A reinvestigation of the D-homoannular rearrangement and subsequent degradation pathways of (11β,16α)-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (triamcinolone)

Edward J. Delaney, Ronald G. Sherrill,* Venkatapuram Palaniswamy, Thomas C. Sedergran, and Stephan P. Taylor

Chemical Process Technology Department, Bristol-Myers Squibb Company, New Brunswick, New Jersey, USA

The commercial anti-inflammatory drug triamcinolone has been shown to rearrange by similar, but distinct pathways when exposed to certain trace metal ions or to dilute aqueous base. In the presence of aqueous base, the 16-hydroxy-20-keto system undergoes reverse aldol cleavage of the 16,17-bond, followed by aldol cyclization linking C-16 to C-20. This base-catalyzed rearrangement gives a 16β,17α-dihydroxy product and a corresponding 16α,17α-dihydroxy product in roughly 4 to 1 ratio. Metal-catalyzed rearrangement provides the 16α,17α-dihydroxy product with extremely high stereoselectivity. Mechanistic models are proposed that help explain the ratio of products isolated from each route. The studies presented suggest that similar forms of rearrangement could be of preparative value in syntheses requiring specific stereochemistry of appropriately substituted bicyclic α,β-dihydroxyketones. Under more vigorous conditions of aqueous base treatment these rearrangement products undergo further decomposition with loss of formaldehyde from the hydroxymethyl group, followed by β-elimination of water. Reaction of the β-elimination product with formaldehyde results in the formation of a dimeric species linked by a methylene group. (*Steroids* **59**:196–204, 1994)

Keywords: degradation; rearrangement; enantioselective; triamcinolone

Introduction

Synthetic corticosteroids continue to be of significant commercial importance as anti-inflammatory agents, and mechanisms for their degradation have been thoroughly studied throughout the last several decades.[1–3] D-ring acyloin rearrangement (D-homoannulation) of 17-hydroxy-20-keto steroids such as **1** was first reported in 1938 by Ruzicka and Mehldahl,[4] and a rationale for stereochemical control of the reaction was later described in 1953 by Turner[5] (Figure 1). Since that time, mechanisms of the reaction under both base and Lewis-acid catalysis have been thoroughly studied and variations of the reaction continue to be reported.[6]

Steroids possessing the 16,17-dihydroxy-20-keto moiety **4** are known to be more prone to rearrangement than 17-hydroxy-20-keto steroids.[1] Yet, while a facile retro-aldol mechanism has been used to account for 17a-keto rearrangement products (**5**) isolated from certain 16,17-dihydroxy-20-keto steroids (Figure 2), 17-keto assignments analogous to **3** have also been rationalized.[7] These latter assignments were supported by data then available, and the 17-keto products were believed to occur by the more energetically demanding D-homoannulation mechanisms shown in Figure 1.

The anti-inflammatory drug triamcinolone **6a** (Figure 3), a representative 16,17-dihydroxy-20-keto steroid, is highly sensitive to rearrangement catalyzed by traces of certain transition-metal ions or by dilute aqueous hydroxide. In 1960, a single rearrangement product was

Address reprint requests to Edward J. Delaney, Chemical Process Technology Department, Bristol-Myers Squibb Company, P.O. Box 900, New Brunswick, NJ 08903, USA.
* Present address of Ronald Sherrill is Glaxo Pharmaceutical Co., Research Triangle, NC, USA.
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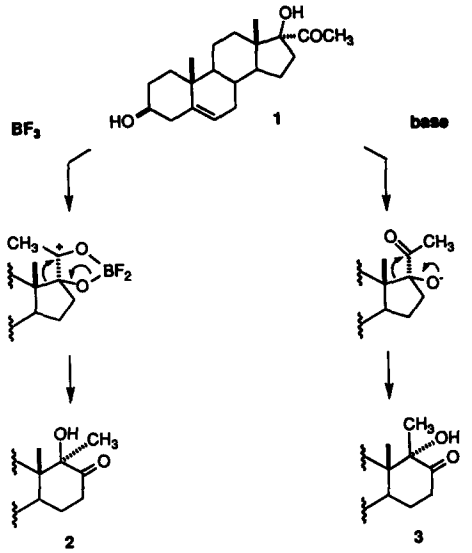


Figure 1 D-homoannulation of 17-hydroxy-20-keto steroids.

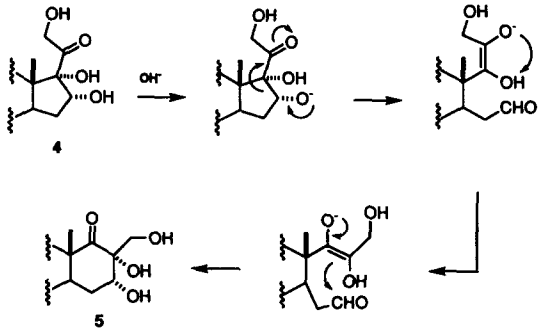


Figure 2 Proposed retro-aldol rearrangement mechanism for 16,17-dihydroxy-20-keto steroids.

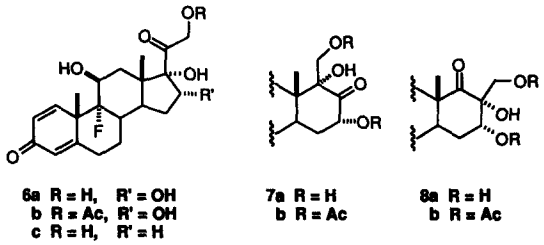


Figure 3 Structures of triamcinolone, related derivatives, and possible structures of triamcinolone rearrangement product.

reported to arise from both the metal- and hydroxide-catalyzed reactions, and this substance was tentatively assigned as the D-homo product, 17-ketone **7a**, rather than 17a-ketone **8a**.[8] Assignment was based on IR data obtained from the rearrangement product's 16,21-diacetate derivative; the observed vicinal interaction, presumed between the saturated 17-carbonyl and the 16-acetate carbonyl, could be explained by structure **7b**, but not as readily by **8b**. In the course of recent process development studies, we were led to question this assignment and the general likelihood of D-homo acyloin rearrangements for 16,17-dihydroxy-20-keto steroids. We have found 17-hydroxy-20-ketone **6c** to be significantly less sensitive to mild aqueous base treatment than triamcinolone, suggesting that the 16-hydroxyl group plays an important role in the base-catalyzed triamcinolone rearrangement. We also found that triamcinolone actually produces two components when exposed to aqueous sodium hydroxide or carbonate under mild conditions. Finally, triamcinolone exposed to traces of iron(III) or copper(II) was observed to produce a single product. This substance possessed an identical retention time by HPLC to the minor component arising from the base-catalyzed reaction. We have analyzed these triamcinolone rearrangement products and their fate in subsequent base-catalyzed transformations. Herein are reported the results of studies which establish distinct routes for metal- and base-catalyzed triamcinolone rearrangements, and which further extend the mechanistic understanding of degradation pathways for 16,17-dihydroxy-20-keto steroids.

Experimental

Uncorrected decomposition points were measured on a Thomas-Hoover melting point apparatus. Infrared absorption spectra were obtained on KBr pellets using a Perkin-Elmer 1710 FTIR spectrophotometer. Proton and carbon NMR spectra were obtained on either a Bruker ACP (300 MHz for ^{1}H and 75.7 MHz for ^{13}C NMR), or a JEOL FX270 MHz NMR spectrometer (270 MHz for ^{1}H and 67.8 MHz for ^{13}C NMR), referenced internally to tetramethylsilane (proton spectra) or d6 DMSO (carbon spectra). INEPT carbon spectra were also obtained on all rearrangement products as an aid to structure assignment, and these data were consistent with all assignments shown. HPLC measurements were obtained using a Chromanetics Spherisorb ODS-2 reverse phase column (5 μm particle size, 25 cm × 4.6 mm). A mobile phase of methanol/acetonitrile/0.5 M sodium phosphate buffer (20:20:60) was used at a flow rate of 1.0 mL/min (HPLC system A). Alternatively, a mobile phase of methanol/water (55:45) was passed at a flow rate of 1.5 mL/min (HPLC system B). In each case products were detected by selective absorbance of 240 nm UV light. Baker silica gel (40 μm average particle size) was used for flash chromatography of acetonide derivatives. Reagent grade solvents were used for syntheses and chromatography without further purification. Bristol-Myers Squibb research samples of triamcinolone (Kenacort™; **6a**), triamcinolone 21-acetate (**6b**), 9α-fluoroprednisolone (**6c**), triamcinolone acetonide (Kenalog™; **12**), and triamcinolone acetonide 21-acetate (**13**) were each known to possess HPLC homogeneity of 99.6+% prior to use in the study.

