K. E.; O'Neil, J. P.; Bonasera, T. A.; Welch, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **1993**, *36*, 1120.

(4) The letter-indicators in the compound numbers refer to the A,B,C-ring moieties of the steroid structures as depicted in Chart 1. Note that this moiety may change during a reaction, for example the dienol ether group of the **a** series will hydrolyse with $H_3O^{\oplus}$ to the enone function of the **b** series. Scheme 1 relates to the **a** series only. Representatives of the other series appear in Table 1 and Scheme 2.

(5) (a) Carruthers, N. I.; Garshasb, S.; McPhail, A. T. *J. Org. Chem.* **1992**, *57*, 961. (b) Batist, J. N. M.; Marx, A. F.; van Zoest, W. J.; Kapur, J. C. *European patent* EP 263,569, 1987; *Chem. Abstr.* **1988**, *109*, 129460y.

(6) Wovcha, M. G.; Antosz, F. J.; Knight, J. C. Komineck, L. A.; Pyke, T. R. *Biochim. Biophys. Acta* **1978**, *539*, 308. See also ref 4.

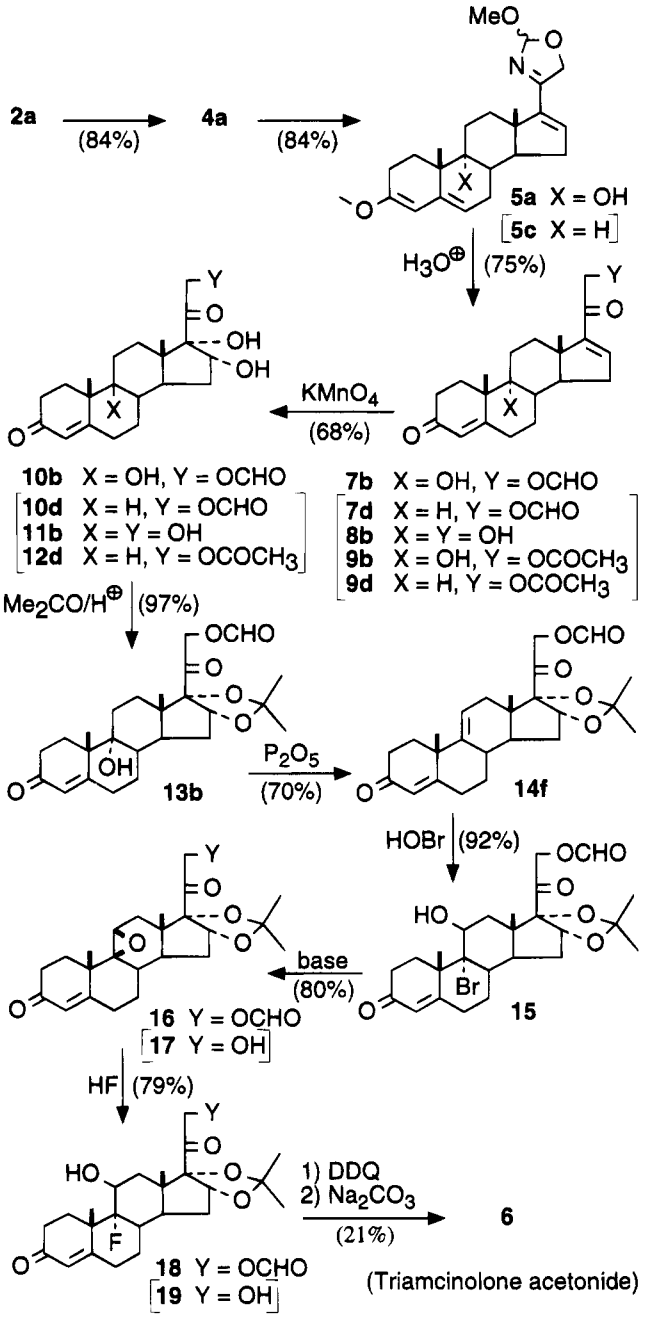
(7) Lednicer, D.; Mitcher, L. A. in *The Organic Chemistry of Drug Synthesis*. Vol I, Wiley, New York, 1977, p 201.

(8) (a) Bernstein, S.; Lenhard, R, H.; Allen, W. S.; Heller, M.; Littell, R.; Stolar, S. M.; Feldman, L. I.; Blank, R. H. *J. Am. Chem. Soc.* **1959**, *81*, 1689. (b) Heller, M.; Stolar, S. M. ; Bernstein, S. *J. Org. Chem.* **1961**, *26*, 5044.

(9) Gardi, R.; Ercoli, A. in *Organic Reactions in Steroid Chemistry*, Fried, J.; Edwards, J. A. Eds., Vol I, Chapter 7, Reinhold, New York 1972.

