Articles

Synthesis and Antiinflammatory Activity of Novel 12β-Substituted Analogues of Betamethasone†

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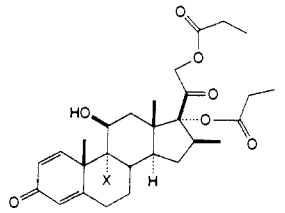
Received April 11, 1989

A series of 9α-halo-12β-hydroxy and 12β-acyloxy analogues of betamethasone 17,21-dipropionate were synthesized and tested for topical antiinflammatory potency in the croton oil ear assay. The compounds were assayed for systemic absorption in the contralateral ear assay, in which it was found that 12β-hydroxy analogues **9**, **13**, and **15** were all absorbed but the corresponding 12β-esters **11a–e**, **14**, and **16** were not. On repeated high-dose applications to the mouse ear, there was no evidence of systemic absorption of any 12β-propionate ester as gauged by thymus weights (thymic involution) and plasma cortisol levels (adrenal suppression). Results of limited SAR studies showed that topical antiinflammatory activity and systemic absorption were not greatly influenced by the 9α-halogen but were largely dependent on the polarity and size of the 12 substituent. While the optimal compounds **14** and **16** were less topically active than the controls beta- and beclomethasone dipropionate, unlike the controls, they displayed no systemic effects, even after repeated high-dose applications. Surprisingly, propionate **14** was devoid of atrophogenic activity.

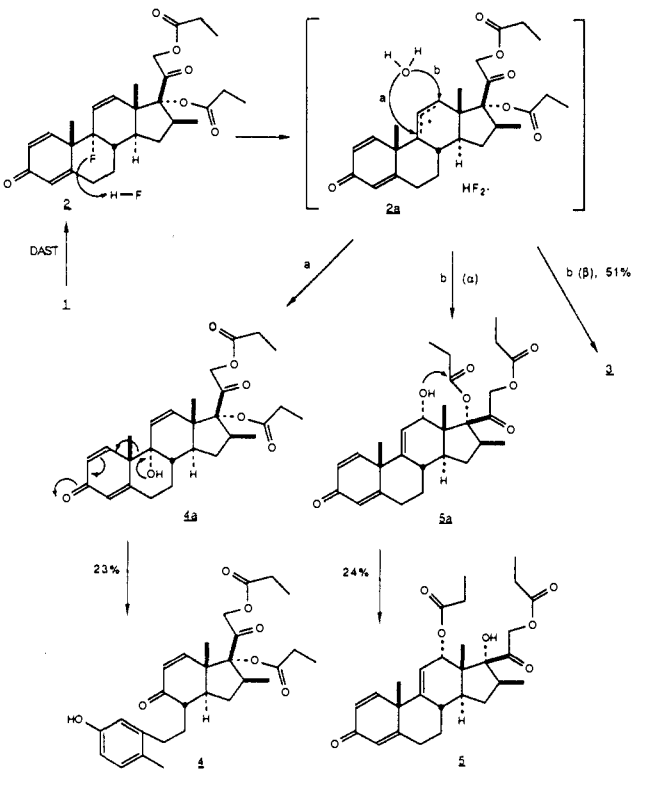
The search for highly potent topically active antiinflammatory corticosteroids has been in progress for decades. Numerous clinically useful agents have resulted, such as triamcinolone acetonide, flucinolone acetonide, betamethasone 17,21-dipropionate[1] (**1**), and beclomethasone 17,21-dipropionate[2] (**1a**). When used judiciously, these steroids find wide application in a variety of inflammatory processes.



1, X = F
1a, X = Cl

Although compounds such as these have been chosen for use based on a relatively superior separation of topical action from unwanted systemic absorption, they are nonetheless readily absorbed through the skin.[3] Unwanted systemic absorption can assume clinically relevant proportions when large areas of skin are treated or when treatment is prolonged.[4] Thus, a clear need exists for topically potent antiinflammatory agents that are either not systemically absorbed or undergo facile systemic metabolism to inactive compounds. Recent success in the latter approach has been reported for androstene 17-thioketals (for example, tipredane)[5] and 17β-carboxyandrostane esters.[6] In the former vein, we have found that the introduction of a hydrophobic 12β-acyloxy group into bromo-, beclo-, or betamethasone 17,21-dipropionate gives rise to novel, topically potent structures that are not systemically absorbed. The chemistry and structure–ac-

Scheme I



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† Dedicated to Professor W. G. Dauben on the occasion of his 70th birthday.

(1) Ferrante, M. G.; Rudy, B. C. In *Analytical Profiles of Drug Substances, 6*; Florey, K., Ed.; Academic Press: New York, 1977; p 43.
(2) Small, P. *Ann. Allergy* **1982**, *49*, 127.
(3) Haynes, R. C., Jr.; Murad, F. In *The Pharmacological Basis of Therapeutics*; Goodman, L. S., Gilman, A. G., Eds.; Macmillan Publishing Co., Inc.: New York, 1980; p 1466.

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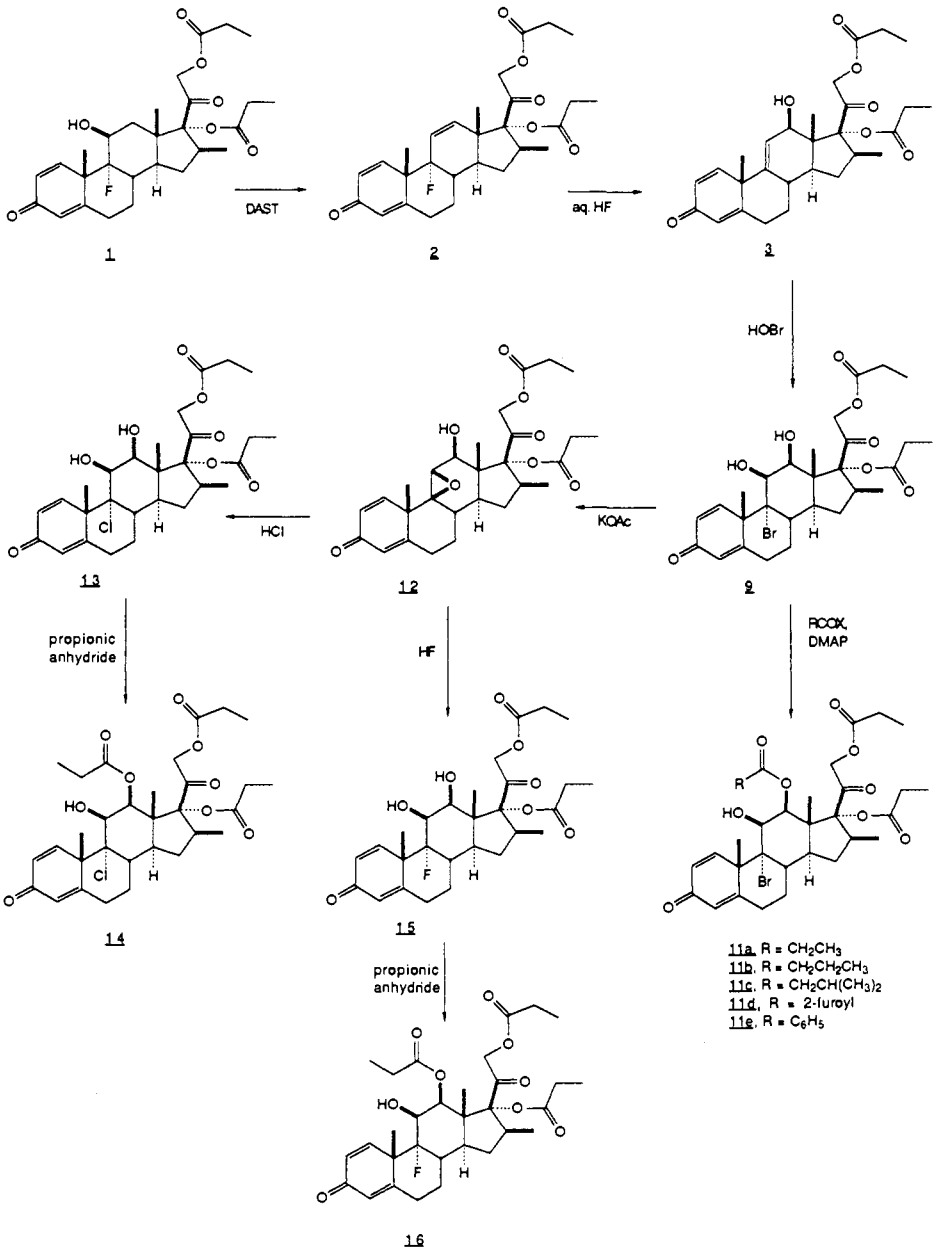
Scheme II



tivity relationships (SAR) of these derivatives are described in this paper.

