Articles

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

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A series of 9α -halo-12 β -hydroxy and 12 β -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 12 β -hydroxy analogues 9, 13, and 15 were all absorbed but the corresponding 12 β -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 12 β -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-dipropionate¹ (1), and beclomethasone 17,21-dipropionate² (1a). When used judiciously, these steroids find wide application in a variety of inflammatory processes.



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 17thioketals (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 Scheme I



rise to novel, topically potent structures that are not systemically absorbed. The chemistry and structure-ac-

(2) Small, P. Ann. Allergy 1982, 49, 127.

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 $^{^{\}dagger}$ Dedicated to Professor W. G. Dauben on the occasion of his 70th birthday.

Ferrante, M. G.; Rudy, B. C. In Analytical Profiles of Drug Substances, 6; Florey, K., Ed.; Academic Press: New York, 1977; p 43.

⁽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.

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 halogen⁷ at C-12 in the corticoid nucleus, but they are not readily adapted to the synthesis of corticoids bearing the 9α -halo-11 β ,12 β -dihydroxy functional arrangement (e.g., 9) that we required.

- (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.

We had previously found that dehydration of betamethasone dipropionate (1) with (diethylamido)sulfur trifluoride (DAST) in CH₂Cl₂ 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 CH₂Cl₂ with a small amount of 48% aqueous HF, C-12 β -hydroxylated species **3** (Scheme II) was obtained (51%) in addition to secosteroid 4 (23%) and the 12 α -hydroxy steroid **5** (24%), as shown in Scheme I.

Acid-catalyzed solvolysis of tert-alkyl fluorides⁹ and benzyl fluorides¹⁰ 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

⁽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-12 α (path b, product 5), or C-12 β (path b, product 3) is consistent with previous mechanistic studies and our findings. The possibility of intramolecular reaction of the 17 α -ester with the incipient C-12 carbonium ion (2 \rightarrow 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 NaHCO₃ in refluxing MeOH afforded diol 6 in excellent yield. On solvolysis of 6 under identical conditions used for the solvolysis of 2 (aqueous HF/ CH₂Cl₂), a similar ratio (ca. 3:1) and yield of $12\beta:12\alpha$ 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 12 β -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 HClO₄) 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-12 β 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 vields. Formation of benzoate 11e required excess DMAP and benzoyl chloride in CH₂Cl₂, 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 CHCl₃, 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 assay¹² (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 doseresponse 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 ED₁₀₀ was not greatly affected on introduction of a 12 β -hydroxyl group into either 1 (i.e., 15) or 1a (i.e., 13). Although the maximum topical response produced by 9α -bromo-12 β -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



		R		% antiinflammatory potency (single applcn)						
	x		dose, µg/mouse			% systemic effect (five applcns)			analysis	
no.				topicalb	systemic ^b	effect	effect ^d	mp	elemental	HRMS (calcd)
1	F	Н	2.5	59	27	30	12	_	_	_
			25	76	30	74	24			
			75	93	72	87	37			
1 a	Cl	н	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 ₂ CCH ₂ CH ₃	50	36	0e	2	2	178(d)	C.H	557.275 (557.275) ^f
		- 2 2 - 0	100	45	0	6	6			
			200	70	0	2	0			
			300	96	0	_	_			
11b	Br	O°CCH°CH°CH°	300	68	0e	-	-	169-171	C.H	571.291 (571.291)
11c	Br	O CCH CH (CH)	300	54	0e	-	_	198(d)	Ċ.H	585,306 (585,306)
11d	Br	O CC H O	300	69	0e	_	-	212-4	Ċ.H	595.257 (595.254)
11e	Br	O.CC.H.	300	84	0e	_	-	150-2	Č.H	-
13	cī	OH	10	41	õ	4	2	207-8	Č.H	536.218 (536.218)
	•••	•••	40	67	5	Ō	13		~,	
			100	81	21	5	14			
14	Cl	O°CCH°CH°	50	47	0e	4		143-4	C.H	592.244 (52.244)
••	•••	02001120113	100	53	õ	5	5		-,	
			200	71	õ	ŏ	Ğ			
			300	84	õ	<u> </u>	-			
15	F	OH	10	46	7	9	1	119-121	CH	520.246 (520.247)
	•	0.11	40	60	11	13	10		0,11	
			100	82	19	21	30			
16	F	0.04.04.	10	21	0e	1	0	203-5	СН	
10	•	0201120113	40	50	ŏ	1	ő	200 0	0,11	
			100	69	ŏ	4	õ			
			200	77	ŏ	-	_			
					~					