0022-3263/94/1959-7534$04.50/0

Scheme 2. Synthesis of Triamcinolone Acetonide (6) from 9-Hydroxy-3-methoxy-17-(2-methoxy-3-oxazolin-4-yl)androsta-3,5,16-triene (5a)[a]



[a] For meaning of letter-indicators in compound-numbers, see Chart 1 and ref 4. Yields refer to the **a/b** series, the mainstream of this scheme. **Analogous compounds given between square brackets are not necessarily prepared according to this scheme (see text).**

or OsO_4). To prevent oxidation of the A,B ring system under these conditions, removal of the enone protection is necessary (acid hydrolysis of the dienol ether function). Such an approach, however, would lead to a rather roundabout synthesis of triamcinolone acetonide (**6**):

(10) The epoxide was obtained in 59% yield, using *t*-BuOOLi (1.5 equiv) in THF, 40 °C, 36 h. Other examples of the use of the 2-methoxy-3-oxazoline protective group are: Reaction of **5c** with MeMgI and 10 mol% of CuCl followed by acid hydrolysis to provide 21-hydroxy-16α-methylpregn-4-ene-3,20-dione in nearly quantitative yield; Reduction of **5c** with $NaBH_4$ (or 9-BBN-H) followed by acid hydrolysis to give desoxycorticosterone in 94% yield: see ref 2d and van Leusen, D., Ph.D Thesis, Groningen University 1990, Chapter V.

Chart 1. Structures of the A,B,C-Ring Moieties, Denoted by the Letters a-h, of the Steroid Derivatives 2-5 and 7-14

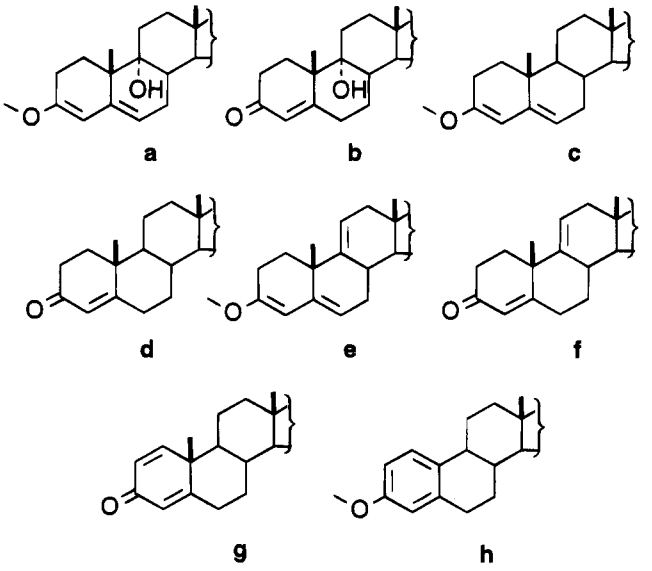


Table 1. Di- and Trihydroxysteroids 10–12 Synthesized by Bishydroxylation of 16-Dehydrosteroids using $KMnO_4$[a]

entry	product	yield (%)	mp (°C)	prepared from[b]
1	**10b**	68	214–217	**7b**
2	**10b**	60	204–217	**5a**
3	**10d**	79	196–198	**7d**
4	**10f**	77	182–184	**7f**
5	**11b**	60	224–227	**10b**
6	**11d**	67	217–220[c]	**5c**
7	**11f**	65	213 dec.	**5e**
8	**11g**	53	217–218 dec.	**5g**
9	**11h**	70	159–160	**5h**
10	**12d**	80	194–201[d]	**9d**

[a] For structures, see Scheme 2, Chart 1, and ref 4. [b] For synthesis, see ref 2b. [c] Mp lit.[19] 238–240 °C. [d] Mp lit.[19] 206–210 °C.

first, 9,21-dihydroxy-3,20-dioxopregna-4,16-diene (**8b**) has to be prepared by acid hydrolysis of **5a** (via the sequence **2a** → **4a** → **5a** → **8b**), followed by protection of the C21-hydroxy group of **8b**,[11] for example, by acetylation to **9b**. There is, however, a shorter route, based on the unique possibility to directly obtain formate **7b** (with a *formyl* protected C21–hydroxy group) by *partial* hydrolysis of **5a**, using 60% aqueous formic acid.[2d] During this process, the dienol ether group of **5a** is hydrolyzed simultaneously, as desired. It thus remained to be shown that the *formyl* protection of **7b** is equally satisfactory as the usual *acetyl* group in the next reaction steps of Scheme 2. We must emphasize here that hydrolysis of **5a** with aqueous *acetic* acid does not give acetate **9b**; the formyl carbon of **7b** originates from the isocyano carbon of **4a**; apparently there is no exchange of acid moieties during the process of hydrolysis of the methoxyoxazoline ring.