(11β,16α)-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (6a)

^{1}H NMR (d6-DMSO, trace DCl) δ 7.23 (d, J = 10.2 Hz, 1H), 6.22 (dd, J = 10.2, 1.6 Hz, 1H), 6.01 (apparent s, 1H), 4.77 (dd, J = 7.9, 1.4 Hz, 1H), 4.30 (AB q, J = 19.5 Hz, $\Delta\nu$ = 123.9 Hz, 1H), 4.13 (apparent d, J = 7.0 Hz, 1H), 2.65–2.52 (m, 1H), 2.45–2.05 (m, 4H), 1.87–1.65 (m, 2H), 1.6–1.2 (m, 2H), 1.48 (s, 3H), 1.40–1.25 (m, 3H), 0.85 (s, 3H); ^{13}C NMR (d6-DMSO) δ 211.5, 185.2, 166.7, 152.6, 128.9, 124.2, 100.9 (d, J = 175.5 Hz), 87.4, 71.3, 70.5 (d, J = 37.1 Hz), 66.6, 47.9 (d, J = 22.5 Hz), 46.5, 43.1, 35.8, 33.6, 33.1 (d, J = 15.6 Hz), 30.2, 27.2, 22.9 (d, J = 5.8 Hz), 16.6.

*(11β,16α)-21-Acetyloxy-9-fluoro-11,16,17-trihydroxypregna-1,4-diene-3,20-dione (**6b**)*

^{1}H NMR (d6-DMSO, trace DCl) δ 7.29 (d, J = 10.2 Hz, 1H), 6.23 (dd, J = 10.2, 1.5 Hz, 1H), 6.02 (apparent s, 1H), 4.91 (AB q, J = 17.7 Hz, $\beta\nu$ = 64.1 Hz, 1H), 4.69 (overlapping d, J = 7.7, 1H), 4.14 (apparent d, J = 9.8 Hz, 1H), 2.70–2.20 (m, 5H), 2.10 (s, 3H), 1.90–1.65 (m, 2H), 1.65–1.50 (m, 1H), 1.48 (s, 3H), 1.45–1.20 (m, 2H), 0.85 (s, 3H); ^{13}C NMR (d6-DMSO) δ 205.4, 185.2, 169.7, 166.8, 152.6, 128.9, 124.1, 101.0 (d, J = 176.0 Hz), 87.8, 71.6, 70.3 (d, J = 37.9 Hz), 68.1, 47.9 (d, J = 22.7 Hz), 46.9, 43.1, 35.5, 33.6, 33.2 (d, J = 18.9 Hz), 30.2, 27.3, 22.9 (d, J = 3.8 Hz), 20.3, 16.2.

*(11β)-9-Fluoro-11,17,21-trihydroxypregna-1,4-diene-3,20-dione (**6c**)*

^{1}H NMR (d6-DMSO, trace DCl) δ 7.31 (d, J = 10.1 Hz, 1H), 6.24 (apparent d, J = 10.1 Hz, 1H), 6.03, 4.30 (AB q, J = 19.2 Hz, $\Delta\nu$ = 123.7 Hz, 2H), 4.16 (apparent d, J = 9.6 Hz 1H), 2.75–2.25 (m, 4H), 2.20–1.95 (m, 2H), 1.95–1.7 (m, 1H), 1.7–1.55 (m, 1H), 1.49 (s, 3H), 1.5–1.2 (M, 2H), 0.78 (s, 3H); ^{13}C NMR (d6-DMSO) δ 211.4, 185.3, 167.1, 152.8, 129.0, 124.2, 101.2, (d, J = 175.9 Hz), 88.3, 70.7 (d, J = 37.1 Hz), 65.9, 47.9 (d, J = 22.7 Hz), 46.1, 44.4, 35.4, 33.6 (d, J = 19.5 Hz), 32.9, 30.3, 27.4, 23.1 (d, J = 5.8 Hz), 22.9, 16.5.

*(11β,16α,17α)-9-Fluoro-11,16,17-trihydroxy-17-(hydroxymethyl)-D-homoandrosta-1,4-diene-3,17a-dione (**10a**)*

Method A To 10.0 g of triamcinolone **6a** (25.4 mmol) dissolved in 100 mL of DMF was added 4.0 mL of 0.1 M aqueous ferric chloride, causing the solution to turn deep orange. After heating at about 90°C for 1.5 h, the solution developed a dark brown color and showed 68% conversion to **10a** with less than 7% remaining starting material by HPLC (Method A). After cooling to ambient temperature, the mixture was passed through a column of Chelex 100 (80 g in its sodium form), and the column was washed with 50 mL DMF. The combined DMF eluates were added to 3 L of deionized water and the product was allowed to crystallize overnight while being held at 5 C. After filtering, the 5.6 g of wet crystals obtained were recrystallized by dissolving in 25 mL hot DMF, and adding 25 mL deionized water, thus raising the homogeneity by HPLC method A from 95% to 99.7%. Yield of dried **10a** was 3.63 g (36%).

Method B A 3.00 g sample of **6a** in 10 mL of DMF was treated with 0.2 mL of titanium isopropoxide at 55–60 C for 4 h, at which time less than 5% triamcinolone remained unreacted by HPLC. A 30 mL portion of 10% by weight aqueous D-tartaric acid was added to the hot solution to complex Ti(IV), and to effect crystallization. After stirring for 10 min, the mixture was filtered, washed with 30 mL water, and the crystals were dried under vacuum to provide **10a** (2.30 g, 77%, 97.0% homogeneous by HPLC method A, containing <0.2% **11**). An analytical sample was obtained by dissolving 1.50 g of the above in 8 mL DMF at 40 C, and adding 5 mL methylene chloride to effect crystallization. The solid obtained was filtered, washed with 5 mL water and dried to provide **10a** possessing 99.9% homogeneity (t_R = 8.8 min) by HPLC Method A (1.04 g, 69% recovery): mp 273–74 C (dec); IR (KBr) C=O stretch 1704, 1663 cm^{-1}, C=C stretch 1620, 1607 cm^{-1}; CIMS m/z: 394 (M + H)$^+$, 374 (-HF), 365 (-HCHO); ^{1}H NMR (d6-DMSO, trace DCl) δ 7.31 (d, J = 10.1 Hz, 1H), 6.22 (dd, J = 10.1, 1.6 Hz, 1H), 6.00 (apparent s, 1H), 4.14 (apparent d, J = 10.0 Hz, 1H), 3.96 (dd, J = 4.5, 4.5 Hz, 1H), 3.59 (AB q, J = 11.0 Hz, $\Delta\nu$ = 35.2 Hz, 2H), 2.7–2.3 (m, 3H), 2.2–2.0 (m, 2H), 1.95–1.7 (m, 3H), 1.6–1.2 (m, 2H), 1.50 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (d6-DMSO) δ 212.5, 185.4, 167.1, 152.7, 129.3, 123.9, 101.0 (d, J = 175 Hz), 80.3, 69.5 (d, J = 35.5 Hz), 67.9, 64.5, 47.9 (d, J = 22.8 Hz), 45.4, 37.7, 37.2, 32.7 (d, J = 19.7 Hz), 30.3, 29.0, 26.9, 23.1 (d, J = 5.6 Hz), 16.2; Analysis Calculated for $C_{21}H_{27}O_6F$: C, 63.95; H, 6.90; F, 4.82. Found: C, 64.18; H, 6.90; F, 4.78.