^aDose of TPA: 8.8 nmol/mouse. ^bCoefficient of variation = 10-25% (n = 6). ^cEffect was measured by weight loss of the thymus. Coefficient of variation = 10-21% (n = 6). ^dEffect was determined by measuring the inhibition of increased plasma cortisol induced by stress. Coefficient of variation = 12-30% (n = 6). ^eNo statistically relevant systemic effect observed. ^fM - Br MS peak.

Table II. Estimated ED₁₀₀ Values of Betamethasone Analogues

no.	$ED_{100}, \mu g/mouse$	no.	$ED_{100}, \mu g/mouse$
1	110	13	160
la	110	11 a	325
15	140	14	400
9	325	16	400

^aObtained 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., alcometasone) 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 ED₁₀₀ 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 12 β -hydroxy analogues 9, 13, and 15 all showed similar, if slightly attenuated, signs of systemic absorption. As can be seen in this series (12 β -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 suppression¹⁵ (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
la	75	8.12 ± 3.08	51
13	200	13.92 ± 1.88	15.7
14	300	16.50 ± 3.43	0.1

^aApplied 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 ED₁₀₀ 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 tipredane¹⁸ 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 (CDCl₃, referenced to CHCl₃ 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 CH₂Cl₂ (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 MgSO4 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 = 7.2Hz, 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 (brs, 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 C₂₈H₃₅O₆F: 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 NaHCO₃ (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 MgSO₄, and filtered. The solvent was removed to give crude diol 6 as a white solid. The solid was washed with Et₂O (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 C₂₂H₂₇O₄F: 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 CH₂Cl₂ (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 $(1.5 \text{ mm thick}, SiO_2)$ 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 NaHCO₃/ 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, NH₃ (m/e): 372, 356, 355, 341, 325, 313, 295. The lower R_f material, 7, weighed 21 mg (57%) and could be recrystallized from Et₂O. 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 NaHCO₃/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, NH₃ (m/e): 373 (M + H), 372 (M^+) , 355, 343, 341, 313, 295, 255,

16 β -Methyl-12 β ,17 α ,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 CH₂Cl₂ (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 Na₂SO₄, and filtered. The solvent was removed to give a crude product mixture consisting of 3 and two other major substances. The desired

⁽¹⁶⁾ Frosch, P. J.; Wendt, H. In Models Dermatol. 1985, 2, 5.

⁽¹⁷⁾ Clement, M.; duVivier, A. In Models Dermatol. 1985, 2, 16.
(18) Lutsky, B. N.; Millonig, R. C.; Wojnar, R. J.; Free, C. A.; Devlin, R. G.; Varma, R. K.; Karanewsky, D. S. Arzneim-Forsh. 1986, 36 (II), No. 12, 1787. Wojnar, R. J.; Alpaugh, W. C.; Dzelykalns, E. Arzneim.-Forsh. 1985, 35 (II), No. 8, 1264.

product 3 could be removed from the mixture in pure form by crystallization from Et₂O. 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): $\lambda_m 222 \ (\epsilon = 16\ 900), 282 \ (\epsilon = 2400) \ nm.$ ¹H NMR (90 MHz): $\delta 0.94$ (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 C₂₈H₃₆O₇: 484.2461. Found: 484.2426. Next was obtained 16β -methyl- 12α , 17α ,21trihydroxypregna-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 C₂₈H₃₆O₇: 484.2461. Found: 484.2450. The desired product 3 eluted last (14.55 g, 51%) and could then be crystallized from Et₂O. Mp: 167-168 °C. ¹H NMR: $\delta 0.76$ (s, 3 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.15 (t, J = 7.5Hz, 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 Hz, 1 H), 6.28 (dd, J = 1.8 Hz, 1 H)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 C₂₈H₃₆O₇: 484.2461. Found: 484.2450. Anal. (C₂₈H₃₆O₇): C, H.

