Organic Process Research & Development **2001**, *5*, 376−382

Process Improvements in the Synthesis of Corticosteroid 9,11β-Epoxides

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Abstract:

Corticosteroid 9,11β-epoxides are key intermediates in the preparation of pharmaceutically important compounds such as betamethasone, mometasone, beclomethasone, and dexamethasone. A new process for the 9,11β-epoxide was developed using a PCl_5-mediated regioselective dehydration of 11α-hydroxysteroid to form the corresponding $\Delta^{9,11}$ double bond. The olefin is then converted into 9α,11β- bromoformate by treatment with 1,3-dibromo-5, 5-dimethyl hydantoin (DBH) in DMF and subsequently cyclized to produce the desired 9,11β-epoxide upon treatment with NaOH. Major process-related impurities such as 21-OH-$\Delta^{9,11}$-triene, 21-OH-$\Delta^{11,12}$-triene, 21-Cl-$\Delta^{9,11}$-triene, and β-epoxide-21-cathylate as well as 11β-Cl are all eliminated or minimized. This new process has been implemented in our manufacturing facility in full-scale production and proved to raise the overall yield and the quality of the product dramatically compared to the existing process.

Pharmacologically important corticosteroid drugs such as betamethasone (**1**), mometasone (**2**), beclomethasone (**4**), and dexamethasone (**5**) have been well received since their introduction to the worldwide market. And they continue to play major roles in dermatological and allergy therapies.[1] Their structural similarity presents an opportunity to develop a general approach to synthesize these steroids (Figure 1). The 9α,11β-halohydrin functionality, which is essential for biological activity,[2−5] is obtained by opening the corresponding 9,11β-epoxide **3** with a suitable acid (HCl or HF).[6] Therefore, it is critical to have a robust process to manufacture the penultimate intermediate epoxide **3** in high yield and good quality. We wish to report here the discovery and development of this new process strategy for β-epoxide **3**.

I. 16β-Me-Epoxide 3a. Schering-Plough has a long history of producing the above-described steroids.[7] The existing manufacturing synthesis[1,3,7a] for β-epoxide **3a** from

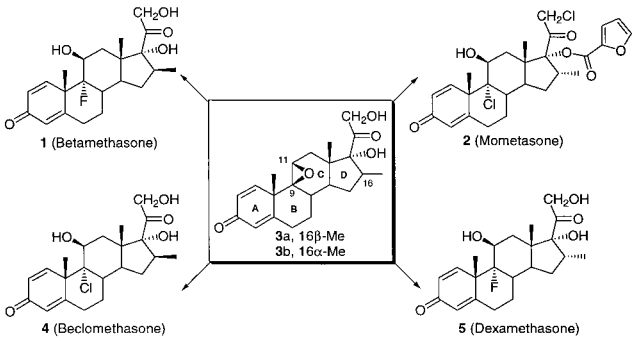

Figure 1.

Scheme 1. **Existing synthesis of β-epoxide (3a)**

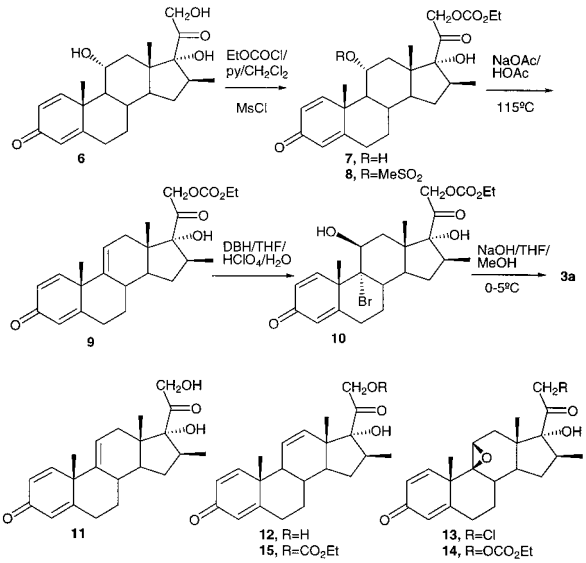

Figure 2.