Chemistry Results

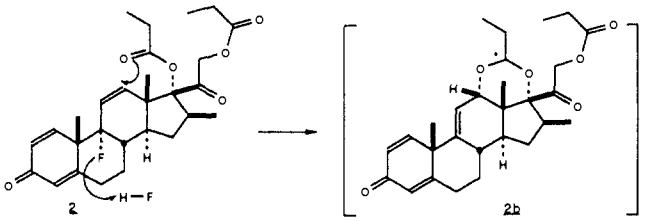
A number of good methods exist for the introduction of halogen[7] at C-12 in the corticoid nucleus, but they are not readily adapted to the synthesis of corticoids bearing the 9α-halo-11β,12β-dihydroxy functional arrangement (e.g., **9**) that we required.

We had previously found that dehydration of betamethasone dipropionate (**1**) with (diethylamido)sulfur trifluoride (DAST) in CH_2Cl_2 gave $\Delta^{11,12}$-allylic fluoride **2** in excellent yield.[8] Although the $\Delta^{11,12}$-unsaturation of **2** did not react with conventional electrophilic reagents as a method for hydroxylation of C-12, the allylic system underwent solvolytic reaction to afford useful products. Thus, on treatment of **2** in CH_2Cl_2 with a small amount of 48% aqueous HF, C-12β-hydroxylated species **3** (Scheme II) was obtained (51%) in addition to secosteroid **4** (23%) and the 12α-hydroxy steroid **5** (24%), as shown in Scheme I.

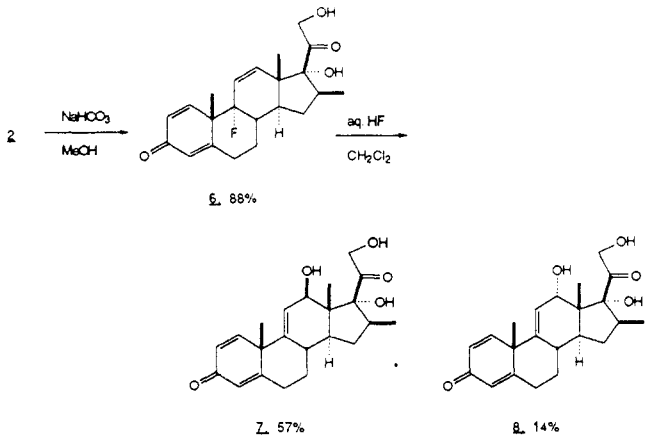
Acid-catalyzed solvolysis of *tert*-alkyl fluorides[9] and benzyl fluorides[10] has been postulated to involve initial complexation of the organofluoride with acid (X–H···F–R) followed by attack of water on the resulting carbonium ion. As suggested in Scheme I, solvolysis of **2** to **2a** followed

(4) Popper, T. L.; Watnick, A. S. In *Medicinal Chemistry, 13-1*; Scherrer, R. A., Whitehouse, M. W., Eds.; Academic Press: New York; 1974, p 247. Elks, J.; Philips, G. H. In *Medicinal Chemistry*; Roberts, S. M., Price, B. J., Eds.; Academic Press, Inc.: London, 1985; p 167.
(5) Wojnar, R. J.; Varma, R. K.; Free, C. A.; Millonig, R. C.; Karanewsky, D.; Lutsky, B. N. *Arzneim.-Forsh.* **1986**, *36(II)*, No. 12, 1782.
(6) Olejniczak, E.; Lee, H. J. *Steroids* **1984**, *43* (6), 657 and references therein.
(7) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Tewson, T. J. *J. Chem. Soc. Perkin Trans. 1* **1977**, 2365. Taub, D.; Hoffsommer, R. D.; Wendler, N. L. *J. Am. Chem. Soc.* **1975**, *79*, 452. Diassi, P. A.; Fried, J.; Palmere, R. M.; Sabo, E. F. *J. Am. Chem. Soc.* **1961**, *83*, 4249.
(8) Green, M. J.; Shue, H.; Tanabe, M.; Yasuda, D. M.; McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Chem. Commun.* **1977**, 611.
(9) Chapman, N. B.; Levy, J. L. *J. Chem. Soc.* **1951**, 1677.
(10) Miller, W. T., Jr.; Bernstein, J. *J. Am. Chem. Soc.* **1948**, *70*, 3600.

by attack of water either at C-9 (path a, product **4**), C-12α (path b, product **5**), or C-12β (path b, product **3**) is consistent with previous mechanistic studies and our findings. The possibility of intramolecular reaction of the 17α-ester with the incipient C-12 carbonium ion (**2** → **2b**) during

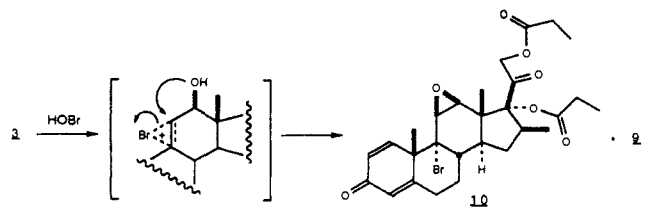


solvolysis seemed an attractive alternate explanation, but it was considered unlikely for the following reasons. First, **2b** is a stable oxocarbonium ion, which on capture by water should lead solely to **5** (not **3** and **4**). The second more compelling reason has to do with the course of this reaction in the absence of both 17- and 21-esters. Treatment of **2** with aqueous $NaHCO_3$ in refluxing MeOH afforded diol **6** in excellent yield. On solvolysis of **6** under identical conditions used for the solvolysis of **2** (aqueous HF/CH_2Cl_2), a similar ratio (ca. 3:1) and yield of 12β:12α products were observed:



These results would tend to favor the mechanism shown in Scheme I. Mechanistic considerations aside, these results demonstrate the utility and generality of this solvolysis as a novel synthetic approach to 12-hydroxy corticoids.

With 12β-hydroxy-$\Delta^{9,11}$-allyl alcohol **3** in hand, its conversion to desired targets, such as **16**, was readily envisaged. Application of standard steroidal C ring methodology to **3** was employed,[11] as shown in Scheme II, in order to reintroduce the crucial 9α-halo-11β-hydroxy functionality. Hydrobromination of **3** with *N*-bromoacetamide in dioxane (trace of aqueous $HClO_4$) afforded the expected target bromohydrin **9** (63%) together with bromo epoxide **10** (15%), derived by intramolecular collapse of the intermediate bromonium ion.



(11) Fieser, L. F.; Fieser, M. In *Steroids*; Reinhold Publishing Co.: New York, 1959; Chapter 19, p 600.

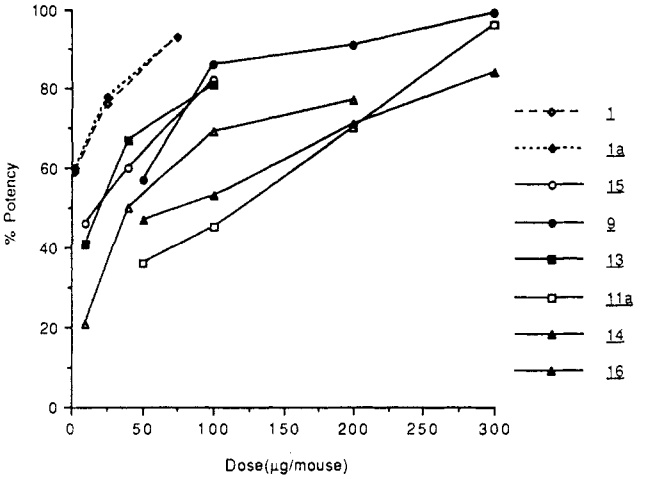


Figure 1. Topical antiinflammatory activity of betamethasone analogues in the mouse ear assay.