Bis-hydroxylation of either formate **7d** or acetate **9d** gave the corresponding 16α,17α-dihydroxy compounds **10d** and **12d** in 79 and 80% yield, respectively (Table 1 entries 3 and 10), showing the equivalence of the formyl and acetyl protection. The bis-hydroxylation reactions

(11) After completion of our work, Katzenellenbogen *et al.* have shown that no C21-OH protection is needed in the C16,C17 bis-hydroxylation of 21-hydroxy-16-dehydro-19-norprogesterone using stoichiometric amounts of OsO_4.[3]

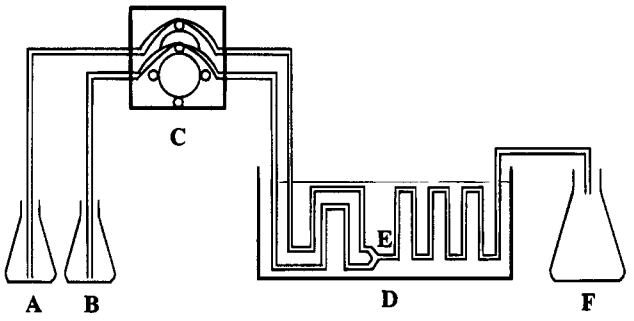


Figure 1. Setup for the $KMnO_4$ bishydroxylation reactions of 16-dehydrosteroids **7** and **9**.

were carried out with $KMnO_4$ using a simple continuous flow reactor (Figure 1), based on a method described by Hydorn *et al.* for the preparation of 16α,17-dihydroxyprogesterone.[12] The advantage of this method is that over-oxidation in this strongly exothermic process is easily prevented by using well-defined short reaction times (in the order of seconds). Also the method is applicable to large scale operations.[12] Formates **7** may but need not be isolated. Thus, the bis-hydroxylation to **10b** was carried out both with isolated **7b** as well as **7b** prepared *in situ* (from **5a** and 60% HCOOH) in 68 and 60% yield, respectively (Table 1, entries 1 and 2). Further examples are given in the same Table (entries 4, 6–9). Removal of the formyl protection was carried out on the crude products **10** to give 16α,17α,21-trihydroxysteroids **11** using 2 N HCl (rt, 17 h, entries 6–9), except in the case of **11b** (entry 5). Compound **11b** was obtained by hydrolysis with base (Na_2CO_3, THF/H_2O) to avoid elimination of the 9α-OH group.

The conversion of **10b** to triamcinolone acetonide (**6**, Scheme 2) essentially employs known chemistry, with certain adaptations to accommodate the use of the formyl protective group at the C21-hydroxyl. Reaction of **10b** with acetone and 70% $HClO_4$ gave acetonide **13b** in 97% yield, showing that the formate group is not affected under these conditions. Elimination of the 9α-hydroxy group of **13b** to the 9(11)-dehydro compound **14f** was carried out with P_2O_5 (2 mol-equiv, toluene, reflux), since the usual methods (polyphosphoric acid[13a] or *p*-toluenesulfonic acid on silica[13b]) caused loss of the formyl group. Compound **14f** was prepared independently from **10f** (Table 1) and acetone (93% yield). Reaction of **14f** with NBS and 10% aqueous $HClO_4$[14] provided bromohydrin **15** in 92% yield. When a standard procedure (KOAc, EtOH, reflux)[14] was applied to the formation of the epoxide ring of **16**, the formyl group was lost to give **17** (86% yield).[15] However, the desired epoxide **16** was obtained (80% yield) by the use of 1,1,2,2-tetramethylguanidine in DMF.[16] For the sake of comparison, the epoxide ring opening with 70% HF was carried out with the C21-formate **16** as well as the C21-unprotected counterpart **17** to give fluorides **18** and **19** in 79 and 52% yield, respectively. 1,2-Dehydrogenation of **18** (1.1 equiv of DDQ, benzene, reflux, 20 h) followed by removal of the formyl protection (Na_2CO_3, MeOH) gave triamcinolone acetonide (**6**) in a yield of 20% only. Similarly, DDQ dehydrogenation of the C21-OH deprotected compound **19** gave **6** in 40% yield. We have not tried to improve the yield of **6** from **18** or **19** by the DDQ method, since microbiological dehydrogenation of **19** with *Nocardia corallina* is known to give triamcinolone acetonide (**6**) in a much better yield (73%).[17]

Experimental Section

General Remarks. Acetone technical grade was distilled from $KMnO_4$. Other solvents and reagents were obtained commercially and used as such. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz (unless stated otherwise). APT ^{13}C NMR spectra were recorded at 75.43 MHz in $CDCl_3$; downward CH and CH_3 signals are reported as (−) chemical shifts. No ^{13}C spectra were recorded of compounds **10b**, **11b**, **11g**, **11h**, and **17**, due to extreme low solubility. Centrifugal liquid chromatography (CLC) separations were carried out on a Hitachi CLC-5 centrifugal liquid chromatograph ("chromatotron"). For the meaning of the letter-indicators **a-h** in compound-numbers, see Chart 1 and ref 4.

Apparatus. The permanganate oxidations of 16-dehydrosteroids **7** and **9d** were carried out in the setup depicted in Figure 1. Reactants are placed in flasks A and B which are connected by silicon tubing of equal length and diameter to a glass-tube reactor placed in ice-bath D. The reactor consists of three pieces (50-cm each) of bended glass tube with an internal diameter of 1.5 mm. A synchronized peristaltic pump C is used to transfer the contents of flask A and B with equal flow in precooled state via the mixing point E to flask F. Flask F contains a quenching solution ($NaHSO_3$ or $NaHCO_3$ in water) to prevent over-oxidation.[18] The reaction time, 20 s in all reactions, is defined by the flow rate with which the solutions from flasks A and B pass through the glass tube from E to F.