11α-hydroxy **6** is depicted in Scheme 1. Selective protection of triol **6** with ethyl chloroformate in the presence of pyridine provided 21-cathylate **7**, which was subsequently converted into 11α-mesylate **8**. Elimination of the mesylate was carried out at 115 °C to provide triene **9**. The latter 9,11-double bond was then reacted with 1,3-dibromo-5,5-dimethyl hydantoin (DBH) to give bromohydrin **10**, followed by cyclization and hydrolysis of the 21-cathylate to form β-epoxide **3a**.

This process produced epoxide **3a** in about 60% overall yield with a purity of about 92%. HPLC analysis of the product revealed four major impurities (Figure 2): 21-OH-$\Delta^{9,11}$-triene (**11**, ∼1%), 21-OH-$\Delta^{11,12}$-triene (**12,** ∼1%),

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 10.1021/op0102013 CCC: $20.00
Published on Web 05/10/2001

Table 1. **Solvent and temperature effects on the PCl_5 dehydration**

solvent	temp (°C)	HPLC area % **9** ($\Delta^{9,11}$)	**15** ($\Delta^{11,12}$)	**16** (11β-Cl)
CH_2Cl_2/pyridine	rt	70.4	11.2	18.4
pyridine	rt	52.3	3.8	44.0
CH_2Cl_2	−20	74.4	14.5	11.0
THF	rt	81.0	7.4	11.3
THF	−20	92.3	4.9	2.8
THF	−45	95.5	3.3	1.2
THF	−78	97.5	1.8	0.7
THF	−85	98.4	1.3	0.3
EtOAc	−20	80.2	17.9	1.9
tBuOMe	−45	95.7	4.3	(80% s.m. after 2 h)
DME	−45	81.4	18.6	
toluene	−45	95.0	5.0	(50% s.m. after 4 h)
CH_3CN	rt	82.8	1.8	3.1 (and new impurities)
i-propyl ether	−30	94.0	6.0	(85% s.m. after 1 h)

21-Cl-$\Delta^{9,11}$-triene (**13**, ∼0.3%) and β-epoxide-21-cathylate (**14**, ∼2%). As a penultimate intermediate, this existing epoxide quality did not meet the minimum 96% purity specifications for the starting material for drug substances such as beclomethasone (**4**). Furthermore, the quality of betamethasone drug substance needed to be upgraded to meet the higher EP and USP specifications. Therefore, there was a strong demand to eliminate or minimize the formation of those impurities in aiming to increase both the product quality and the overall chemical yield. Described below is our systematic approach to achieve the above objectives.

21-OH-$\Delta^{11,12}$-Triene (12). It was clear that impurity **12** was carried over from the elimination[2,8−10] step (Scheme 1). The conversion of **8** to **9** produced a considerable amount of unwanted $\Delta^{11,12}$ isomer (**15**, ∼15%). It has been well understood that the problem in the elimination step was associated with the configuration of carbon C-11. With an 11β-OH,[11−15] the base-catalyzed anti E_2 elimination provided the $\Delta^{9,11}$ double bond in greater than 90% yield. Obviously, with the 11α-OH, the leaving group cannot be anti-coplanar with the H-9 to form the $\Delta^{9,11}$ double bond exclusively. We envisioned that this problem could be resolved by a *syn*-elimination approach.

Bernstein et al.[16a] have reported that reaction of a 3,17-bisketal-11α-OH-steroid with phosphorus oxychloride in pyridine gave $\Delta^{9,11}$ double bond in 90% yield. Under the Bernstein conditions, $\Delta^{9,11}$ **9** was formed from **7** with excellent regioselectivity, 98:2 by HPLC area to the $\Delta^{11,12}$ **15** isomer. However, the reaction yield was less than 15%. Alternatives to $POCl_3$, such as PCl_5 were used to optimize the reaction yield. Shoppee et al.[16b] reported that reaction of 5α-androstan-11α-ol with PCl_5 in $CHCl_3$ at room temperature gave 5α-androst-9(11)-ene in 65% isolated yield. When compound **7** was reacted with PCl_5 in CH_2Cl_2/py at room temperature, HPLC analysis of the reaction mixture indicated three main peaks with an 86:14 ratio of $\Delta^{9,11}$ to $\Delta^{11,12}$. The third peak was isolated and identified as 11β-Cl **16** by mass spectrum and NMR studies.