Selective acylation of the C-12β hydroxyl group of **9** was straightforward. Under catalysis by 4-(*N*,*N*-dimethylamino)pyridine (DMAP), **9** underwent acylation in CH_2Cl_2 in the presence of pyridine to afford esters **11a–d** in good yields. Formation of benzoate **11e** required excess DMAP and benzoyl chloride in CH_2Cl_2, but as a result improved yields (>85%) were realized. Although the improved procedure was not applied to esters **11a–d**, it is anticipated to be applicable to them as well. With a series of 9α-bromo 12β-esters available for SAR, the next step involved replacement of chloro or fluoro groups at C-9. This was accomplished through the intermediacy of bromohydrin **9**, by dehydrobromination with KOAc leading to the expected 9β,11β-epoxide **12** (85%). Upon exposure of **12** to anhydrous HCl in $CHCl_3$, the desired chlorohydrin **13** was obtained (69%). As before, acylation of **13** with propionic anhydride afforded tripropionate ester **14** (61%). Finally, reaction of **12** with HF in THF gave the target fluorohydrin **15** (85%), acylation of which produced 12β-hydroxybetamethasone 12,17,21-tripropionate (**16**; 68%).

Structure–Activity Relationships

The 12β-hydroxy (**9**, **13**, **15**) and 12β-acyloxy (**11a–e**, **14**, **16**) analogues of betamethasone 17,21-dipropionate (**1**) were tested for topical efficacy in a modified croton oil ear assay[12] (mouse), with both **1** and beclomethasone 17,21-dipropionate (**1a**) as standards, as shown in Figure 1 or Table I.

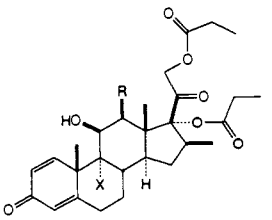
As can be gathered from the nonlinearity of the dose–response curves in Figure 1, it is difficult to estimate relative potencies for all of the analogues. If the maximal topical antiinflammatory responses are approximated by extrapolation, then rough ED_{100} values can be obtained as shown in Table II.

The ED_{100} was not greatly affected on introduction of a 12β-hydroxyl group into either **1** (i.e., **15**) or **1a** (i.e., **13**). Although the maximum topical response produced by 9α-bromo-12β-hydroxy analogue **9** is only about $^1/_2$ that of the analogous Cl or F analogues, **9** was more potent than would be expected based on the Fried–Bormann enhancement factors (systemic) for 9α-halogens.[13] On the other hand, the result for **9** relative to Cl or F analogues is perhaps not unusual in light of studies by Shue et al.,[14]

(12) Tonelli, G.; Thibault, L.; Ringler, I. *Endocrinology* **1965**, *77*, 625. The procedure was modified to use TPA/ethanol (8.5 nmol/10 μL) in place of croton oil.

(13) Wolff, M. E. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley & Sons: New York, 1981; Part III, Chapter 63.

Table I. Antiinflammatory Activities of Betamethasone Analogues in the TPA-Induced[a] Mouse Ear Edema Assay



no.	X	R	dose, μg/mouse	% antiinflammatory potency (single applcn) topical[b]	% antiinflammatory potency (single applcn) systemic[b]	% systemic effect (five applcns) thymolytic effect[c]	% systemic effect (five applcns) adrenal suppression effect[d]	mp	analysis elemental	analysis HRMS (calcd)
1	F	H	2.5	59	27	30	12	–	–	–
			25	76	30	74	24			
			75	93	72	87	37			
1a	Cl	H	2.5	60	12	12	1	–	–	–
			25	78	40	52	32			
			75	93	52	67	36			
9	Br	OH	50	57	16	7	12	175(d)	C,H	580.1619 (580.1672)
			100	86	17	0	14			
			200	91	17	7	15			
			300	99	22	–	–			
11a	Br	$O_2CCH_2CH_3$	50	36	0[e]	2	2	178(d)	C,H	557.275 (557.275)[f]
			100	45	0	6	6			
			200	70	0	2	0			
			300	96	0	–	–			
11b	Br	$O_2CCH_2CH_2CH_3$	300	68	0[e]	–	–	169–171	C,H	571.291 (571.291)[f]
11c	Br	$O_2CCH_2CH(CH_3)_2$	300	54	0[e]	–	–	198(d)	C,H	585.306 (585.306)[f]
11d	Br	$O_2CC_4H_3O$	300	69	0[e]	–	–	212–4	C,H	595.257 (595.254)[f]
11e	Br	$O_2CC_6H_5$	300	84	0[e]	–	–	150–2	C,H	–
13	Cl	OH	10	41	0	4	2	207–8	C,H	536.218 (536.218)
			40	67	5	0	13			
			100	81	21	5	14			
14	Cl	$O_2CCH_2CH_3$	50	47	0[e]	4	5	143–4	C,H	592.244 (52.244)
			100	53	0	5	5			
			200	71	0	0	6			
			300	84	0	–	–			
15	F	OH	10	46	7	9	1	119–121	C,H	520.246 (520.247)
			40	60	11	13	10			
			100	82	19	21	30			
16	F	$O_2CH_2CH_3$	10	21	0[e]	0	0	203–5	C,H	
			40	50	0	1	6			
			100	69	0	4	0			
			200	77	0	–	–			

[a] Dose of TPA: 8.8 nmol/mouse. [b] Coefficient of variation = 10–25% (n = 6). [c] Effect was measured by weight loss of the thymus. Coefficient of variation = 10–21% (n = 6). [d] Effect was determined by measuring the inhibition of increased plasma cortisol induced by stress. Coefficient of variation = 12–30% (n = 6). [e] No statistically relevant systemic effect observed. [f] M – Br MS peak.

Table II. Estimated ED_{100} Values of Betamethasone Analogues

no.	ED_{100}, μg/mouse	no.	ED_{100}, μg/mouse
1	110	13	160
1a	110	11a	325
15	140	14	400
9	325	16	400

[a] Obtained via extrapolation of data from Table I, which has a coefficient of variation of 10–25%.

who have examined the effect of 7α-halogen substitution on topical potency in betamethasone-like base structures (e.g., alclometasone) and shown that potencies range on the order of 7α-Br > Cl > F > I.

The degree of systemic absorption of these analogues was measured in three ways. First, contralateral (distal ear) topical application, in the modified croton oil ear assay,[12] allowed for an indirect determination of the degree of systemic absorption. As shown in Table I, both BMDP (1) and BCDP (1a) exhibited marked systemic absorption at the topical ED_{100} values. When applied at a site distant from the inflammation, 1 was 75% as effective as when applied directly; similarly, 1a was 50% as potent. The 12β-hydroxy analogues 9, 13, and 15 all showed similar, if slightly attenuated, signs of systemic absorption. As can be seen in this series (12β-OH), varying the halogen substituent at C-9 did not greatly influence the degree of systemic absorption as all three analogues displayed about 15–20% distal topical potency (at concentrations for 80% of the maximal topical antiinflammatory response).

The other method used to assess the degree of systemic absorption was to examine hypothalamic–pituitary–adrenal axis function, based on thymic involution (thymus weight) and adrenal suppression[15] (plasma cortisol) after multiple topical applications of the corticoid. The results, shown in Table I for the controls BMDP (1) and BCDP (1a), are consistent with those obtained for the single distal topical application. Thymus weights were dramatically reduced (by 70–90%) as were plasma cortisol levels (36%),

(14) Shue, H.; Green, M. J.; Berkenkoph, J.; Monahan, M.; Fernandez, X.; Lutsky, B. N. *J. Med. Chem.* **1980**, *23*, 430. *Ibid. Arzneim.-Forsh.* **1980**, *30* (*II*), No. 10, 1618.