9,16α,17-Trihydroxy-3,20-dioxopregn-4-en-21-yl Formate (10b). From formate 7b. Flask A was charged with a solution of **7b**[2d] (3.72 g, 10.0 mmol) in acetone (300 mL) and formic acid (0.8 mL, 11 mmol), flask B with a solution of $KMnO_4$ (1.61 g, 10.2 mmol) in a mixture of water (75 mL) and acetone (225 mL), and flask F with a solution of $NaHSO_3$ (2.0 g, 19 mmol) in water (100 mL). After the reaction was complete, the contents of flask F was filtered through Celite. The Celite was extracted with CH_2Cl_2 (100 mL) and the combined filtrates were concentrated to a volume of *ca.* 10 mL. The concentrate was chilled in ice. After 1 h the solid was collected, washed with water and dried to give 2.76 g (68%) of **10b**, mp 214–217 °C (dec.) Analytically pure **10b** was obtained by one crystallization from acetone-water, mp 217 °C (dec.); $[\alpha]^{20}_D$ +61° (*c* 0.2, MeOH); IR (KBr) 3520, 3470, 3420 (OH), 1735, 1715, 1665 cm^{-1} (C=O); ^1H NMR δ 0.71 (s, 3H), 0.8–2.8 (m), 1.16 (s, 3H), 2.9–4.4 (m, 1H), 3.89 (s, 1H), 4.85 (s, br) and 4.66, 4.97, 5.02, 5.32 (AB q, 3H), 5.67 (s, 1H), 8.07 (s, 1H). Anal. Calcd for $C_{22}H_{30}O_7$ (406.480): C, 65.01; H, 7.44. Found: C, 64.8; H, 7.3. **From oxazoline 5a.** A solution of oxazoline **5a**[2d] (0.40 g, 1.0 mmol) in 60% aqueous formic acid (6 mL) was placed in flask A (Figure 1). After 1 h, in order to achieve partial hydrolysis to **7b**, the solution was diluted with acetone (54 mL). Flask B was charged with a solution of $KMnO_4$ (0.16 g, 1.0 mmol) in a mixture of water (12 mL) and acetone (48 mL). Flask F was filled with a solution of $NaHCO_3$ (10 g) in water (60 mL). Oxidation and workup as above yielded 0.24 g (60%) of **10b**, mp 204–209 °C (dec.).

16α,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl formate (10d) was prepared analogously to **10b** (first procedure). Flask A was charged with a solution of formate **7d**[2d] (0.18 g, 0.5 mmol) in acetone (30 mL) and formic acid (40 μL, 1.0 mmol), flask **B** with a solution of $KMnO_4$ (0.08 g, 0.5 mmol) in water (7.5 mL)

(12) Hydorn, A. E.; Korzun, J. N., Moetz, J. R. *Steroids* **1964**, *3*, 493.
(13) (a) Solyom, S.; Toldy, L. *Hungarian Patent* HU 36,138, 1983; *Chem. Abstr.* **1986**, *104*, 88894u. (b) Batist, J. N. M.; Marx, A. F. *European Patent* EP 253,415, 1987; *Chem. Abstr.* **1988**, *108*, 221967w.
(14) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1957**, *79*, 1130.
(15) In a comparable reaction the *acetyl* protection of C21-OH was lost also.[8a]
(16) Sacks, C. E. *U. S. Patent* US 4,442,035, 1984; *Chem. Abstr.* **1984**, *101*, 73011t.
(17) Holmlund, C. E.; Feldman, L. I.; Blank, R. H.; Barbacci, N.; Nielsen, B. *Sci. Repts. 1 st. Super. Sanita* **1961**, *1*, 289; *Chem. Abstr.* **1962**, *57*, 3865c.
(18) One reviewer remarks, based on his experience with $KMnO_4$ bis-hydroxylations, that yields are improved considerably when these reactions are quenched into $NaHSO_3$ containing sufficient formic acid to maintain the pH in the 4.5 - 5.0 range, so as to convert MnO_2 into colorless Mn^{2+} salts.

and acetone (22.5 mL), and flask F with $NaHSO_3$ (0.10 g, 1 mmol) in water (10 mL). Yield 0.16 g (79%), mp 188–192 °C. Analytically pure **10d**: mp 196–198 °C (from acetone/water); $[\alpha]^{20}_D$ +108° (*c* 0.5, $CHCl_3$); IR (KBr) 3460 (OH), 1735, 1715, 1675 cm^{-1} (C=O); ^1H NMR δ 0.69 (s, 3H), 0.95–2.5 (m), 1.14 (s, 3H), 3.13 (br, 1H), 3.92 (s, 1H), 4.91, 4.97, 5.09, 5.15 (AB q, 2H), 4.94 (s, br, 1H), 5.69 (s, 1H), 8.12 (s, 1H). ^{13}C NMR δ 205.1, 199.7, 171.2, 160.2, (−)123.8, 88.4, (−)72.9, 67.9, (−)52.9, (−)49.0, 48.1, 38.4, 35.4, (−)35.1, 33,7, 33.6, 32.6, 31.8, 30.3, 20.0, (−)17.2, (−)14.3. Anal. Calcd for $C_{22}H_{30}O_6$ (390.480): C, 67.67; H, 7.74. Found: C, 67.5; H, 7.7.