One can speculate that the $\Delta^{9,11}$ double bond was formed by the base-catalyzed E_2 elimination via the 11β-chloro intermediate since the latter compound was detected in the reaction. To minimize the level of 11β-Cl, the reaction medium (mixture of CH_2Cl_2 and pyridine) was replaced with pure pyridine so that all of the 11β-Cl formed would be converted to **9**. On the contrary, an even higher level of 11β-Cl was obtained. These results clearly suggested that the elimination did not go through the 11β-Cl intermediate. Therefore, a better ratio (Table 1) of **9** to **15** might be obtained as a result of a solvent effect. With this idea in mind, the PCl_5-mediated dehydration was carried out in various solvents at different temperatures. After various experiments, THF was found to be the solvent choice, and −78 to −90 °C was found to be the optimum reaction temperature (see Table 1 for results of solvent and temperature effects). Under these conditions, $\Delta^{9,11}$ **9** was isolated in greater than 90% yield (vs ∼75% in the existing process) with a $\Delta^{9,11}$ **9** to $\Delta^{11,12}$ **15** ratio at about 99:1. A *syn* elimination mechanism as shown in Scheme 2 was proposed for this reaction. The possibility of the formation of a free carbonium ion reactive intermediate was excluded on the basis of experimental observations.[17] It should be emphasized that anhydrous conditions are essential to ensure a reproducible high yield for the elimination, since moisture reacts with PCl_5 or 11α-chlorophosphate to prevent further dehydration. The triene **9** prepared by the new reaction was converted to the epoxide **3a**. It was no surprise that impurity **12** was only detected in much less than 0.1% in a purified **3a**, since the level of **15** in the olefin **9** was dramatically reduced.

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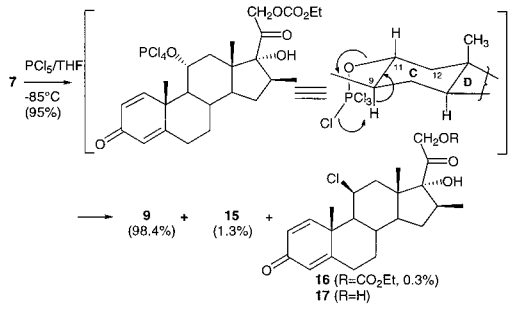
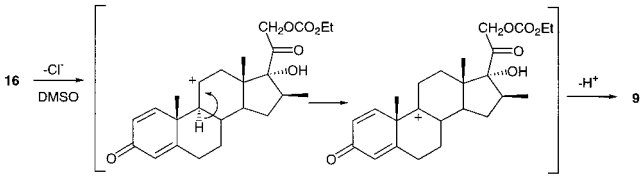
Scheme 2. **Synthesis of triene (9) by PCl_5-mediated elimination of (7)**