(15) Lutsky, B. N.; Berkenkopf, I.; Fernandez, X.; Monahan, M.; Watnick, A. S. *Arzneim.-Forsh.* **1979**, *29* (II), No. 7, 992 and ref 5.

Table III. Atrophogenicity of Betamethasone Analogues

no.	dose,[a] μg/mouse	skin thickness, μm	% potency
vehicle		16.52 ± 2.35	0
1	75	9.39 ± 1.99	43
1a	75	8.12 ± 3.08	51
13	200	13.92 ± 1.88	15.7
14	300	16.50 ± 3.43	0.1

[a] Applied topically on a daily basis for 3 weeks at the approximate ED_{90} value.

clearly demonstrating a high degree of systemic absorption. For fluoro alcohol **15**, both thymus weight and adrenal suppression were influenced by increasing dose in a regular manner, whereas the bromo (**9**) and chloro (**13**) alcohols were not. This effect is presumably related to the lower relative intrinsic systemic activities of **9**/**13** compared to **15**. In any event, all three 12-hydroxy analogues are clearly absorbed through the skin.

In stark contrast are the corresponding propionate esters **11**, **14**, and **16**, none of which demonstrate any evidence of systemic absorption (Table I) even after multiple high-dose applications. It is interesting to note that, upon esterification of the 12β-hydroxy group, the ED_{100} values become relatively independent of the 9α-halogen (Table II).

As can be seen in Table I, topical efficacy is sensitive to the 12-ester. Thus, potency follows the order propionyl (**11a**) > butyryl (**11b**) > isovaleryl (**11c**) for aliphatic esters. On the other hand, bulky aromatic esters such as benzoyl (**11e**) or furoyl (**11d**) are still quite potent. Furthermore, none of these esters were systemically absorbed.

In addition to systemic toxicity, prolonged topical corticosteroid therapy can result in clinically significant atrophy of the skin,[16] which is thought to arise primarily by an inhibition of DNA synthesis.[17] Consequently, we sought to examine 9α-chloro-12β-hydroxycorticoid **13** and the corresponding propionate **14** for atrophogenicity, as previously described in the mouse.[18] The results of repeated topical applications of the analogues **13** and **14**, vs **1** and **1a**, on skin thickness are shown in Table III.

Both beta- and beclomethasone dipropionate (**1** and **1a**, respectively) are quite atrophogenic whereas 12β-alcohol **13** is moderately toxic. In contrast, the corresponding tripropionate **14** is completely inert. To the best of our knowledge, **14** is the first example of a moderately potent topical corticoid that is virtually devoid of atrophogenic activity. By comparison, even noteworthy topical agents such as tipredane[18] and clobetasone butyrate[4,18] have, respectively, 10 and 20% atrophogenic potency (relative to halcinonide).

Work in progress is aimed at gaining an understanding of the highly localized and selective action of this promising new class of topical antiinflammatory agents.

Experimental Section

All solvents were dried over 4-Å molecular sieves after preliminary drying by distillation and were stored under argon. Glassware was flame-dried under argon, and solvent/reagent transfers were accomplished via dry syringe. Standard chromatographic techniques were employed, i.e., flash chromatography using E. Merck silica gel (Keiselgel 60, 230–400 mesh) with HPLC-grade solvents and TLC on 0.2-mm silica gel Merck F254 plates. Unless otherwise indicated, ^1H NMR spectra ($CDCl_3$, referenced to $CHCl_3$ at δ 7.27) were obtained with a Varian XL-400 spectrometer operating at 400 MHz. IR spectra were recorded with a Perkin-Elmer 1310 spectrometer. All melting points were determined on a Thomas capillary melting point apparatus and are uncorrected. Mass spectral data were obtained on a CEC 21-110B high-resolution, double-focusing spectrometer. Elemental analyses were determined by Desert Analytics, Tucson, AZ.

17α,21-Dihydroxy-9α-fluoro-16β-methylpregna-1,4,11-(12)-triene-3,20-dione 17,21-Dipropionate (2). To a solution of betamethasone dipropionate (1; 39.25 g or 0.078 mmol) in CH_2Cl_2 (400 mL) at 0 °C under argon was added, dropwise, DAST (25 g or 0.156 mol). The mixture was warmed to ambient temperature, stirred for 16 h, and poured into ice water (400 mL). The aqueous layer was washed with CH_2Cl_2 (1 × 400 mL) and then the combined organic layer was washed with water (2 × 200 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated to afford crude **2**. Flash chromatography on silica gel (600 g) with 2:3 EtOAc/hexane gave pure **2**, 36.55 g (93%) as a white solid, which was recrystallized from EtOAc/hexane. Mp: 136–137 °C. ^1H NMR (90 MHz): δ 0.85 (s, 3 H), 1.15 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.35 (d, J = 8 Hz, 3 H), 1.75 (m, 3 H), 2.40 (q, J = 7.2 Hz, 2 H), 2.50 (q, J = 7.2 Hz, 2 H), 4.35 (d, J = 16.2 Hz, 1 H), 5.01 (d, J = 16.2 Hz, 1 H), 5.99 (dd, J = 2, 11 Hz, 1 H), 6.20 (br s, 1 H), 6.35 (dd, J = 2.5, 11 Hz, 1 H), 6.65 (dd, J = 5, 11 Hz, 1 H), 7.12 (d, J = 11 Hz, 1 H). EIMS (m/e): 486 (M^+), 468, 412, 399, 392, 356, 351. Exact mass calcd for $C_{28}H_{35}O_6F$: 486.2417. Found: 486.2435.

17α,21-Dihydroxy-9α-fluoro-16β-methylpregna-1,4,11-(12)-triene-3,20-dione (6). To a solution of vinyl fluoride **2** (200 mg or 0.41 mmol) in MeOH (10 mL) was added $NaHCO_3$ (1 g). The mixture was refluxed for 1 h, cooled, and added to saturated aqueous NaCl (100 mL). The mixture was extracted with EtOAc (2 × 75 mL), dried over $MgSO_4$, and filtered. The solvent was removed to give crude diol **6** as a white solid. The solid was washed with Et_2O (3 × 2 mL) and dried under vacuum to give pure **6** (135 mg or 88%). Mp 195 °C. ^1H NMR (90 MHz): δ 1.05 (s, 3 H), 1.07 (d, J = 7 Hz, 3 H), 1.27 (s, 3 H), 4.50 (s, 2 H), 6.10 (m, 3 H), 6.30 (dd, J = 2, 11 Hz, 1 H), 7.07 (d, J = 11 Hz, 1 H). EIMS (m/e): 374 (M^+), 356, 354, 344, 342, 315, 314, 297, 295. Exact mass calcd for $C_{22}H_{27}O_4F$: 374.1893. Found: 374.1909.