16α,17-Dihydroxy-3,20-dioxopregna-4,9(11)-dien-21-yl formate (10f) was prepared analogously to **10b** (first procedure) from formate **7f** [2d] (0.28 g, 0.8 mmol) in acetone (30 mL) and formic acid (64 μL, 1.6 mmol) (flask A), $KMnO_4$ (0.13 g, 0.8 mmol) in water (7.5 mL) and acetone (22.5 mL) (flask B) and a solution of $NaHCO_3$ (0.13 g, 1.6 mmol) in water (10 mL) (flask F) to give 0.24 g (77%) of **10f**, mp 182–184 °C (dec.; from MeOH); $[\alpha]^{20}_{578}$ +101° (*c* 1.0, $CHCl_3$); IR (KBr) 3380 (OH), 1730, 1705, 1655 (C=O), 1610 cm^{-1} (C=C); ^1H NMR δ 0.66 (s, 3H), 1.08–2.9 (m), 1.32 (s, 3H), 2.82 (s, 1H), 3.91 (s, 1H), 4.94, 5.00, 5.13, 5.19 (AB q, 2H), 5.05, 5.09 (d, br. 1H), 5.52, 5.54 (d, 1H), 5.74 (s, 1H), 8.16 (s, 1H); ^{13}C NMR δ 204.7, 199.2, 169.4, 160.1, 143.7, (−)123.9, (−)118.4, 88.2, (−)73.3, 67.6, (−)46.7, 46.3, 40.9, (−)37.0, 34.2, 34.1, 33.6, 32.7, 32.2, 32.0, (−)26.1, (−)14.1. Anal. Calcd for $C_{22}H_{28}O_6$ (388.464): C, 68.02; H, 7.27. Found: C, 68.1; H, 7.3.

9,16α,17,21-Tetrahydroxypregn-4-ene-3,20-dione (11b) was obtained by hydrolysis of **10b** (0.081 g, 0.20 mmol) in THF (10 mL) with Na_2CO_3 (0.02 g) and water (0.5 mL) for 20 h at rt in a yield of 0.045 g (60%). Analytically pure **11b** (by one crystallization from MeOH): mp 224–227 °C (dec.); $[\alpha]^{20}_D$ +66° (*c* 0.1, MeOH); IR (KBr) 3450 (OH), 1715, 1660, cm^{-1} (C=O); ^1H NMR δ 0.73 (s, 3H), 1.0–2.7 (m), 1.31 (s, 3H), 2.99 (t, J = 4 Hz), 3.77 (s, 1H), 4.28, 4.34, 4.68, 4.74 (d AB q, J = 4 Hz, 2H), 5.06 (br. d, J = 9 Hz, 1H), 5.87 (s, 1H). Anal. Calcd for $C_{21}H_{30}O_6$ (378.469): C, 66.65; H, 7.99. Found: C, 66.2; H, 8.0.

16α,17,21-Trihydroxypregn-4-ene-3,20-dione[19] (11d). A solution of oxazoline **5c**[2d] (0.38 g, 1.0 mmol) in 60% aqueous formic acid (6 mL) was placed in flask A. After 1 h, analogously to **10b** (second procedure), the solution was diluted with acetone (54 mL), and the *in situ* formed **7d** was reacted with $KMnO_4$ (0.16 g, 1.0 mmol) in water (12 mL) and acetone (48 mL, flask B). Flask F was filled with a solution of $NaHCO_3$ (10 g) in water (60 mL). The aqueous suspension of the formate **10d** was extracted with CH_2Cl_2 (50, 25 and 10 mL) and the combined extracts were concentrated. The residue was dissolved in MeOH (25 mL) and 2 N HCl (6 mL) and kept at rt for 17 h. The solution was concentrated to a volume of *ca.* 10 mL. The solid was collected, washed with water and dried to give 0.24 g (67%) of **11d**, mp 217–220 °C (dec.); $[\alpha]^{20}_D$ +81° (*c* 0.2, MeOH), {lit.[19] 238–240 °C, $[\alpha]^{20}_D$ +93° (*c* 0.1, MeOH)}. Mixed mp with authentic material provided by Gist-brocades, gave no depression. IR (KBr) 3430 (OH), 1720, 1675 (C=O), 1615 cm^{-1} (C=C); ^1H NMR (200 MHZ) δ 0.72 (s, 3H), 0.8–2.6 (m), 1.17 (s, 3H), 3.02 (s, 1H), 3.73 (s, 1H), 4.24, 4.34, 4.64, 4.74 (AB q, 2H), 5.03, 5.07 (d, 1H), 5.74 (s, 1H).