 9α -Bromo-16 β -methyl-11 β , 12 β , 17 α , 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-17 α ,21-dihydroxy-11\$,12\$-epoxy-16\$-methylpregna-1,4-diene-3,20dione 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))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 C₂₈H₃₅O₇⁷⁹Br: 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, <math>J = 4.0, 11.2, 11.2 Hz, 1H), 2.25 (m, 2 H), 2.44 (q, J = 7.5 Hz, 2 H), 2.46 (dq, J = 4.0, 7.5Hz, 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 = 16.6Hz, 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-16 β -methyl-11 β ,12 β ,17 α ,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 CH₂Cl₂ (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,Ndimethylamino)pyridine (DMAP, 30 mg or 0.24 mmol). The reaction was monitored by TLC (30% benzene/Et₂O, silica gel) and was complete in 30 min. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous NH₄Cl (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/Et₂O. The pure product 11a (159 mg, 73%) was crystallized from Et₂O/CH₂Cl₂. 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, NH₃ (m/e): 639, 637 (M + H).

 9α ·Bromo-16 β -methyl-11 β , 12 β , 17 α , 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), CH₂Cl₂ (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 - C₃H₅O), 571 (M -Br), 565, 563, 537, 535, 522, 520, 491, 489, 481, 479. DCIMS, NH₃ (m/e): 653, 651 (M⁺), 590, 588.

 9α -Bromo-16 β -methyl-11 β , 12 β , 17 α , 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), CH₂Cl₂ (8 mL), and DMAP (30 mg). PTLC as before gave 11c (96 mg, 42%), as a white solid, which was crystallized from CH₂Cl₂/Et₂O. 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 = 7.1Hz, 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)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, NH₃ (m/e): 667, 665 (M + H).

 9α -Bromo-16 β -methyl-11 β , 12 β , 17 α , 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), CH₂Cl₂ (8 mL), and DMAP (30 mg). PTLC as before gave 11d (144 mg, 62%), as a white solid, which was crystallized from CH₂Cl₂/Et₂O. 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-16 β -methyl-11 β ,12 β ,17 α ,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 CH₂Cl₂ (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 \times 75 mL), water (1 \times 75 mL), and saturated aqueous NaCl (1 \times 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 CHCl₃/EtOAc gave pure 11e (196 mg, 86%), as a white solid, which was crystallized from Et₂O/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 = 100)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 = 3.6Hz, 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 (CHCl₃): 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, NH₃ (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 \times 100 mL). The combined organic layer was washed with saturated aqueous NaCl $(1 \times 100 \text{ mL})$, 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 Et₂O/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)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)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-16 β -methyl-11 β ,12 β ,17 α ,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 CHCl₃ (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/CHCl₃) and the volatiles were removed under vacuum. The crude mixture was dissolved in 40 mL of 3:7 Et-OAc/CHCl₃ 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/CHCl₃, affording pure 13 (563 mg or 69%) as a white solid. The product was crystallized from CH₂Cl₂/Et₂O. 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-16 β -methyl-11 β ,12 β ,17 α ,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 CH₂Cl₂ (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 $(1 \times 100 \text{ mL})$. The combined organic layer was dried over Na₂SO₄ and filtered, and the solvent was removed to give a glass which was purified by silica gel PTLC (2 mm thick) with 8:2 CHCl₃/EtOAc. The resultant white solid, 14 (250 mg or 61%), was crystallized from Et₂O. 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, NH₃ (m/e): 595, 593 (M + H), 576, 575, 574, 559, 558, 557, 539, 538, 537.

 9α -Fluoro-16 β -methyl-11 β , 12 β , 17 α , 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 NaHCO₃ (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, 1H), 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-16 β -methyl-11 β ,12 β ,17 α ,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 CH₂Cl₂ (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 NH₄Cl (100 mL) and extracted with EtOAc $(3 \times 30 \text{ mL})$. The combined organic layer was washed with water $(1 \times 50 \text{ mL})$ and saturated aqueous NaCl $(1 \times 50 \text{ mL})$, dried over MgSO₄, and filtered, and the solvent was removed. The residue was purified by silica gel PTLC $(3 \times 2 \text{ mm thick})$ eluting with 7:3 Et₂O/benzene. The pure product 16 (188 mg or 68%) was crystallized from CH2Cl2/Et2O. 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 = 7.5Hz, 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 = 1.8, 10.1 Hz, 1 Hz, 1 H), 7.18 (d, J = 1.8, 10.1 Hz, 1 Hz, 1J = 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, 127034-69-7; 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.