16β-Methyl-12,17α,21-trihydroxypregna-1,4,9(11)-triene-3,20-dione (7 and 8). To a solution of diol **6** (37 mg or 0.099 mmol) in CH_2Cl_2 (2 mL) at 22 °C under argon was added 48% aqueous HF (0.01 mL). The mixture was vigorously stirred for 90 min and passed through silica gel (1 g), washing with EtOAc. After evaporation of the solvent, the mixture was placed on one PTLC plate (1.5 mm thick, SiO_2) and eluted with EtOAc. The higher R_f material, **8**, weighed 7 mg (19%). This material was shown to be the 12α-alcohol by comparison of TLC/NMR to those of a sample of **5**, which had been hydrolyzed with $NaHCO_3$/MeOH. ^1H NMR (90 MHz): δ 0.90 (s, 3 H), 1.05 (d, J = 7 Hz, 3 H), 1.40 (s, 3 H), 4.55 (s, 2 H), 4.61 (d, J = 6.5 Hz, 1 H), 5.60 (d, J = 6.5 Hz, 1 H), 6.0 (br s, 1 H), 6.20 (dd, J = 2, 11 Hz, 1 H), 7.15 (d, J = 11 Hz, 1 H). EIMS (m/e): 372 (M^+), 356, 354, 342, 327, 325, 313. DCIMS, NH_3 (m/e): 372, 356, 355, 341, 325, 313, 295. The lower R_f material, **7**, weighed 21 mg (57%) and could be recrystallized from Et_2O. Mp: 144–146 °C. This material was shown to be the 12β-alcohol by comparison to a sample of **3**, which had been hydrolyzed with $NaHCO_3$/MeOH. ^1H NMR (90 MHz): δ 0.90 (s, 3 H), 1.15 (d, J = 7 Hz, 3 H), 1.45 (s, 3 H), 4.55 (AB, J = 20 Hz, 2 H), 4.60 (br s, 1 H), 5.40 (br s, 1 H), 6.10 (br s, 1 H), 6.30 (dd, J = 2, 11 Hz, 1 H), 7.20 (d, J = 11 Hz, 1 H). EIMS (m/e): 372 (M^+), 357, 354, 342, 339, 336, 327, 325, 313, 297, 295. DCIMS, NH_3 (m/e): 373 (M + H), 372 (M^+), 355, 343, 341, 313, 295, 255.

16β-Methyl-12β,17α,21-trihydroxypregna-1,2,9(11)-triene-3,20-dione 17,21-Dipropionate (3). To a solution of vinyl fluoride **2** (28.65 g or 0.059 mol) in CH_2Cl_2 (1.5 L) was added 48% aqueous HF (7.0 mL). The heterogeneous mixture was stirred rapidly at 23 °C under argon for 5 h and then poured into water (500 mL). The organic layer was washed with water (2 × 500 mL) and saturated aqueous NaCl (1 × 100 mL), dried over Na_2SO_4, and filtered. The solvent was removed to give a crude product mixture consisting of **3** and two other major substances. The desired

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product **3** could be removed from the mixture in pure form by crystallization from Et_2O. Mp: 167–169 °C. Alternatively, if desired, the mixture could be flash chromatographed on silica gel (EtOAc/hexane, 1:1) to afford **3** and the following, in the order of elution: **16β-Methyl-3,17α,21-trihydroxy-9,10-secopregna-1,3,5,11-tetraene-9,20-dione 17,21-dipropionate (4)** (6.87 g, 24%), as a white foam. IR (Nujol): 3350, 1740, 1670 cm^{-1}. UV (MeOH): λ_m 222 (ε = 16 900), 282 (ε = 2400) nm. ^1H NMR (90 MHz): δ 0.94 (s, 3 H), 1.1 (d, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 6 H), 2.23 (s, 3 H), 2.45 (q, J = 7 Hz, 4 H), 4.74 (q, J = 16 Hz, 2 H), 5.99 (d, J = 10 Hz, 1 H), 6.60 (d, J = 8 Hz, 1 H), 6.70 (br s, 1 H), 7.0 (d, J = 8 Hz, 1 H), 7.38 (d, J = 10 Hz, 1 H). EIMS (m/e): 484 (M^+). Exact mass calcd for $C_{28}H_{36}O_7$: 484.2461. Found: 484.2426. Next was obtained **16β-methyl-12α,17α,21-trihydroxypregna-1,4,9-triene-3,20-dione 12,21-dipropionate (5)** (6.44 g, 23%). Mp: 135–136 °C. IR (Nujol): 3420, 1740, 1670 cm^{-1}. ^1H NMR (90 MHz): δ 0.77 (s, 3 H), 1.09 (d, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 6 H), 1.43 (s, 3 H), 2.44 (q, J = 7 Hz, 4 H), 4.85 (br, 1 H), 5.03 (q, J = 16 Hz, 1 H), 5.47 (br, 1 H), 6.11 (br, 1 H), 6.31 (dd, J = 2, 10 Hz, 1 H), 7.24 (d, J = 10 Hz, 1 H). EIMS (m/e): 484 (M^+). Exact mass calcd for $C_{28}H_{36}O_7$: 484.2461. Found: 484.2450. The desired product **3** eluted last (14.55 g, 51%) and could then be crystallized from Et_2O. Mp: 167–168 °C. ^1H NMR: δ 0.76 (s, 3 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.15 (t, J = 7.5 Hz, 3 H), 1.30 (d, J = 7.2 Hz, 3 H), 1.40 (s, 3 H), 1.60 (m, 2 H), 2.16 (m, 6 H), 2.38 (q, J = 7.5 Hz, 2 H), 2.43 (q, J = 7.5 Hz, 2 H), 2.64 (dddd, J = 1, 6, 14, 14 Hz, 1 H), 4.44 (d, J = 16.8 Hz, 1 H), 4.76 (br dt, J = 2, 7.3 Hz, 1 H), 5.40 (br t, J = 2 Hz, 1 H), 5.52 (d, J = 16.8 Hz, 1 H), 6.06 (br t, J = 1.8 Hz, 1 H), 6.29 (dd, J = 1.8, 10 Hz, 1 H), 7.15 (d, J = 10 Hz, 1 H). IR (Nujol): 3400, 1740, 1670 cm^{-1}. EIMS (m/e): 484 (M^+), 469, 413, 410, 397, 395. Exact mass calcd for $C_{28}H_{36}O_7$: 484.2461. Found: 484.2450. Anal. ($C_{28}H_{36}O_7$): C, H.

9α-Bromo-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate (9). To a solution of allylic alcohol **3** (4.1 g or 8.5 mmol) in dioxane (250 mL) under argon at 23 °C was added recrystallized *N*-bromoacetamide (3.94 g or 28.5 mmol) and 0.5 N $HClO_4$ (2.9 mL). The flask was wrapped in foil, and after stirring for 22 h, was poured into 5% aqueous Na_2SO_3 (500 mL). The mixture was extracted with EtOAc (3 × 150 mL), the combined organic layer was washed with 5% aqueous Na_2SO_3 (2 × 100 mL) and then H_2O (1 × 200 mL) and dried over $MgSO_4$. Filtration and evaporation gave crude **4** as an oil, which was flash chromatographed on silica gel (200 g) with 1:1 EtOAc/hexane to separate **9α-bromo-17α,21-dihydroxy-11β,12β-epoxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate (10)** (720 mg, 15%), as a white foam. ^1H NMR (90 MHz): δ 0.90 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.22 (t, J = 7 Hz, 3 H), 1.34 (d, J = 7 Hz, 3 H), 1.61 (s, 3 H), 1.75 (m, 3 H), 2.48 (q, J = 7 Hz, 4 H), 3.67 (d, J = 3 Hz, 1 H), 3.80 (d, J = 3 Hz, 1 H), 4.40 (d, J = 16 Hz, 1 H), 5.0 (d, J = 16 Hz, 1 H), 6.20 (br s, 1 H), 6.35 (dd, J = 2, 10 Hz, 1 H), 7.20 (d, J = 10 Hz, 1 H). EIMS (m/e): 562 (M^+), 475, 391. Exact mass calcd for $C_{28}H_{35}O_7{}^{79}Br$: 562.1566. Found: 562.1588. The desired product **9** eluted last and was obtained as a white solid (3.10 g, 63%). Mp: 175 °C dec. ^1H NMR: δ 0.99 (s, 3 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.27 (d, J = 7.3 Hz, 3 H), 1.32 (ddd, J = 9.7, 12.1, 13.0 Hz, 1 H), 1.69 (s, 3 H), 1.86 (m, 1 H), 1.94 (ddd, J = 5.9, 8.0, 11.9 Hz, 1 H), 2.16 (ddd, J = 4.0, 11.2, 11.2 Hz, 1 H), 2.25 (m, 2 H), 2.44 (q, J = 7.5 Hz, 2 H), 2.46 (dq, J = 4.0, 7.5 Hz, 2 H), 2.60 (dddd, J = 2.2, 7.0, 13.8, 15.2 Hz, 1 H), 3.15 (s, 1 H, exchangeable), 3.70 (br, 1 H, exchangeable), 4.50 (d, J = 16.6 Hz, 1 H), 4.54 (d, J = 3.8 Hz, 1 H), 4.75 (d, J = 3.8 Hz, 1 H), 5.34 (d, J = 16.6 Hz, 1 H), 6.08 (br t, J = 1.7 Hz, 1 H), 6.35 (dd, J = 1.8, 10.1 Hz, 1 H), 7.19 (d, J = 10.1 Hz, 1 H). EIMS (m/e): 580 (M^+), 522, 506, 466.