16α,17,21-Trihydroxypregna-4,9(11)-diene-3,20-dione (11f) was prepared analogous to **11d** from **5e**[2d] (0.38 g, 1.0 mmol) in 0.24 g (65%) yield, mp 203–206 °C (dec.). Analytically pure **11f** (from MeOH): mp 213 °C (dec.); $[\alpha]^{20}_D$ +63° (*c* 0.1, MeOH); IR (KBr) 3400 (OH), 1720, 1680 cm^{-1} (C=O); ^1H NMR δ 0.64 (s, 3H), 0.8–2.8 (m), 1.33 (s, 3H), 3.02 (t, J = 5 Hz, 1H), 3.74 (s, 1H), 4.25, 4.32, 4.69, 4.75 (d AB q, J = 5 Hz, 2H), 5.12 (m, 1H), 5.51, 5.53 (d, 1H), 5.75 (s, 1H); ^{13}C NMR δ 212.2, 198.8, 168.9, 144.0, (−)124.1, (−)118.3, 87.7, (−)73.7, 67.4, (−)46.9, 41.0, (−)37.1, 34.5, 34.2, 33.7, 32.7, 32.5, 32.1, (−)26.2, (−)14.5. Anal. Calcd for $C_{21}H_{28}O_5$ (360.454): C, 69.98; H, 7.83. Found: C, 69.7; H, 7.9.

16α,17,21-Trihydroxypregna-1,4-diene-3,20-dione (11g) was prepared analogous to **11d** from **5g**[2d] (0.37 g, 1.0 mmol) in 0.19 g (53%) yield, mp 217–218 °C (dec.); $[\alpha]^{20}_D$ +37° (*c* 0.1, MeOH); IR (KBr) 3440 (OH), 1730, 1675 (C=O), 1640 cm^{-1} (C=C); ^1H NMR δ 0.74 (s, 3H), 0.9–2.7 (m), 1.23 (s, 3H), 3.01 (t, br, J = 4 Hz, 1H), 3.73 (s, 1H) 4.26, 4.33, 4.65, 4.72 (d AB q, J = 4 Hz, 2H), 5.03, 5.07 (d, 1H), 6.08 (s, 1H), 6.24 (d, J = 12 Hz, 1H), 7.04 (d, J = 12 Hz, 1H). Anal. Calcd for $C_{21}H_{28}O_5$ (360.454): C, 69.98; H, 7.83. Found: C, 70.1; H, 7.8.

16α,17,21-Trihydroxy-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (11h) was prepared analogous to **11d** from **5h**[2d] (0.37 g, 1.0 mmol) in 0.25 g (70%) yield, mp 159–160 °C; IR (KBr) 3400 (OH), 1715 cm^{-1} (C=O); ^1H NMR δ 0.70 (s, 3H), 1.2–2.5 (m), 2.80–2.96 (m, 2H), 3.08 (br, 1H), 3.78 (s, 3H), 3.82 (s, 1H), 4.30, 4.37, 4.69, 4.76 (AB q, 2H), 5.07 (d, J = 9 Hz, 1H), 6.63 (s, br, 1H), 6.71 (d, J = 7 Hz, 1H), 7.19 (d, J = 7 Hz, 1H). Anal. Calcd for $C_{21}H_{28}O_5$ (360.454): C, 69.98; H, 7.83. Found: C, 69.8; H, 7.9.

16α,17-Dihydroxy-3,20-dioxopregn-4-en-21-yl acetate[19] (12d) was prepared analogous to **10d** from **9d**[20] (0.18 g, 0.5 mmol) in 0.16 g (80%) yield after one crystallization from CH_2Cl_2/Et_2O, mp 194–201 °C (lit.[19] 206–210 °C); IR (KBr) 3400 (OH), 1750, 1725, 1660 (C=O), 1610 cm^{-1} (C=C); ^1H NMR (60 Mz) δ 0.6–3.1 (m), 0.72 (s, 3H), 1.17 (s, 3H), 2.13 (s, 3H), 3.7–4.2 (m, 2H), 4.95 (s, br. 2H), 5.69 (s, 1H).

9-Hydroxy-16α,17-(isopropylidenedioxy)-3,20-dioxopregn-4-en-21-yl formate (13b). To a stirred suspension of **10b** (2.75 g, 6.8 mmol) in acetone (275 mL) was added 70% aqueous $HClO_4$ (1 mL). After stirring for 1 h at rt water (100 mL) was added, then the mixture was chilled in an ice-bath. The solid was collected, washed with water and dried, to give 2.95 g (97%) of **13b**, mp 270–271 °C (dec.); $[\alpha]^{20}_{578}$ +120° (*c* 0.2, CH_2Cl_2); IR (KBr) 3530 (OH), 1745, 1720, 1650 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.70 (s, 3H), 1.0–2.7 (m), 1.27 (s, 3H), 1.33 (s, 3H), 1.50 (s,3H), 4.9–5.2 (m, 3H), 5.94 (s, 1H), 8.25 (s, 1H); C^{13} NMR δ 203.1, 198.6, 167.4, 159.8, (−)127.1, 111.3, 97.7, (−)82.1, 75.9, 66.9, 46.3, 44.3, (−)42.4, (−)36.5, 33.9, 33.5, 31.5, 28.4, 27.0, (−)26.5, 26.2, (−)25.6, 25.5, (−)19.8, (−)13.5. Anal. Calcd for $C_{25}H_{34}O_7$ (446.546): C, 67.24; H, 7.67. Found: C, 67.0; H, 7.6.