*(11β,16α,17α)-17-[(Acetyloxy)methyl]-9-fluoro-11,16,17-trihydroxy-D-homoandrosta-1,4-diene-3,17a-dione (**10b**)*

A 3.25 g (7.45 mmol) sample of triamcinolone 21-acetate **6b** in 10 mL DMF was treated with 0.2 mL (0.67 mmol) of titanium isopropoxide for 4 h at 55–60°C, at which time less than 5% triamcinolone 21-acetate remained by HPLC. A 30 mL portion of 10 wt% aqueous D-tartaric acid was added to the hot solution to complex Ti(IV), and to effect product crystallization. After stirring for 10 min, the mixture was filtered, washed with 30 mL water, and the crystals were dried under vacuum to provide **10b** (3.10 g, 95%, 97.8% homogeneous by HPLC method A). An analytical sample was obtained by dissolving 1.84 g of the above in 10 mL DMF at 60 C, and adding 25 mL deionized water to effect crystallization. The solid obtained was filtered, washed with 25 mL water and dried to provide **10b** possessing 99.5% homogeneity (t_R = 14.7 min) by HPLC Method A (1.48 g, 80% recovery): mp 229–230 C (dec); IR(KBr) C=O stretch 1704, 1663 cm^{-1}, C=C stretch 1620, 1607 cm^{-1}; CIMS m/z: 437 (M + H)$^+$, 419 (-H_2O), 417 (-HF), 399 (-AcOH); ^{1}H NMR (d6-DMSO, trace D_2O) δ 7.28 (d, J = 10.1 Hz, 1H), 6.22 (apparent d, J = 10.1 Hz, 1H), 6.02 (apparent s, 1H), 4.17 (overlapping m, 1H), 4.11 (AB q, J = 10.4 Hz, $\Delta\nu$ = 49.7 Hz, 2H), 4.02 (overlapping m, 1H), 2.8–1.6 (m, 8H), 1.94 (s, 3H), 1.6–1.2 (m, 2H), 1.50 (s, 3H), 1.24 (s, 3H), ^{13}C NMR (d6-DMSO) δ 210.4, 185.2, 166.8, 152.4, 129.1, 123.8, 100.7 (d, J = 175 Hz), 76.9, 69.2 (d, J = 36 Hz), 66.0, 63.6, 47.7 (d, J = 22.7 Hz), 44.6, 37.5, 36.0, 33.1 (d, J = 18.9 Hz), 30.1, 29.7, 26.6, 23.0 (d, J = 3.8 Hz), 20.5, 16.9; Analysis Calculated for $C_{23}H_{29}O_7F \cdot 0.5\ H_2O$: C, 62.07; H, 6.78; F, 4.27. Found: C, 62.07; H, 6.88; F, 4.04.

*(11β,16β,17α)-9-Fluoro-11,16,17-trihydroxy-17-(hyroxymethyl)-D-homoandrosta-1,4-diene-3,17a-dione (**11**)*

A 2.0 g sample of triamcinolone **6a** (5.08 mmol) dissolved in 700 mL methanol and 400 mL water containing 100 mg EDTA disodium was treated with sodium carbonate 800 mg (7.55 mmol). The reaction, monitored by HPLC method B, was allowed to proceed at ambient temperature until less than 15% starting material remained (22 h). The reaction was halted by the addition of 1 mL acetic acid, the solution was concentrated to about half of its original volume under vacuum to remove methanol, and the concentrate was extracted three times with 300 mL methylene chloride to remove apolar impurities and residual starting material. The aqueous layer was concentrated to about three-quarters of its original volume, and the crude product was allowed to crystallize from the aqueous concentrate over thirty minutes. This material, 94% homogeneous **11** by HPLC, contained about 5% **10a**. Further purification of crude **11** was achieved by preparative HPLC; enriched fractions were combined and concentrated to effect crystallization of **11** as a white solid possessing 99.8% homogeneity (t_R = 8.0 min) by HPLC Method A (440 mg,

1.12 mmol, 22%): mp 283–84 C (dec); IR (KBr) C=O stretch 1704, 1663 cm^{-1}, C=C stretch 1620, 1607 cm^{-1}; CIMS *m/z*: 394 $(M + H)^+$, 374 (-HF), 365 (-HCHO); ^1H NMR (d6-DMSO/trace DCl) δ 7.33 (d, J = 10.1 Hz, 1H), 6.24 (dd, J = 10.1, 1.7 Hz, 1H), 6.04 (apparent s, 1H), 4.20 (apparent d, J = 7.0 Hz, 1H), 3.90–3.66 (AB, J = 12.0 Hz, $\Delta\nu$ = 48.6 Hz, 2H), 3.55 (dd, J = 10.7, 5.4 Hz, 1H), 2.75–2.50 (m, 1H), 2.45–2.38 (m, 1H), 2.20–2.09 (m, 1H), 2.00–1.87 (m, 2H), 1.80–1.32 (m, 5H), 1.55 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (d6-DMSO) δ 211.9, 185.1, 166.5, 152.2, 129.1, 123.8, 100.8 (d, J = 174 Hz), 83.5, 75.4, 69.5 (d, J = 36 Hz), 64.9, 47.7 (d, J = 22 Hz), 45.4, 39.0, 37.7, 32.1 (d, J = 20.8 Hz), 30.0, 29.6, 26.8, 22.9 (d, J = 5.7 Hz) 15.6; Analysis Calculated for $C_{21}H_{27}O_6F$: C, 63.95; H, 6.90; F, 4.82. Found: C, 64.18; H, 6.90; F, 4.78.

(11β,16α,17α)-11,21-Dihydroxy-9-fluoro-16,17-[1-methylethylidenebis(oxy)]androsta-1,4-diene-3,17-dione (12)

^1H NMR (d6-DMSO, trace DCl) δ 7.33 (d, J = 10.2 Hz, 1H), 6.23 (dd, J = 10.2, 1.6 Hz, 1H), 6.02 (apparent s, 1H), 4.91 (apparent d J = 3.1 Hz, 1H), 4.30 (AB q, J = 19.3 Hz, $\Delta\nu$ = 135.2 Hz, 2H), 4.19 (apparent d, J = 9.0 Hz, 1H), 2.75–2.25 (m, 3H), 2.1–1.7 (m, 4H), 1.7–1.55 (m, 1H), 1.55–1.45 (m, 1H), 1.49 (s, 3H), 1.4–1.25 (m, 1H), 1.32 (s, 3H), 1.08 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (d6-DMSO) δ 209.7, 185.1, 166.5, 152.4, 129.0, 124.2, 110.3, 100.9 (d, J = 176.0 Hz), 97.1, 80.7, 70.4 (d, J = 36.0 Hz), 65.8, 47.7 (d, J = 22.5 Hz), 44.7, 42.8, 36.0, 33.0, 32.5 (d, J = 18.9 Hz), 30.1, 27.4, 26.3, 25.2, 22.7 (d, J = 5.7 Hz), 16.3.

(11β,16α,17α)-21-Acetyloxy-9-Fluoro-11-hydroxy-16,17-[1-methylethylidenebis(oxy)]-androsta-1,4-diene-3,17-dione (13)

^1H NMR (d6-DMSO, trace DCl) δ 7.31 (d, J = 10.2 Hz, 1H), 6.25 (dd, J = 10.2, 1.5 Hz, 1H), 6.04 (apparent s, 1H), 4.94 (AB q, J = 17.9 Hz, $\Delta\nu$ = 119.0 Hz, 2H) 4.87 (apparent d, J = 3.8 Hz, 1H), 4.21 (apparent d, J = 8.9 Hz, 1H), 2.75–2.25 (m, 3H), 2.15–1.35 (m, 7H), 2.13 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H), 1.15 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (d6-DMSO) δ 203.4, 185.1, 169.5, 166.4, 152.3, 129.0, 124.2, 110.8, 100.9 (d, J = 176.0 Hz), 97.1, 81.1, 70.2 (d, J = 36.0 Hz), 67.0, 47.7 (d, J = 22.7 Hz), 45.1, 42.8, 36.0, 33.0, 32.4 (d, J = 18.9 Hz), 30.1, 27.4, 26.3, 25.3, 22.8 (d, J = 5.7 Hz), 16.0.