Scheme 3. **11β-Cl elimination**

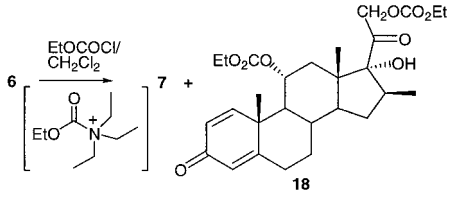


11β-Cl Impurity (17). The epoxide **3a** resulting from **9** (Scheme 1) was further converted into betamethasone (**1**) via the existing process to compare the impurity profile. HPLC analysis indicated the presence of a new impurity, 11β-Cl-21-OH (**17**) arising from **16**, present in ~0.1% in the final drug substance **1** obtained from the new process. Since it was difficult to remove **16** by recrystallization of **9**, our efforts were directed to towards converting **16** into **9**. It was interesting to note that when **16** was heated at 80 °C in a large volume mixture of acetonitrile and water, **9** was detected as a predominate product. Since water was necessary for the dehydrochlorination with a possible E_1-type mechanism, a more polar solvent such as DMSO would push the elimination at a much faster rate and in a smaller volume. When **16** was heated at ~100 °C in DMSO, $\Delta^{9,11}$ double bond **9** was produced exclusively. Mechanistically, this may be rationalized as ionization of the 11β-Cl group followed by a rearrangement of secondary carbonium ion to a tertiary ion (a similar mechanism was proposed for the dehydration of 11β-OH steroids under the Burgess conditions[8]). Elimination of the 11-H would then provide the desired $\Delta^{9,11}$ function (Scheme 3). This argument is also supported by the literature reports that 9α-OH with strong acid[18a] and 9α-Cl[18b] with $AgNO_3$ were regioselectively converted into $\Delta^{9,11}$ respectively.

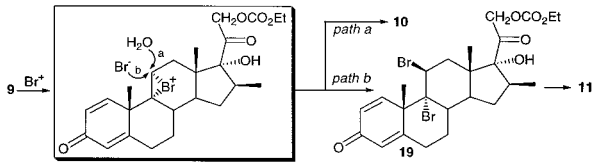
With the new dehydrochlorination process in hand, the purity of the elimination product can easily be upgraded via a conversion of **16** into **9** by heating the crude **9** at ~100 °C for 1 h in DMSO. HPLC analysis of the drug substance **1** from the DMSO-treated **9** did not show any impurity **17**. It should be noted that this clean up method was occasionally being employed only when the level of **17** was higher than 0.5%.

β-Epoxide-21-Cl (13). The unprotected 21-OH **6** was transformed to the corresponding 21-Cl in the existing mesylation step, which was then subsequently converted into **13** via the same chemistry described in Scheme 1. The existing 21-cathylation (with pyridine) could generate a significant amount (>10%) of 11,21-dicathylate **18**. To avoid the formation of the impurity in such a large quantity, the reaction was quenched when the starting triol **6** was depleted to about 0.5%. However, quenching the reaction with a higher level of **6** would lead to a higher level of **13**. It was believed that the necessary base not only acted as an acid scavenger but also served to further activate the acylation reagent. The latter function of the base could significantly affect the selectivity. Therefore, a more sterically hindered base in place of pyridine would enhance the regioselectivity of the cathylation. Results from fine-tuning of the reaction by selecting different bases indicated that triethylamine was the best choice. When triethylamine was employed as a base, the reaction went to completion (<0.1% of **6**) with less than 0.1% of 11,21-dicathylate (Scheme 4) by HPLC, hence eliminating the source of impurity **13**.

Scheme 4. **Selective protection of 21-hydroxyl**



Scheme 5. **Formation of 9,11-dibromo (19)**



$\Delta^{9,11}$-Triene-21-OH (11). The impurity $\Delta^{9,11}$-triene-21-OH **11** could be formed by a simple hydrolysis of unreacted $\Delta^{9,11}$-triene-21-cathylate **9** in the epoxide formation step. Careful analysis by HPLC indicated that there was about 2% of impurity **11** present in the crude epoxide **3a**. This level of **11** was much higher than the amount one would expect from the incompleteness of the bromohydrin reaction (typically <0.5%). Hence, the alcohol **11** must come from some other source. This triggered our interest to search for the origin of this impurity in order to eliminate its formation.

We suspected that there could be a side reaction taking place at the olefin double bond during the bromohydrin formation. The side product could then convert back to the double bond during the NaOH-catalyzed epoxidation step. To understand the suspected double bond conversions, a 9,11-dibromo byproduct **19** was identified from the bromohydrin crude material. Its structure (Scheme 5) was confirmed by an independent synthesis of **19** from olefin **9** with bromine. The impurity from the bromohydrin **10** had an identical retention time with the synthesized dibromo compound by HPLC analysis. When dibromo **19** was subjected to the ring closure conditions, $\Delta^{9,11}$-triene-21-OH **11** was detected as a major product by HPLC although the reaction was not very clean.