9α-Bromo-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 12,17,21-Tripropionate (11a). To a solution of bromohydrin **9** (200 mg or 0.43 mmol) in CH_2Cl_2 (8 mL) at 22 °C under argon were added propionic anhydride (0.3 mL, 2.2 mmol), pyridine (0.45 mL or 5.5 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 30 mg or 0.24 mmol). The reaction was monitored by TLC (30% benzene/Et_2O, silica gel) and was complete in 30 min. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous NH_4Cl (3 × 75 mL). The volatiles were evaporated, and the residue was chromatographed on two silica gel PTLC plates (2 mm thick) with 7:3 benzene/Et_2O. The pure product **11a** (159 mg, 73%) was crystallized from Et_2O/CH_2Cl_2. Mp: 178 °C dec. ^1H NMR: δ 1.08 (s, 3 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.25 (d, J = 7.3 Hz, 3 H), 1.36 (ddd, J = 10.3, 12.8, 13.1 Hz, 1 H), 1.67 (s, 3 H), 1.86 (m, 1 H), 1.92 (ddd, J = 5.5, 7.5, 11.8 Hz, 1 H), 2.22 (ddd, J = 4.4, 10.7, 10.7 Hz, 1 H), 2.34 (m, 4 H), 2.42 (q, J = 7.5 Hz, 2 H), 2.43 (q, J = 7.5 Hz, 2 H), 2.44 (q, J = 7.5 Hz, 2 H), 2.60 (dddd, J = 2.2, 6.5, 13.5, 15.5 Hz, 1 H), 4.55 (d, J = 16.5 Hz, 1 H), 4.65 (d, J = 16.5 Hz, 1 H), 4.68 (d, J = 3.5 Hz, 1 H), 6.08 (br t, J = 2.04 Hz, 1 H), 6.11 (d, J = 3.9 Hz, 1 H), 6.31 (dd, J = 1.8, 10.1 Hz, 1 H), 7.08 (d, J = 10.1 Hz, 1 H). DEIMS (m/e): 639, 637 (M + H), 559, 557 (M − Br), 551, 549, 523, 521, 467, 465. DCIMS, NH_3 (m/e): 639, 637 (M + H).

9α-Bromo-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,20-Dipropionate 12-Butyrate (11b). The procedure for the synthesis of **5a** was followed with **9** (200 mg or 0.34 mmol), butyric anhydride (0.28 mL or 1.72 mmol), pyridine (0.42 mL or 5.1 mmol), CH_2Cl_2 (8 mL), and DMAP (30 mg). PTLC as before gave **11b** (130 mg, 58%) as a white solid, which was crystallized from CH_2Cl_2/Et_2O. Mp: 169–171 °C. ^1H NMR: δ 0.96 (t, J = 7.5 Hz, 3 H), 1.10 (s, 3 H), 1.19 (t, J = 7.5 Hz, 3 H), 1.20 (t, J = 7.5 Hz, 3 H), 1.28 (ddd, J = 2.5, 7.5, 14.9 Hz, 1 H), 1.70 (s, 3 H), 1.73 (m, 1 H), 1.90 (m, 1 H), 1.95 (ddd, J = 5.5, 7.7, 12.0 Hz, 1 H), 2.24 (ddd, J = 4.4, 11.5, 11.5 Hz, 1 H), 2.27 (m, 1 H), 2.41 (br t, J = 7.5 Hz, 2 H), 2.45 (q, J = 7.5 Hz, 2 H), 2.47 (q, J = 7.5 Hz, 2 H), 2.63 (dddd, J = 2.0, 6.5, 12.9, 14.8 Hz, 1 H), 4.64 (AB q, J = 16.3 Hz, 2 H), 4.70 (d, J = 3.6 Hz, 1 H), 6.11 (br t, J = 1.8 Hz, 1 H), 6.13 (d, J = 3.6 Hz, 1 H), 6.35 (dd, J = 1.8, 10.1 Hz, 1 H), 7.11 (d, J = 10.1 Hz, 1 H). DEIMS (m/e): 653, 651 (M^+), 595, 594 (M − C_3H_5O), 571 (M − Br), 565, 563, 537, 535, 522, 520, 491, 489, 481, 479. DCIMS, NH_3 (m/e): 653, 651 (M^+), 590, 588.

9α-Bromo-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate 12-Isovalerate (11c). The procedure for the synthesis of **11a** was followed with **9** (200 mg or 0.34 mmol), isovaleryl chloride (0.21 mL or 1.72 mmol), pyridine (0.42 mL or 5.1 mmol), CH_2Cl_2 (8 mL), and DMAP (30 mg). PTLC as before gave **11c** (96 mg, 42%), as a white solid, which was crystallized from CH_2Cl_2/Et_2O. Mp: 198 °C dec. ^1H NMR: δ 0.97 (d, J = 6.5 Hz, 6 H), 1.07 (s, 3 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.26 (d, J = 7.1 Hz, 3 H), 1.36 (ddd, J = 10, 11.9, 12.8 Hz, 1 H), 1.67 (s, 3 H), 1.70 (m, 1 H), 1.87 (m, 1 H), 1.92 (ddd, J = 5.6, 7.7, 11.9 Hz, 1 H), 2.10 (m, 1 H), 2.20 (d, J = 6.9 Hz, 1 H), 2.29 (dd, J = 1.3, 6.9 Hz, 1 H), 2.42 (q, J = 7.5 Hz, 2 H), 2.44 (q, J = 7.5 Hz, 2 H), 2.60 (dddd, J = 2, 6.8, 13.9, 15.3 Hz, 1 H), 4.61 (AB, J = 16.3 Hz, 2 H), 4.68 (d, J = 3.5 Hz, 1 H), 6.08 (br t, J = 1.8 Hz, 1 H), 6.10 (d, J = 3.5 Hz, 1 H), 6.32 (dd, J = 1.8, 10.1 Hz, 1 H), 7.07 (d, J = 10.1 Hz, 1 H). DEIMS (m/e): 667, 665 (M + H), 587, 585 (M − Br), 579, 577, 551, 549, 536, 534, 495, 493. DCIMS, NH_3 (m/e): 667, 665 (M + H).

9α-Bromo-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate 12-(2-Furoate) (11d). The procedure for the synthesis of **11a** was followed with **9** (200 mg or 0.34 mmol), 2-furoyl chloride (0.17 mL or 1.72 mmol), pyridine (0.42 mL or 5.1 mmol), CH_2Cl_2 (8 mL), and DMAP (30 mg). PTLC as before gave **11d** (144 mg, 62%), as a white solid, which was crystallized from CH_2Cl_2/Et_2O. Mp: 212–214 °C. ^1H NMR: δ 1.05 (t, J = 7.5 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.18 (s, 3 H), 1.27 (d, J = 7.3 Hz, 3 H), 1.40 (ddd, J = 10.2, 11, 13 Hz, 1 H), 1.68 (s, 3 H), 1.74 (dddd, J = 2, 5.3, 13, 13.5 Hz, 1 H), 1.89 (m, 1 H), 1.95 (ddd, J = 5.6, 7.8, 12 Hz, 1 H), 2.23 (dq, J = 7.5, 16.8 Hz, 2 H), 2.25 (m, 1 H), 2.42 (m, 1 H), 2.44 (q, J = 7.5 Hz, 2 H), 2.62 (dddd, J = 2, 6.8, 12.9, 15.5 Hz, 1 H), 4.53 (AB, J = 16.4 Hz, 2 H), 4.82 (d, J = 3.6 Hz, 1 H), 6.10 (br t, J = 1.8 Hz, 1 H), 6.30 (dd, J = 1.8, 10 Hz, 1 H), 6.305 (d, J = 3.6 Hz, 1 H), 6.51 (dd, J = 1.7, 3.5 Hz, 1 H), 7.08 (d, J = 10 Hz, 1 H), 7.28 (dd, J = 0.75, 3.5 Hz, 1 H), 7.59 (dd, J = 0.75, 1.7 Hz, 1 H). DEIMS (m/e): 677, 675 (M + H), 589, 587, 561, 559, 505, 503. DCIMS, NH_3 (m/e): 677, 675 (M + H), 614, 612, 603, 601, 567, 595.