(11β)-9-Fluoro-11-hydroxy-17,21-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione (14)

Preparation starting from 0.40 g of **6c** was carried out according to a literature procedure.[9] The product, **14**, was obtained in 99.4% homogeneity (t_R = 5.0 min) by HPLC Method B (0.32 g, 73%): mp 233–240 (dec); IR (KBr) C=O stretch 1719, 1706 cm^{-1}, C=C stretch 1663, 1606 cm^{-1}; CIMS *m/z*: 419 $(M + H)^+$, 399 (-HF); ^1H NMR (d6-DMSO, trace DCl) δ 7.32 (d, J = 10.1 Hz, 1H), 6.24 (dd, J = 10.2, 1.8 Hz, 1H), 6.03 (apparent s, 1H), 4.20 (AB q, J = 18.6 Hz, $\Delta\nu$ = 7.0 Hz, 2H), 4.21 (overlapping m, 1H), 2.75–2.20 (m, 5H), 2.10–1.90 (m, 1H), 1.9–1.75 (m, 1H), 1.75–1.20 (m, 5H) 1.50 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (d6-DMSO) δ 208.3, 185.1, 166.7, 152.6, 128.9, 124.1, 101.0 (d, J = 176 Hz), 98.4, 92.0, 70.4 (d, J = 36 Hz), 68.7, 48.3, 47.7 (d, J = 22.7 Hz), 44.7, 36.3, 33.9, 33.6 (d, J = 19 Hz), 30.2, 28.1, 27.4, 23.7, 23.5, 23.0 (d, J = 5.7 Hz), 16.9; Analysis Calculated for $C_{21}H_{27}O_6F \cdot 0.5\ H_2O$: C, 67.49; H, 7.54; F, 4.45. Found: C, 67.49; H, 7.48; F, 4.62.

General procedure for acetonide derivatization

On a per mmol starting material basis, steroid was dissolved in dioxane (5 mL) and acetone (4 mL), and 70% perchloric acid (0.15 mL) was added. When the reaction was determined complete by TLC (0.5–2 h), sodium acetate (0.17 g) dissolved in water (2 mL) was added to neutralize the acid catalyst. The solutions were concentrated to effect direct crystallization, or if necessary, oils obtained were chromatographed to provide the crystalline products.

(11β,16α,17α)-9-Fluoro-11-hydroxy-17-(hydroxymethyl)-16,17-[1-methylethylidene-bis(oxy)]-D-homoandrosta-1,4-diene-3,17a-dione (15)

A 600 mg sample of **10a** was treated according to the general derivatization procedure. The quenched reaction mixture was concentrated in vacuo to dryness. The residue was dissolved in water (25 mL) and methylene chloride (25 mL). Upon trituration, a waxy solid formed in the methylene chloride layer. The entire mixture was filtered, and the solids obtained were dissolved in 50 mL $CHCl_3$ at reflux, dried with $MgSO_4$, filtered, and cooled. Upon addition of 100 mL heptane, the solution became cloudy and crystallization followed. After standing for 30 min, the crystalline solid was filtered and dried for 1 h in vacuo to provide **15** possessing 99.1% homogeneity (t_R = 4.8 min) by HPLC Method B (252 mg, 38%): mp 255–257 C (dec); IR (KBr) C=O stretch 1711, 1665 cm^{-1}, C=C stretch 1621, 1609 cm^{-1}; CIMS *m/z*: 435 $(M + H)^+$, 415 (-HF); ^1H NMR (d6-DMSO), trace DCl) δ 7.32 (d, J = 10.2 Hz, 1H), 6.23 (dd, J = 10.2, 1.5 Hz, 1H), 6.03 (apparent s, 1H), 4.45 (apparent s, 1H), 4.16 (apparent d, J = 6.8 Hz, 1H), 3.54 (AB q, J = 11.7 Hz, $\Delta\nu$ = 38.0 Hz, 2H), 2.75–2.50 (m, 2H), 2.5–2.3 (m, 2H), 2.20–1.75 (m, 6H), 1.50 (s, 3H), 1.27 (s, 6H), 1.13 (s, 3H); ^{13}C NMR (d6-DMSO) δ 212.3, 185.4, 166.8, 152.5, 129.2, 123.9, 107.3, 100.8 (d, J = 176 Hz), 85.0, 75.6, 69.3 (d, J = 34 Hz), 64.0, 48.8 (d, J = 22.7 Hz), 46.4, 37.3, 36.5, 32.9 (d, J = 20.8 Hz), 30.2, 29.6, 27.3, 27.0, 26.6, 24.3, 23.1, (d, J = 5.7 Hz), 16.5; Analysis Calculated for $C_{24}H_{31}O_6F \cdot 0.25\ H_2O$: C, 65.70; H, 7.23; F, 4.33. Found: C, 65.70; H, 7.24; F, 4.39.

(11β,16α17R)-9-Fluoro-11,16-dihydroxy-2',2'-dimethylspiro[D-homoandrosta-1,4-diene-17,4'-[1,3]dioxolane]-3,17a-dione (16)

The water/methylene chloride filtrate obtained during **15** isolation was allowed to stand overnight, and the mixture was filtered to remove additional solids (primarily **15** by HPLC). The methylene chloride layer was separated, concentrated to dryness, and the residue was purified by flash chromatography (silica eluted with $CHCl_3$/MeOH; 95:5). Product-rich fractions as determined by TLC (silica eluted with CHCl3/MeOH/AcOH; 95:5:0.5), were concentrated to approximately one-fifth volume. The crystalline product precipitated was filtered and dried in vacuo to provide **16** possessing 99.8% homogeneity (t_R = 4.6 min) by HPLC Method B (59 mg, 9%): mp 241–244 C (dec); IR (KBr) C=O stretch 1717, 1666 cm^{-1}, C=C stretch 1624, 1610 cm^{-1}; CIMS *m/z*: 435 $(M + H)^+$, 415 (-HF); ^1H NMR (d6-DMSO), trace DCl) δ 7.28 (d, J = 10.2 Hz, 1H), 6.23 (apparent d, J = 10.2, 1H), 6.03 (apparent s, 1H), 4.16 (apparent d, J = 6.8 Hz, 1H), 3.95 (AB q, J = 8.9 Hz, $\Delta\nu$ = 142.1 Hz, 2H), 3.82 (apparent s, 1H), 2.8–2.3 (m, 4H), 2.20–1.95 (m, 2H), 1.95–1.7 (m, 3H), 1.65–1.45 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 126 (s, 6H), 1.20 (s, 3H); ^{13}C NMR (d6-DMSO) δ 211.2, 186.6, 168.6, 153.9, 129.5, 124.1, 110.4, 101.6 (d, J = 174.0 Hz), 87.8, 72.8, 69.9 (d, J = 36 Hz), 69.4, 48.6 (d, J = 22.7 Hz), 47.5, 37.5,

37.2, 32.5 (d, J = 20.8 Hz), 30.7, 29.6, 28.5, 27.8, 27.5, 25.4, 23.4 (d, J = 3.8 Hz), 16.6; Analysis Calculated for $C_{24}H_{31}O_6F \cdot 0.42$ H_2O: C, 65.22; H, 7.26; F, 4.30. Found: C, 65.22; H, 7.45; F, 4.18.