16α,17-(Isopropylidenedioxy)-3,20-dioxopregna-4,9(11)-dien-21-yl formate (14f). From 13b. A suspension of **13b** (2.68 g, 6.0 mmol) and P_2O_5 (2.5 g, 12 mmol) in dry toluene (250 mL) was refluxed for 1.5 h. The mixture was cooled to rt and the yellow solution was decanted from a black tar into aqueous $NaHCO_3$ (100 mL). The upper layer was washed with brine (50 mL), dried (Na_2SO_4) and concentrated. Et_2O (15 mL) was added to the concentrate and the mixture was placed in an ultrasone bath for 5 min, then the solid was collected to give 1.8 g (70%) of **14f**, mp 118–123 °C. Analytically pure **14f** (from acetone/water): mp 224 °C (dec.); $[\alpha]^{20}_{578}$ +110° (*c* 0.5, CH_2Cl_2); IR (KBr) 1750, 1740, 1678 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.60 (s, 3H), 1.1–2.8 (m), 1.25 (s, 3H), 1.33 (s, 3H), 1.47 (s, 3H), 4.85, 4.91, 5.14, 5.20 (AB q, 2H), 5.04, 5.05 (d, 1H), 5.56, 5.57 (d, 1H), 5.75 (s, 1H), 8.18 (s, 1H); ^{13}C NMR δ 203.1, 198.9, 169.0, 159.8, 143.9, (−)124.1, (−)118.3, 110.9, 97.3, (−)82.4, 66.7, (−)46.4, 44.9, 40.9, (−)36.6, 34.5, 34.1, 33.7, 33.1, 32.6, 32.1, (−)26.4, (−)26.0, (−)25.4, (−)14.1. Anal. Calcd for $C_{25}H_{32}O_6$ (428.530): C, 70.07; H, 7.53. Found: C, 70.2; H, 7.5. **From 10f.** Two drops of 70% aqueous $HClO_4$ were added to a stirred solution of **10f** (0.038 g, 0.10 mmol) in acetone (6 mL) at rt. After 15 min 15 mL of water was added. The solid was collected, washed with water and dried to give 0.040 g (93%) of **14f**, mp 223–224 °C (dec.). Mixed mp with material described above gave no depression.

9-Bromo-11β-hydroxy-16α,17-(isopropylidenedioxy)-3,20-dioxopregn-4-en-21-yl formate (15). Water (15 mL), NBS (0.85 g, 4.8 mmol) and 10% aqueous $HClO_4$ (3.5 mL) were added successively to a solution of **14f** (1.50 g, 3.5 mmol) in dioxane (75 mL). After stirring for 45 min in the dark at rt, the solution was neutralized with $NaHCO_3$, then water (300 mL) was added. After stirring for 30 min at 0 °C the solid was collected, washed with water and dried to give 1.7 g (92%) of **15**, mp 119 °C (dec.). This material was used immediately (as such) for the preparation of **16** and **17**. IR (KBr) 3440 (OH), 1740, 1725, 1655 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.90 (s, 3H), 1.0–3.3 (m), 1.25 (s, 3H), 1.52 (s, 3H), 1.75 (s, 3H), 4.5–4.84 (m, 1H), 4.8–5.5 (m, 3H), 5.75 (s, 1H), 8.20 (s, 1H).

9β,11β-Epoxy-16α,17-(isopropylidenedioxy)-3,20-dioxopregn-4-en-21-yl formate (16). 1,1,2,2-Tetramethylguanidine (0.4 mL, 3.2 mmol) was added to a stirred solution of **15** (1.58 g, 3.0 mmol) in DMF (10 mL) at rt.[16] After 10 min, 0.5 N HCl (40 mL) was added. The solid was collected, washed with water and

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dried to give 1.06 g (80%) of **16**, mp 235–243 °C (dec.). Analytically pure **16** (by one crystallization from CH_2Cl_2/Et_2O): mp 247–248 °C (dec.); $[\alpha]^{20}_{578}$ +41° (*c* 1.0, CH_2Cl_2); IR (KBr) 1735, 1720, 1660 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.83 (s, 3H), 1.0–3.0 (m), 1.24 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 3.48 (s, br, 1H), 4.62, 4.93, 4.99, 5.08, 5.12, 5.90 (AB q + d, 3H), 5.84 (s, 1H), 8.26 (s, 1H); ^{13}C NMR δ 202.1, 198.4, 169.2, 159.6, (–)124.2, 112.2, 97.2, (–)81.1, 66.4, 65.2, (–)60.0, (–)44.7, 44.6, 39.3, 34.5, 33.7 (–)33.7, 31.2, 31.0, 29.1, (–)26.6, 26.0, (–)25.5, (–)23.4, (–)16.8. Anal. Calcd for $C_{25}H_{32}O_7$ (444.530): C, 67.55; H, 7.26. Found: C, 67.6; H, 7.4.