9α-Bromo-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate 12-Benzoate (11e). To a solution of bromohydrin **9** (192 mg or 0.33 mmol) in CH_2Cl_2 (8 mL) at 23 °C under argon was added benzoyl chloride

(0.4 mL or 3.32 mmol) followed by DMAP (488 mg or 4 mmol). After 5 h at 23 °C, the reaction mixture was diluted with EtOAc (150 mL) and washed with saturated aqueous NH_4Cl (3 × 73 mL). The organic layer was then washed with 2% aqueous NaOH (3 × 75 mL), water (1 × 75 mL), and saturated aqueous NaCl (1 × 75 mL), then dried over $MgSO_4$, and filtered; the solvent was removed to give crude 11e. PTLC on two silica gel plates (2 mm thick) with 8:2 $CHCl_3$/EtOAc gave pure 11e (196 mg, 86%), as a white solid, which was crystallized from Et_2O/petroleum ether. Mp: 150–152 °C. ^1H NMR: δ 0.86 (m, 1 H), 0.97 (t, J = 7.5 Hz, 3 H), 1.21 (t, J = 7.5 Hz, 3 H), 1.28 (s, 3 H), 1.30 (d, J = 7.1 Hz, 3 H), 1.44 (ddd, J = 10.3, 11.5, 12.7 Hz, 1 H), 1.71 (s, 3 H), 1.77 (ddd, J = 5.5, 12.7, 12.7 Hz, 1 H), 1.98 (m, 2 H), 2.00 (dq, J = 7.5, 16.8 Hz, 1 H), 2.17 (dq, J = 7.5, 16.8 Hz, 1 H), 2.31 (ddd, J = 4.3, 10.9, 10.9 Hz, 1 H), 2.33 (m, 1 H), 2.44 (m, 1 H), 2.47 (q, J = 7.5 Hz, 2 H), 2.65 (dddd, J = 1.9, 6.9, 13.1, 14.5 Hz, 1 H), 4.40 (d, J = 16.5 Hz, 1 H), 4.61 (d, J = 16.5 Hz, 1 H), 4.85 (d, J = 3.6 Hz, 1 H), 6.31 (dd, J = 1.8, 10.1 Hz, 1 H), 6.38 (d, J = 3.6 Hz, 1 H), 7.09 (d, J = 10.1 Hz, 1 H), 7.46 (br t, J = 8.5 Hz, 2 H), 7.61 (br tt, J = 1.5, 8.5 Hz, 1 H), 8.60 (br dd, J = 1.5, 8.5 Hz, 2 H). IR ($CHCl_3$): 3400, 3000, 2940, 1730, 1665, 1630, 1610, 1450, 1270, 1190, 1090, 970, 940, 890 cm^{-1}. DEIMS (m/e): 687, 685 (M + H), 599, 597 (M - $CH_2O_2CCH_2CH_3$), 571, 569, 515, 513. DCIMS, NH_3 (m/e): 687, 685, 624, 622, 613, 611, 605, 589, 588, 587, 531, 513, 500, 483.

9β,11β-Epoxy-16β-methyl-12β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate (12). To a solution of bromohydrin **9** (1.52 g or 2.62 mmol) in acetone (60 mL) under argon was added anhydrous KOAc (2.0 g or 20.4 mmol). The mixture was refluxed for 4 h, cooled, added to water (500 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with saturated aqueous NaCl (1 × 100 mL), dried over Na_2SO_4, and filtered. The solvent was removed to give 1.3 g of white powder, which was not stable to silica gel chromatography but could be readily crystallized from Et_2O/hexane, affording pure **12** (1.11 g or 85%). Mp: 239–241 °C. ^1H NMR: δ 0.91 (s, 3 H), 1.12 (t, J = 7.5 Hz, 3 H), 1.15 (t, J = 7.5 Hz, 3 H), 1.19 (ddd, J = 7.3, 12.1, 13 Hz, 1 H), 1.26 (d, J = 7.3 Hz, 3 H), 1.31 (m, 1 H), 1.40 (s, 3 H), 1.42 (m, 1 H), 1.73 (br, exchangeable, 1 H), 1.98 (ddd, J = 5.9, 8, 12.6 Hz, 1 H), 2.06 (m, 1 H), 2.24 (ddd, J = 6.5, 9.9, 9.9 Hz, 1 H), 2.38 (dq, J = 7.5, 17.5 Hz, 2 H), 2.39 (q, J = 7.5 Hz, 2 H), 2.62 (dddd, J = 1.5, 4.8, 13.9, 14.2 Hz, 1 H), 3.32 (d, J = 1.2 Hz, 1 H), 4.39 (d, J = 16.5 Hz, 1 H), 4.43 (br s, 1 H), 5.50 (d, J = 16.5 Hz, 1 H), 6.14 (br s, 1 H), 6.22 (dd, J = 1.8, 10.1 Hz, 1 H), 6.57 (d, J = 10.1 Hz, 1 H). EIMS (m/e): 500 (M^+), 484, 482, 471, 469, 455, 451, 450, 428, 426, 413.

9α-Chloro-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate (13). To a solution of epoxide **12** (760 mg or 1.52 mmol) in $CHCl_3$ (35 mL) was slowly bubbled anhydrous HCl gas (10 min). After stirring an additional 50 min, the reaction was complete by TLC (silica gel, 3:7 EtOAc/$CHCl_3$) and the volatiles were removed under vacuum. The crude mixture was dissolved in 40 mL of 3:7 EtOAc/$CHCl_3$ and treated with silica gel (20 g). After stirring for 30 min, the mixture was filtered and the silica gel was washed with EtOAc. The combined organic layer was evaporated and the residue was flash chromatographed on silica gel (30 g) with 3:7 EtOAc/$CHCl_3$, affording pure **13** (563 mg or 69%) as a white solid. The product was crystallized from CH_2Cl_2/Et_2O. Mp: 207–208 °C. ^1H NMR: δ 0.98 (s, 3 H), 1.15 (t, J = 7.5 Hz, 3 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.27 (d, J = 7.3 Hz, 3 H), 1.30 (ddd, J = 9, 11.9, 12.8 Hz, 1 H), 1.64 (s, 3 H), 1.68 (ddd, J = 6, 11.7, 12.9 Hz, 1 H), 1.82 (m, 1 H), 1.92 (ddd, J = 6, 8, 11.7 Hz, 1 H), 2.18 (ddd, J = 6, 11.8, 13.9 Hz, 1 H), 2.22 (dddd, J = 2.2, 7, 15.5, 15.5 Hz, 1 H), 2.42 (q, J = 7.5 Hz, 2 H), 2.46 (dq, J = 4, 7.5 Hz, 2 H), 2.56 (ddd, J = 6, 11.7, 11.7 Hz, 1 H), 2.60 (dddd, J = 2.2, 7, 13.9, 15.5 Hz, 1 H), 3.12 (br s, exchangeable, 1 H), 3.68 (br, exchangeable, 1 H), 4.35 (d, J = 3.8 Hz, 1 H), 4.49 (d, J = 16.6 Hz, 1 H), 4.57 (d, J = 3.8 Hz, 1 H), 5.34 (d, J = 16.6 Hz, 1 H), 6.09 (br t, J = 1.8 Hz, 1 H), 6.30 (dd, J = 1.8, 10.1 Hz, 1 H), 7.17 (d, J = 10.1 Hz, 1 H). IR (Nujol): 3430, 3000, 1730, 1660, 1610, 1380, 1190 cm^{-1}. DEIMS (m/e): 538, 536 (M^+), 505, 471, 462, 449, 433, 421. DCIMS, NH_3 (m/e): 556, 554 (M + NH_4^+), 539, 537 (M + H), 520, 518, 503, 501, 483, 481, 465, 463.