(11β,16α,17α)-17-[(Acetyloxy)methyl]-9-fluoro-11-hydroxy-16,17-[1-methylethylidene-bis(oxy)]-D-homoandrosta-1,4-diene-3,17a-dione (17)

A 100 mg sample of **10b** was treated according to the general derivatization procedure, providing **17** possessing 97.9% homogeneity (t_R = 7.5 min) by HPLC Method B (70 mg, 64%): mp 275–277 C (dec); IR (KBr) C=O stretch 1751, 1720 cm^{-1}, C=C stretch 1666, 1625 cm^{-1}, CIMS m/z: 477 $(M + H)^+$, 457 (-HF); ^1H NMR (d6-DMSO, trace DCl) δ 7.28 (d, J = 10.2 Hz, 1H), 6.23 (apparent d, J = 10.2, 1H), 6.03 (apparent s, 1H), 4.43 (apparent s, 1H), 4.22 (AB q, J = 11.9 Hz, $\Delta\nu$ = 16.7 Hz, 2H), 4.16 (overlapping m, 1H), 2.8–2.3 (m, 3H), 2.20–1.85 (m, 5H), 1.95–1.7 (m, 3H), 1.65–1.45 (m, 1H), 1.50 (s, 3H), 1.30 (s, 3H), 1.28 (s, 6H), 1.35–1.2 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (d6-DMSO) δ 210.4, 185.2, 169.9, 166.6, 152.3, 129.2, 123.9, 107.8, 100.7 (d, J = 174 Hz), 82.5, 75.6, 69.4 (d, J = 34.1 Hz), 64.3, 47.8 (d, J = 22.7 Hz), 37.0, 36.5, 31.9 (d, J = 20.8 Hz), 30.1, 27.0, 26.2, 23.9, 23.0 (d, J = 3.8 Hz), 20.5, 16.7; Analysis Calculated for $C_{26}H_{33}O_7F \cdot 0.11$ H_2O: C, 65.26; H, 7.00; F, 3.97. Found: C, 65.26; H, 6.94; F, 3.95.

(11β,16β,17R)-9-Fluoro-11,16-dihydroxy-2',2'-dimethylspiro[D-homoandrosta-1,4-diene-17,4'-[1,3]dioxolane]-3,17a-dione (18):

A 48 mg sample of **11** was treated according to the general derivatization procedure, providing **18** possessing 99.0% homogeneity (t_R = 3.6 min) by HPLC Method B (37 mg, 70%): mp 295–298 C (dec); IR (KBr) C=O stretch 1710, 1665 cm^{-1}, C=C stretch 1616, 1609 cm^{-1}; CIMS m/z: 435 $(M + H)^+$, 415 (-HF); ^1H NMR (d6-DMSO, trace DCl δ 7.27 (d, J = 10.0 Hz, 1H), 6.23 (apparent d, J = 10.0, 1H), 6.02 (apparent s, 1H), 4.15 (apparent d, J = 6.8 Hz, 1H), 3.98 (AB q, J = 8.2 Hz, $\Delta\nu$ = 166.2 Hz, 2H), 3.82 (dd, J = 9.5, 4.7 Hz, 1H), 2.75–2.3 (m, 4H), 2.20–1.80 (m, 3H), 1.60–1.25 (m, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.26 (s, 6H), 1.22 (s, 3H);^{13}C NMR (d6-DMSO) δ 210.2, 185.1, 166.5, 152.3, 129.1, 123.8, 109.4, 100.7 (d, J = 174 Hz), 89.2, 72.3, 69.2 (d, J = 34.1 Hz), 66.2, 47.7 (d, J = 122.7 Hz), 46.1, 38.1, 37.3, 32.1 (d, J = 20.8 Hz), 30.1, 26.9, 26.3, 25.4, 23.0 (d, J = 3.8 Hz), 16.6; Analysis Calculated for $C_{24}H_{31}O_6F \cdot 0.28$ H_2O: C, 65.59; H, 7.24; F, 4.32. Found: C, 65.59; H, 7.23; F, 4.19.

(11β)-9-Fluoro-11,17-dihydroxy-D-homoandrosta-1,4,16-triene-3,17a-dione (19) and (11β)-9-fluoro-11,17-dihydroxy-16-(hydroxymethyl)-D-homoandrosta-1,4,16-triene-3,17a-dione (20)

A 350 mg sample of **10a** dissolved in 90 mL methanol and 105 mL of deionized water was reacted with 8.8 mL of 1N aqueous NaOH at room temperature. After 30 min, reaction was stopped by the addition of 8.8 mL of 1N aqueous HCl. The solution was concentrated under vacuum to about two-thirds of its original volume, and chromatographed by preparative HPLC (Spherisorb ODS-2 column eluted with methanol/water, 60:40, at 2 mL/min). Fractions containing a component eluting at 20.5 min (HPLC method A) were combined and concentrated to effect precipitation. After filtering and drying, a sample of **19** possessing 98.5% homogeneity (t_R = 3.1 min) by HPLC method B was obtained (93 mg, 30%): mp 255–256 C (dec); (KBr) C=O stretch 1664 cm^{-1}, C=C stretch 1639, 1605 cm^{-1}; FABMS m/z: 347 $(M + H)^+$, 327 (-HF); ^1H NMR (d6-DMSO) δ 8.10 (exch. s, 1H), 7.28 (d, J = 10.1 Hz, 1H), 6.23 (dd, J = 10.1, 1.5 Hz), 6.03 (apparent s, 1H), 5.90 (m, 1H), 5.43 (exch. d, J = 5 Hz, 1H), 4.19 (m, 1H), 2.70–2.20 (m, 4H), 2.20–1.90 (m, 3H), 1.80–1.45 (m, 2H), 1.50 (s, 3H), 1.40–1.20 (m, 1H), 1.27 (s, 3H); ^1H NMR (d6-DMSO), trace DCl) δ 7.28 (d, J = 10.1 Hz, 1H), 6.23 (dd, J = 10.1, 1.5 Hz), 6.03 (apparent s, 1H), 5.90 (m, 1H), 4.19 (m, 1H), 2.70–2.20 (m, 4H), 2.20–1.90 (m, 3H), 1.80–1.45 (m, 2H), 1.50 (s, 3H), 1.40–1.20 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (d6-DMSO) δ 199.5, 185.0, 166.4, 152.1, 144.9, 129.0, 123.8, 116.1, 100.2 (d, J = 176.0 Hz), 68.6 (d, J = 34.1 Hz), 47.5 (d, J = 22.7 Hz), 42.9, 41.5, 36.0, 32.4 (d, J = 18.9 Hz), 30.0, 26.1, 24.1, 23.0 (d, J = 5.7 Hz), 17.7; Analysis Calculated for $C_{20}H_{23}O_4F \cdot 0.12$ H_2O: C, 68.91; H, 6.72; F, 5.45. Found: C, 68.91; H, 6.60; F, 5.69. Fractions containing a component eluting at 11.5 min (HPLC method A) were combined and concentrated under vacuum to effect precipitation. After filtering and drying, a sample of **20** possessing 98.5% homogeneity (t_R = 3.1 min) by HPLC method B was obtained (66 mg, 20%): mp 285–290C (dec); (KBr) C=O stretch 1666 cm^{-1}, C=C stretch 1624, 1609 cm^{-1}; FABMS m/z: 377 $(M + H)^+$, 347 (-HCHO), 327 (-HCHO, -HF); ^1H NMR (d6-DMSO) δ 7.29 (d, J = 10.1 Hz, 1H), 6.23 (dd, J = 10.1, 1.7 Hz), 6.02 (apparent s, 1H), 5.45 (exch. d, J = 4 Hz, 1H), 4.83 (exch. t, J = 5 Hz, 1H), 4.18 (d, J = 5 Hz, 2H), 4.18 (overlapping m, 1H), 2.75–2.30 (m, 4H), 2.20–1.90 (m, 3H), 1.80–1.45 (m, 2H), 1.50 (s, 3H), 1.35–1.20 (m, 1H), 1.27 (s, 3H); (d6-DMSO, trace DCl) δ 7.29 (d, J = 10.1 Hz 1H), 6.23 (dd, J = 10.1, 1.7 Hz), 6.02 (apparent s, 1H), 4.18 (s, 2H), 4.18 (overlapping m, 1H), 2.75–2.30 (m, 4H), 2.20–1.90 (m, 3H), 1.80–1.45 (m, 2H), 1.50 (s, 3H), 1.35–1.20 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (d6-DMSO) δ 199.2, 185.1, 166.6, 152.2, 139.8, 130.4, 129.1, 123.8, 100.4 (d, J = 176.0 Hz), 68.7 (d, J = 34.1 Hz), 57.9, 47.6 (d, J = 22.7 Hz), 42.1, 40.7, 36.2, 32.4 (d, J = 20.8 Hz), 30.0, 26.2, 25.2, 23.0 (d, J = 5.7 Hz), 17.8; Analysis Calculated for $C_{21}H_{25}O_5F \cdot 0.39$ H_2O: C, 65.77; H, 6.78; F, 4.95. Found: C, 65.77; H, 6.71; F, 4.87. This experiment was also performed on 100 mg of **11**, and provided virtually identical results.