9β,11β-Epoxy-21-hydroxy-16α,17-(isopropylidenedioxy)-pregn-4-en-3,20-dione (17). A mixture of **15** (1.70 g, 3.2 mmol), KOAc (2.80 g, 28.0 mmol) and absolute EtOH (50 mL) was refluxed for 1 h. The solution was poured into water and the mixture was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated to give 1.26 g (86%) of **17**, mp 190–205 °C. Analytically pure **17** (from CH_2Cl_2/Et_2O): mp 215–216 °C; $[\alpha]^{20}_{578}$ +46° (*c* 0.15, CH_2Cl_2); IR (KBr) 3490 (OH), 1725, 1675 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.79 (s, 3H), 1.0–3.3 (m), 1.19 (s, 3H), 1.43 (s, 3H), 1.48 (s, 3H), 3.3–3.6 (m, br, 1H), 3.93, 4.28, 4.56, 4.88 (AB q, 2H), 5.01, 5.09 (d, 1H), 5.81 (s, 1H). Anal. Calcd for $C_{24}H_{32}O_6$ (416.519): C, 69.21; H, 7.74. Found: C, 69.3; H, 7.7.

9-Fluoro-11β-hydroxy-16α,17-(isopropylidenedioxy)-3,20-dioxopregn-4-en-21-yl formate (18). A solution of 70% aqueous HF (5 mL) in a polyethylene flask was chilled to −30 °C. Epoxide **16** (1.5 g, 3.4 mmol) was added to the cooled solution and the mixture was stirred for 45 min at −25 °C. The wine-red solution was poured (with care!) into an Erlenmeyer flask (2-L) containing a stirred solution of $NaHCO_3$ (20 g) in water (500 mL). The solid was collected, washed with water and dried to give 1.24 g (79%) of **18**, mp 190–210 (dec.). Analytically pure **18** (from acetone/Et_2O): mp 228–230 °C; $[\alpha]^{20}_{578}$ +131° (*c* 0.6, CH_2Cl_2); IR (KBr) 3420 (OH), 1730, 1710, 1655 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.93 (s, 3H), 1.0–3.0 (m), 1.28 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 4.2–4.7 (m, br, 1H), 5.10 (s, br, 1H), 5.85 (s, 1H), 8.28 (s, 1H). Anal. Calcd for $C_{25}H_{33}FO_7$ (464.538): C, 64.64; H, 7.16; F, 4.09. Found: C, 65.0; H, 7.2, F, 3.5.

9-Fluoro-11β,21-dihydroxy-16α,17-(isopropylidenedioxy)pregn-4-ene-3,20-dione[8a] (19) was prepared analogous to **18** from **17** (0.70 g, 1.7 mmol). By CLC (silicagel, CH_2Cl_2/MeOH 98:2) 0.38 g (52%) of **19** was obtained, mp 254–256 °C; $[\alpha]^{20}_D$ +146° (*c* 1.0, CH_2Cl_2) [lit.[8a] mp 262 °C, $[\alpha]^{25}_D$ +144° (*c* 0.8, $CHCl_3$)]; IR (KBr) 3450 (OH), 1735, 1655 cm^{-1} (C=O); ^1H NMR δ 0.80 (s, 3H), 1.10 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.2–2.6 (m), 3.04 (br, 1H), 4.10, 4.16, 4.60, 4.67 (q, 2H), 4.32 (br d, J = 7 Hz, 1H), 5.01 (d, J = 5 Hz, 1H), 5.75 (s, 1H); ^{13}C NMR δ 210.4, 198.8, 168.5, (–)124.8, 111.4, 99.5 (d, $J_{C\text{-}F}$ = 173 Hz), 97.0, (–)81.8, (–)70.2 (d, $J_{C\text{-}F}$ = 38 Hz,), 67.0, 45.0, 43.6 (d, $J_{C\text{-}F}$ = 20 Hz), (–)43.4, 37.3, 33.6, 33.3, (–)33.0, 30.7, 28.4, (–)26.3, 26.0, (–)25.5, (–)21.8, (–)16.7.

9-Fluoro-11β,21-dihydroxy-16α,17-(isopropylidenedioxy)pregna-1,4-diene-3,20-dione *i. e.* triamcinolone acetonide (6). From 18. A stirred mixture of **18** (0.093 g, 0.20 mmol), DDQ (0.05 g, 0.2 mmol) and dry benzene (10 mL) was refluxed for 20 h. The mixture was dissolved in EtOAc (30 mL), then washed with aqueous $NaHCO_3$, with brine, and concentrated. The red concentrate (0.12 g) was dissolved in MeOH (10 mL) and Na_2CO_3 (0.1 g) was added. The mixture was refluxed for 30 min, then poured into water. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 0.080 g of a solid residue. By CLC (silicagel, CH_2Cl_2/MeOH 98:2) 0.018 g (21%) of **6** was obtained, mp 270–272 °C. IR (KBr) 3400 (OH), 1700, 1658 (C=O), 1608, 1598 cm^{-1} (C=C). Mixed mp with a commercial sample (mp 271–273 °C) showed no depression. **From 19.** To a stirred solution of **19** (0.087 g, 0.20 mmol) in dry benzene was added DDQ (0.05 g, 0.2 mmol) and the mixture was refluxed for 70 h. After removal of solvent, 0.035 g (40%) of **6**, was obtained by CLC (silicagel, CH_2Cl_2/MeOH 98:2), mp 260–264 °C.

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