9α-Chloro-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 12,17,21-Tripropionate (14). To a solution of chlorohydrin **13** (370 mg or 0.69 mmol) in CH_2Cl_2 (15 mL) at 22 °C under argon were added propionic anhydride (0.5 mL or 3.7 mmol), pyridine (0.6 mL or 7.6 mmol), and DMAP (50 mg). After stirring for 4 h, the mixture was poured into CH_2Cl_2 (100 mL), washed with 2% aqueous HCl (2 × 100 mL), and saturated aqueous NaCl (1 × 100 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed to give a glass which was purified by silica gel PTLC (2 mm thick) with 8:2 $CHCl_3$/EtOAc. The resultant white solid, **14** (250 mg or 61%), was crystallized from Et_2O. Mp: 143–144 °C. ^1H NMR: δ 1.08 (s, 3 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.15 (t, J = 7.5 Hz, 3 H), 1.26 (d, J = 7.3 Hz, 3 H), 1.33 (ddd, J = 10.2, 12.1, 13.4 Hz, 1 H), 1.62 (s, 3 H), 1.69 (dq, J = 5.5, 13.8 Hz, 1 H), 1.83 (m, 1 H), 1.90 (ddd, J = 6, 7.8, 11.8 Hz, 1 H), 2.23 (ddd, J = 7.8, 9.8, 13.8 Hz, 1 H), 2.27 (m, 1 H), 2.40 (dq, J = 3.2, 7.5 Hz, 2 H), 2.43 (q, J = 7.5 Hz, 2 H), 2.61 (m, 2 H), 4.50 (dd, J = 1, 3.6 Hz, 1 H), 4.60 (AB, J = 16.3 Hz, 2 H), 5.93 (d, J = 3.6 Hz, 1 H), 6.09 (br t, J = 1.8 Hz, 1 H), 6.31 (dd, J = 1.8, 10 Hz, 1 H), 7.08 (d, J = 10 Hz, 1 H). IR (Nujol): 3420, 1760, 1680, 1610, 1390, 1190 cm^{-1}. DEIMS (m/e): 595, 593 (M + H), 507, 505, 423, 421, 385, 367, 347, 329, 321, 311. DCIMS, NH_3 (m/e): 595, 593 (M + H), 576, 575, 574, 559, 558, 557, 539, 538, 537.

9α-Fluoro-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 17,21-Dipropionate (15). To a solution of anhydrous HF (3 mL) in THF (4 mL) in a Teflon reaction vessel at 5 °C was added epoxide **12** (100 mg or 0.2 mmol). After 24 h at 5 °C, the reaction mixture was poured into a stirred suspension of $NaHCO_3$ (15 g) in EtOAc (100 mL). The mixture was stirred for 60 min and filtered, and the solvent was evaporated. The residue was purified by silica gel PTLC (2 mm thick) eluting with Et_2O/benzene (7:3). The pure product **15** (88 mg or 85%) was crystallized from Et_2O/hexane. Mp: 119–121 °C. ^1H NMR: δ 0.98 (s, 3 H), 1.13 (t, J = 7.6 Hz, 3 H), 1.15 (t, J = 7.6 Hz, 3 H), 1.27 (d, J = 7.3 Hz, 3 H), 1.52 (dq, J = 5.1, 13.8 Hz, 1 H), 1.53 (s, 3 H), 1.88 (m, 1 H), 1.93 (ddd, J = 5.7, 7.9, 15.5 Hz, 1 H), 2.19 (dq, J = 7.3, 15.2 Hz, 1 H), 2.32 (ddd, J = 5.1, 11.6, 11.6 Hz, 1 H), 2.38 (dq, J = 1.5, 7.6 Hz, 2 H), 2.45 (dq, J = 4.2, 7.6 Hz, 2 H), 2.61 (dddd, J = 1.5, 5.8, 11.6, 11.6 Hz, 1 H), 2.93 (br s, exchangeable, 1 H), 4.22 (dd, J = 4, 12.5, Hz, 1 H), 4.24 (dd, J = 4, 7 Hz, 1 H), 4.48 (d, J = 16.5 Hz, 1 H), 5.36 (d, J = 16.5 Hz, 1 H), 6.11 (br t, J = 1.8 Hz, 1 H), 6.33 (dd, J = 1.8, 10.1 Hz, 1 H), 7.19 (d, J = 10.1 Hz, 1 H). IR (Nujol): 3430, 1730, 1660, 1610, 1375, 1180 cm^{-1}. EIMS (m/e): 520 (M^+), 502, 446, 433, 417, 390, 372, 359.

9α-Fluoro-16β-methyl-11β,12β,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 12,17,21-Tripropionate (16). To a solution of fluorohydrin **15** (250 mg or 0.48 mmol) in CH_2Cl_2 (10 mL) at 23 °C under argon were added propionic anhydride (0.32 mL or 2.5 mmol), pyridine (0.5 mL or 6 mmol), and DMAP (30 mg). After 30 min, the reaction mixture was poured into saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with water (1 × 50 mL) and saturated aqueous NaCl (1 × 50 mL), dried over $MgSO_4$, and filtered, and the solvent was removed. The residue was purified by silica gel PTLC (3 × 2 mm thick) eluting with 7:3 Et_2O/benzene. The pure product **16** (188 mg or 68%) was crystallized from CH_2Cl_2/Et_2O. Mp 203–205 °C. ^1H NMR: δ 1.07 (s, 3 H), 1.12 (t, J = 7.5 Hz, 3 H), 1.14 (t, J = 7.5 Hz, 3 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.26 (d, J = 7.2 Hz, 3 H), 1.30 (ddd, J = 9.2, 10.2, 13.3 Hz, 1 H), 1.51 (s, 3 H), 1.53 (m, 1 H), 1.57 (m, 1 H), 1.90 (m, 2 H), 1.98 (ddd, J = 5.7, 12.2, 12.2 Hz, 1 H), 2.16 (m, 1 H), 2.19 (ddd, J = 7.5, 10.1, 14.8 Hz, 1 H), 2.37 (q, J = 7.5 Hz, 2 H), 2.43 (q, J = 7.5 Hz, 2 H), 2.44 (q, J = 7.5 Hz, 2 H), 2.61 (dddd, J = 1.5, 6, 13.9, 13.9 Hz, 1 H), 4.38 (dd, J = 4, 8 Hz, 1 H), 4.60 (AB, J = 16.2 Hz, 2 H), 5.59 (dd, J = 2.2, 4 Hz, 1 H), 6.11 (br t, J = 1.8 Hz, 1 H), 6.32 (dd, J = 1.8, 10.1 Hz, 1 H), 7.18 (d, J = 10.1 Hz, 1 H). EIMS (m/e): 576, (M^+).

Registry No. 1, 5593-20-4; **1a**, 59047-65-3; **2**, 65669-64-9; **3**, 127034-57-5; **4**, 127034-58-6; **5**, 127063-59-6; **6**, 127034-59-7; **7**, 127034-60-0; **8**, 127034-61-1; **9**, 127034-62-2; **10**, 127034-63-3; **11a**, 127034-64-4; 11b, 127034-65-5; **11c**, 127063-38-1; **11d**, 127034-66-6; 11e, 127034-67-7; **12**, 127034-68-8; **13**, 127034-69-9; 14, 127034-70-2; **15**, 127034-71-3; **16**, 127034-72-4; betamethasone, 378-44-9; propionic anhydride, 123-62-6; butyric anhydride, 106-31-0; isovaleryl chloride, 108-12-3; 2-furoyl chloride, 527-69-5.