(11β,11β)-16,16-Methylenebis[9-fluoro-11,17-dihydroxy-D-homoandrosta-1,4,16-triene-3,17a-dione] (22)

A 300 mg sample of **10a** (0.76 mmol) was dissolved in 20 mL DMF and 20 mL deionized water at reflux temperature (~80°C). After adding 1.2 mL of 1N aqueous NaOH (1.2 mmol), the solution was maintained at about 80 C for 2 h. After cooling to room temperature, the solution was concentrated to dryness under vacuum. The solid obtained was redissolved in 100 mL of deionized water and filtered. Upon treating the filtrate with 1.0 mL AcOH (1.75 mmol), crystallization was allowed to proceed overnight. Upon filtering and drying, **22** nearly homogeneous by TLC (dichloromethane/MeOH/AcOH, (90:10:2), R_f = 0.85) was obtained (224 mg, 83%). An analytical sample was obtained by dissolving 200 mg of **22** in AcOH (5 mL) with heat, adding 5 mL of deionized water, and allowing the solution to stand overnight at room temperature. After filtering and drying, **22** possessing 99.5% homogeneity (t_R = 42.6 min) by HPLC Method B was obtained (67 mg, 34% recovery): mp 285–290 C (dec); (KBr) C=O stretch 1664 cm^{-1}, shoulder C=C stretch 1637, 1617 cm^{-1}; FABMS m/z: 705 $(M + H)^+$, 703 $(M-H)^{-1}$; ^1H NMR (d6-DMSO) δ 8.00 (exch. s, 2H), 7.28 (d, J = 10.1 Hz, 2H), 6.23 (apparent d, J = 10.1 Hz, 2H), 6.02 (apparent s, 2H), 5.48 (exch. d, J = 2.3 Hz, 2H), 4.18 (m, 2H), 3.21 (s, 2H), 2.75–1.85 (m, 16H),

1.85–1.65 (m, 2H), 1.65–1.45 (m, 2H), 1.49 (s, 6H), 1.25 (s, 6H); ^{1}H NMR (d6-DMSO, trace DCl) δ 7.29 (d, J = 10.1 Hz, 2H), 6.23 (apparent d, J = 10.1 Hz, 2H), 6.02 (apparent s, 2H), 5.48 (exch. d, J = 2.3 Hz, 2H), 4.18 (apparent d, J = 7.0 Hz, 2H), 3.21 (s, 2H), 2.75–1.85 (m, 16H), 1.85–1.65 (m, 2H), 1.65–1.45 (m, 2H), 1.49 (s, 6H), 1.25 (s, 6H); ^{13}C NMR (d6-DMSO) δ 198.9, 185.2, 166.7, 152.4, 141.9, 129.2, 128.0, 123.9, 100.5 (d, J = 175.4 Hz), 68.6 (d, J = 34.8 Hz), 47.7 (d, J = 22.8 Hz), 42.3, 40.8, 36.2, 32.3 (J = 20.0 Hz), 31.6, 30.0, 28.6, 26.3, 23.1 (J = 5.3 Hz), 17.9; Exact mass MS analysis: Calculated $(M + H)^+$ for $C_{41}H_{47}O_8F_2$: 705.3239 Found: 705.3244.

Results

All reactions were monitored by reverse-phase HPLC with detection of the A-ring chromophore common to each substance at 240 nm. An authentic sample of the metal-catalyzed rearrangement product was prepared by treating **6a** with a catalytic amount of ferric chloride in DMF at 90°C, and this substance was confirmed to have the same molecular ion as **6a** by FAB MS. Similarly, **6b** was subjected to the same metal-catalyzed rearrangement, providing the rearrangement product as its 21-acetate analog.

On treating **6a** with 7 mM sodium carbonate at room temperature, 60% of the starting material (t_R 11.9 min) was lost within 30 min and two products appeared in 4:1 ratio. The predominant component (t_R 8.0 min), subsequently isolated by preparative HPLC, was also shown to possess the same molecular ion as **6a** by FAB MS. The minor product (t_R 8.8 min) was noted to possess the same retention time as the product obtained by the metal-catalyzed route, suggesting identity. To rule out possible involvement of trace metal ions in generating the late-eluting rearrangement product, the base-catalyzed rearrangement was repeated in the presence of EDTA (in a control experiment, metal-catalyzed rearrangement was demonstrated to be completely suppressed in the presence of a molar excess of EDTA). A similar 4:1 ratio of products was observed, and a sample isolated from the mixture and known to contain both components was examined by proton NMR. Resonances characteristic of the metal-catalyzed rearrangement product were observed, and the relative intensities of resonances corresponding to each product were found to roughly match the ratio of products evident by HPLC. This experiment clearly confirmed that the substance eluting at 8.8 min was common to both degradation routes.

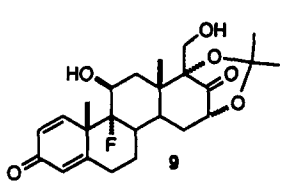
Each rearrangement product was treated with acetone/perchloric acid and their respective acetonide derivatives were isolated and studied to establish structural identity. The metal-catalyzed product yielded two acetonides in about 3:1 ratio. Changes in chemical shift observed for protons on the 16 and 21 positions (relative to starting material) indicated reaction at the 16,17 diol in the predominant product, while union of 17 and 21 hydroxyl groups was evident for the minor acetonide product. The 21-acetate of the metal-catalyzed rearrangement product also formed an acetonide linking the 16 and 17 hydroxyl groups, while the major product obtained from base-catalyzed rearrangement yielded a single acetonide in which the 17 and 21 hydroxyl groups were joined.

CMR chemical shift data provided by acetonide derivatives is often of value in determining the orientation of hydroxyl groups on cyclic structures, and this information has been widely used to support stereochemical assignments and conformational preferences of carbohydrates and natural products.[10] In particular, the chemical shift of quaternary acetonide carbons has proven highly diagnostic for determining the ring size of cyclic acetonides.[11] Specifically applicable to this study, quaternary carbons of 5-membered cyclic acetonides (1,3-dioxolanes) have been shown to appear about 10 ppm downfield relative to those of 6-membered cyclic acetonides (1,3-dioxanes) typically present at 97–101 ppm. Also, the acetonide methyl groups of 6-membered 1,3-dioxanes generally show larger differences in chemical shift.

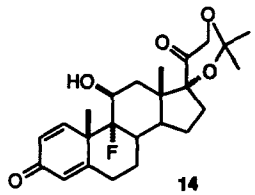
The presence of 1,3-dioxolanes was clearly indicated for the 16,17-acetonides of the metal-catalyzed products, rather than 1,3-dioxanes (as would be required for **9**, the 16,17-acetonide of **7a**, and its corresponding 21-acetate; Table 1). The unambiguous assignment of a 98 ppm

Table 1 Comparison of key chemical shifts of rearrangement product acetonide derivatives with those of known structure

	Acetonide quaternary carbon (O—C—O)	Acetonide methyl 1	Acetonide methyl 2
6a 16,17-acetonide (**12**)	110.3	26.2	25.2
6b 16,17-acetonide (**13**)	110.8	26.3	25.3
6c 17,21-acetonide (**14**)	98.8	28.4	23.9
metal-catalyzed product 16,17-acetonide (**15**)	107.3	27.3	26.6
metal-catalyzed product 17,21-acetonide (**16**)	110.4	27.8	25.4
metal-catalyzed product 16,17-acetonide 21 acetate (**17**)	107.8	27.0	26.2
major base-catalyzed product, 17,21-acetonide (**18**)	109.4	26.3	25.4



9



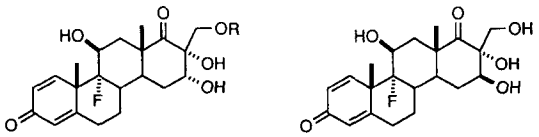
14

resonance to the quaternary carbon of the 6-membered acetonide of **6c** (i.e., **14**) provided specific validation of the assumptions used in assigning acetonide ring size, and these findings clearly ruled out the possibility of a D-homo acyloin rearrangement pathway for the metal-catalyzed rearrangement.

The metal-catalyzed rearrangement products from **6a** and **6b** were subsequently assigned structures **10a** and **10b**, while the predominant base-catalyzed rearrangement product was assigned structure **11** (Figure 4). A comparison of key proton NMR resonances for these substances, their acetonides and related compounds is shown in Table 2.

Pivotal to these assignments was the determination of stereochemistry about the 16 position for **10a** and **11**. A 0.5-ppm difference in chemical shift for their respective 16-protons indicated opposite orientation at this position and suggested chair conformations for their D-rings. Furthermore, the presence of the 16-proton of **11** upfield relative to the corresponding **10a** resonance implied an α (axial) orientation for H-16 of **11** and a β (equatorial) disposition for H-16 or **10a**.[12] The coupling patterns observed for the C-15–C-16 protons of each product were consistent with this interpretation: $J_{15,16}$ values of 10.7 and 5.4 Hz were measured for **11** (approximating H-15-H16 dihedral angles of 180° and 60° predicted by the Karplus equation), while $J_{15,16}$ values of 4.7 and 4.7 Hz were noted for **10a** (approximating the predicted value for a dihedral angle of 60° for both). Thus, the 16-hydroxyl substituent was shown to be oriented α (axial) for **10a** and β (equatorial) for **11**.

The formation of **15** (Figure 4) requires that an α hydroxyl group be present at the 17 position; this fact



10a R = H
b R = Ac

11

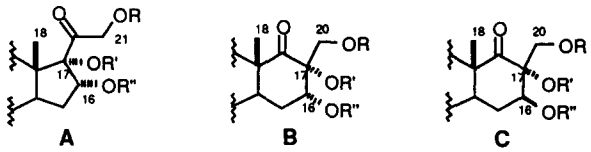
Figure 4 Structures established for metal ion catalyzed (**10a,b**) and base-catalyzed (**11**) triamcinolone rearrangement product.

established the stereochemistry of the 17 position of **10a**. Similarly, the absence of a 16,17-acetonide derivative from **11** suggests α orientation of the 17-hydroxyl group for this product also. NOE experiments were subsequently performed and the data obtained indicated a close proximity of the 21-methylene to the C-18 methyl protons for both **10a** and **11**; the β (axial) orientation of the 21-hydroxymethyl group was thereby confirmed for each product.

Attempts were made to subject **10a** and **11** to more forceful base-catalyzed conditions in order to facilitate the reverse reaction and a reestablishment of the 4:1 thermodynamic product ratio. However, in separate experiments both **10a** and **11** were found to degrade with loss of stereochemistry to mixtures of **19** and **20** (Figure 5).

Structures assigned to these isolated degradants are clearly supported by NMR, MS, and IR data. Both substances are readily soluble in aqueous base in the absence of cosolvents, and this finding is consistent with the presence of an ionizable α-diketone (16,17α-dione) in each substance. Similar behavior has been observed with other α-diketones.[13] A possible β-diketone assign-

Table 2 Key ^1H and ^{13}C chemical shift data for triamcinolone, triamcinolone rearrangement products, and their respective derivatives



X = $>C<^{CH_3}_{CH_3}$

		^1H (ppm)			^{13}C (ppm)		
		16	*21*	*18*	*16*	*17*	*21*
A	**6a** R, R′, R″ = H	4.77	4.30	0.85	71.3	87.4	66.6
	6b R = Ac, R′, R″ = H	4.69	4.91	0.85	71.6	87.8	68.1
	12 R = H, R′, R″ = X	4.91	4.30	0.80	80.7	97.1	65.8
	13 R = Ac, R′, R″ = X	4.87	4.94	0.83	81.1	97.1	67.1
		16	*20*	*18*	*16*	*17*	*20*
B	**10a** R, R′, R″ = H	3.95	3.58	1.31	67.9	80.3	64.5
	10b R = Ac, R′, R″ = H	4.02	4.11	1.24	66.0	76.9	63.6
	15 R = H, R′, R″ = X	4.45	3.54	1.13[a]	75.6	85.0	64.0
	16 R′, R″ = X, R″ = H	3.82	3.95	1.20[a]	72.8	87.8	69.4
	17 R = Ac, R′, R″ = X	4.43	4.22	1.14[a]	75.5	82.4	64.2
C	**11** R, R′, R″ = H	3.55	3.66	1.41	75.4	83.5	64.9
	18 R′, R″ = X, R″ = H	3.62	4.04	1.38[a]	72.3	89.2	66.2

[a] Alternate assignment as acetonide methyl also possible.

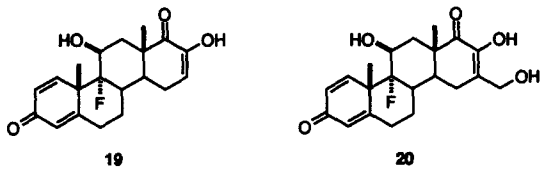


Figure 5 Structures for base-catalyzed degradants **19** and **20**.

ment was ruled out by NMR COSY experiments (which show a close proximity of the proton on position 16 to both those on position 15), and by comparison of the carbon NMR spectra of **19** and **20** to those of authentic samples of 1,2-cyclohexanedione and 1,3-cyclohexanedione.

Discussion

We have rationalized two distinct mechanisms for metal-catalyzed and base-catalyzed rearrangements based on the above assignments and the limited distribution of products generated from each route. In the base-catalyzed rearrangement (Figure 6, upper), abstraction of the triamcinolone 16-hydroxyl proton is followed by retro-aldol ring opening, thereby relieving the steric strain present in the vicinity of the C-13-C-17 bond. Presumably, the enolate formed is stabilized by a hydrogen bond with the 17-hydroxy group, and this interaction fixes the local stereochemistry about the C-17–C-20 double bond (intermediate A). Formal proton transfer to the 20-hydroxyl group accompanies or just precedes the aldol ring closure.

Although molecular models indicate that free rotation may occur about the C-13–C-17 bond in intermediate A, reversal of the enolate facing would give rise to a highly strained and disfavored boat geometry in the aldol cyclization. The C-16 aldehyde may be aligned in one of two possible conformations in the chair-like transition state; as might be expected, a pseudo-equatorial positioning of the carbonyl (conformer 1) predominates over a pseudo-axial positioning (conformer 2), resulting in the 4:1 ratio of **11** to **10a**. Thus, the combined effects of two rotationally-constrained stereogenic centers (C-13 and C-14), an enolate assembly of fixed orientation, and a chair-like cyclic transition state results in a high preference for one of four possible diastereomeric products.

In the metal-catalyzed rearrangment (Figure 6, lower), chelation of the divalent or trivalent metal ion by the 20-keto and 17α-hydroxyl groups takes place initially, and this interaction catalyzes the retro-aldol ring opening. Analogous to the situation with base-catalyzed rearrangement, the C-17–C-20 double bond stereochemistry is fixed by metal-ion chelation, and the aldol cyclization occurs through a chair-like transition state. However, the C-16 aldehyde carbonyl appears to assume a pseudo-axial position exclusively in the transition state (as no **11** is subsequently measurable at an HPLC detection limit of 0.2%). This dramatic shift in product ratio is presumably due to a direct (intermediate B) or indirect interaction (intermediate C) between the C-16 carbonyl and the metal ion during ring closure. The factors that cause one specific product to be produced (out of four possible diastereomeric outcomes) include those rationalized above for the base-catalyzed route and, in addition, control of the C-16 stereochemistry by the metal ion. The fact that triamcinolone (**6a**) and triamcinolone 21-acetate (**6b**) undergo the metal-catalyzed transformation with equal facility indicate that chelation of the 21-hydroxyl is not important from a mechanistic standpoint.

While a variety of metal ions are capable of catalyzing the latter transformation, the most effective we have found is titanium(IV); rapid, near quantitative conversions of **6a** and **6b** to their respective rearrangement products **10a** and **10b** have been effected with titanium isopropoxide. Unoptimized, isolated yields of 75% and 78% were obtained, respectively, which provided sufficient material for the study of base-catalyzed degradation of **10a** and **10b**.

The formation of **19** can be easily rationalized by a retro-aldol loss of formaldehyde, followed by β-elimination of hydroxide. Once formed, some of the **19** reacts with formaldehyde to produce **20** (Figure 7). When

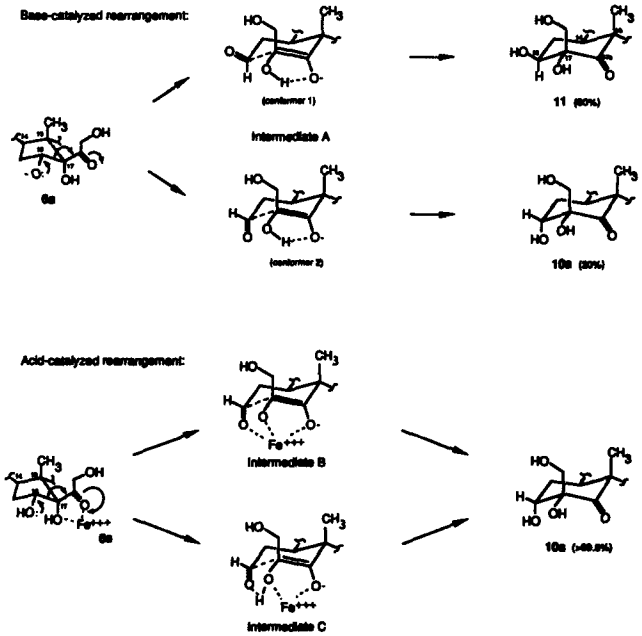


Figure 6 Rational mechanisms for base and metal ion catalyzed rearrangement of triamcinolone.

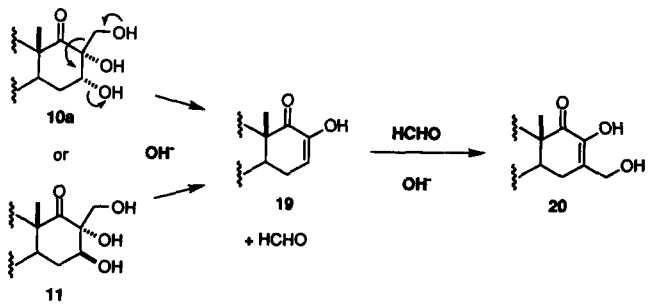


Figure 7 Proposed mechanism for **19** and **20** formation.

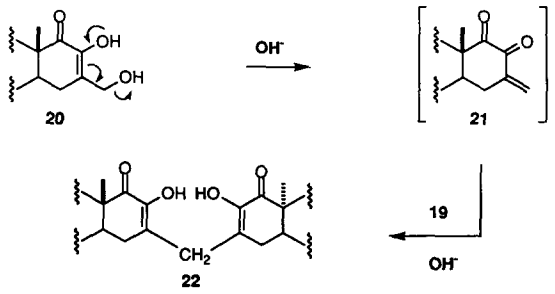


Figure 8 Proposed mechanism for **22** formation.

aqueous base solutions of **10a** or **11** were heated, **19** and **20** initially formed were further converted to **22** in high yield (Figure 8). Formation of the latter can be rationalized as proceeding through reaction of the anion of **19** with a reactive vinylidene intermediate, **21**, originating from **20** through to second β-elimination.

In conclusion, the commercial antiinflammatory drug triamcinolone has been shown to rearrange by separate but similar pathways to **10a** and **11** when exposed to trace metals or to dilute aqueous base. Mechanistic models are proposed to explain each route, and they are consistent with the ratio of products isolated. Under more vigorous conditions of aqueous base treatment, the rearrangement products undergo further decomposition with loss of stereochemistry. While these pathways have been demonstrated specifically for triamcinolone, other 16,17-dihydroxy-20-ketosteroids have also been reported to be sensitive to base and/or trace metals, and different rearrangement products and pathways have been rationalized.[7,8,14] The structures assigned in these earlier reports were not strongly supported by spectroscopic data, however, and reanalysis of the reported proton NMR data strongly suggests behavior analogous to that described in this work. Thus, it appears that these pathways are generally applicable to 16,17-dihydroxy-20-ketosteroids as a class.

This investigation also identifies a window of stability for compounds such as **10a** and **11**, and it demonstrates experimental conditions allowing for two chiral centers to be generated in one synchronous operation. Thus, in principle, it should be possible to extend the observations and interpretations of this study to the stereoselective synthesis of other 6-membered α,β-dihydroxyketones.

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References

1. Wendler NL (1964). The acyloin rearrangement in D-homoannulation. In: de Mayo P (ed), *Molecular Rearrangements*, Vol. 2. Interscience, New York, pp. 1114–1121.
2. Kirk DN, Hartshorn MP (1968). II. The D-homo rearrangement. In: *Steroid Reaction Mechanisms*. Elsevier, Amsterdam, pp. 294–313.
3. Boswell GA (1972). Ring D homoannulation of 17-hydroxy-20-ketopregnane derivatives In: Fried J, Edwards JA (eds), *Organic Reactions in Steroid Chemistry*, Vol. II Van Nostrand Reinhold, New York, pp. 382–386.
4. Ruzicka L, Mehldahl HF (1938). The conversion of 17-ethynyl-androstene derivatives into pregnenone derivatives. Preparation of the 17-oxy-progesterones. *Helv Chim Acta* **21**:1760.
5. Turner RB (1953). Stereospecificity in the rearrangement of 17-hydroxy-20-ketosteroids. *J Am Chem Soc* **75**:3584–3488.
6. For example, see Bischofberger N, Walker KAM (1985). Effects of 16-heterosubstitution on the regiochemistry of the D-homo rearrangement. *J Org Chem* **50**:3604–3609.
7. For an example, see Heller M, Stolar SM, Bernstein S (1961). 16-Hydroxylated steroids. XX. Some transformations of 16β,21-diacetoxy-17a-hydroxypregn-4-ene-3,20-dione. *J Org Chem* **26**:5036–5043.
8. Smith LL, Marx M, Garbarini JJ, Foell T, Ortigoni VE, Goodman JJ (1960). 16α-Hydroxysteroids. VII. The isomerization of triamcinolone. *J Am Chem Soc* **82**:4616–4625.
9. Tanabe M, Bigley B (1961). 17α-21-Isopropylidenedioxy steroids. *J Am Chem Soc* **83**:756–757.
10. Examples include: Pachler KGR, Rathbone EB, Woolard GR, Woudenberg M (1980). Conformational analysis of 1,2:3,4-di-O-isopropylidene-a-D-galacto-octapyranose derivatives: a ^{1}H and ^{13}C-NMR-spectral and x-ray comparative study. *Carbohydr Res* **79**:29–37 and Clayton JP, Oliver RS, Rogers NH (1979). The chemistry of Pseudomonic Acid. Part 3. The rearrangement of pseudomonic acid A in acid and basic solution. *J Chem Soc, Perkin Trans I*: 838–846.
11. Buchanan JG, Edgar AR, Rawson DI, Shahidi P, Wightman RH (1982). Assignment of ring size in isopropylidene acetals by carbon-13 NMR spectroscopy. *Carbohyd Res* **100**:75–86.
12. Bhacca NS, Williams DH (1964). Factors affecting coupling constants. In: *Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field.* Holden-Day, London, pp. 49–53.
13. Kruger H-R, Marschall H, Weyerstahl P, Nerdel F (1973). 4,7-Dimethyl-2,9-dioxatricyclo[5.3.0.0^{4,10}]dedane from 3,6-bis-(iodmethyl)- and 3,6-bis(*p*-tolysulfonyloxymethyl)-3,6-dimethyl-1,2-cyclohexandione. *Chem Ber* **106**:2255–2262.
14. Wendler NL, Taub D, Kuo H (1960). Mechanism of alkali-catalyzed D-homoannulation of 16,17α-dihydroxy-20-keto steroids. A contribution to the mechanism of dehydrobromination of α-bromo ketones. *J Am Chem Soc* **82**:5701–5704.