The formation of 9,11-dibromo **19** can be rationalized by what is depicted in Scheme 5. The β-nucleophilic attack of

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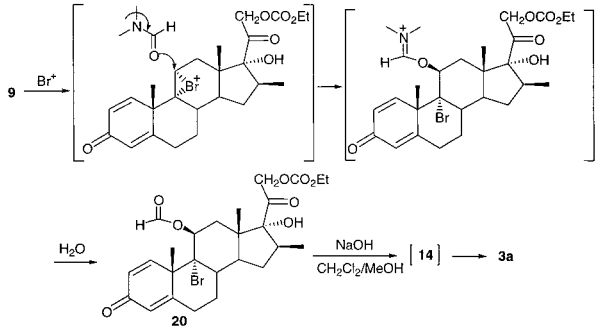
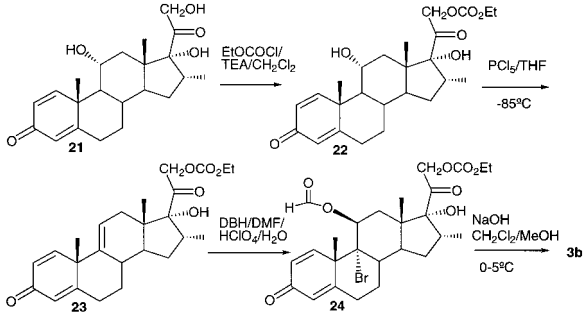
Scheme 6. **New preparation of epoxide (3a)**



Scheme 7. **Process for 16α-Me epoxide (3b)**



water to the bromonium ion produced the desired bromohydrin **10**, while the reaction with bromide ion gave the unwanted dibromide **19**. Due to its better nucleophilicity than water, the bromide can give rise to an impurity such as **11** via **19** at a level that is not purgable by the existing purification procedure.

Since a trace amount of bromide ion is always present in the reaction mixture, increasing either the nucleophilicity of the desired nucleophile or its concentration would favor the product formation. With this idea in mind, DMF was selected as the reaction solvent. The bromoformate[19−21] formation, similar to that of "path *a*", should be a much more facile reaction than the bromohydrin formation, since DMF is a better nucleophile than water and it is also present in much higher concentration (solvent). There was no surprise that the 9,11-dibromo impurity was not detected from the bromoformate reaction mixture by HPLC analysis.

The formation of bromoformate **20** is illustrated in Scheme 6. Reaction of the $\Delta^{9,11}$ double bond with DBH in the presence of perchloric acid provides an active bromonium intermediate. The latter is then trapped by DMF to form an iminium ion, which can be easily hydrolyzed to generate the bromoformate during the work up. Bromoformate **20** was isolated by a direct precipitation of the batch with water.

***β*-Epoxide-21-cathylate (14).** In the existing process, *β*-epoxide-21-cathylate (**14**) was present in epoxide **3a** in about 1 to 2%. This compound **14** was an intermediate in the formation of **3a**. Further addition of NaOH did not resolve this problem, suggesting that intermediate **14** was trapped in the crystals of epoxide since the crystallization of **3a** took place prior to the completion of the hydrolysis in the solvent mixture of THF and MeOH. Replacing the reaction medium with a better solvent system to maintain a homogeneous mixture should ensure a complete hydrolysis of the 21-cathylate. This was achieved by carrying out the reaction in a mixture of CH_2Cl_2 and MeOH. HPLC analysis indicated that there was no 21-cathylate **14** left in the reaction mixture (<0.1). Epoxide **3a** was obtained in 92% overall yield from **9** with a purity of 99% after recrystallization.

II. 16α-Me Epoxide 3b. Epoxide **3b** (16α-Me) is the starting material for mometasone (**2**). Historically, this epoxide was outsourced from a competitor. The existing Schering epoxide process could not produce **3b** to meet the 96% purity specification. In view of an increase in the requirement of mometasone furoate,[22−25] there was a good incentive to manufacture **3b** in house for the production of mometasone.

Application of the new chemistry to 16α-methyl series would provide an efficient process for epoxide **3b**. The reaction of 16α-methyl triol (**21**) with ethyl chloroformate in CH_2Cl_2 in the presence of TEA provided a regioselective protection of 21-hydroxyl group. Elimination of 11α-hydroxy **22** with PCl_5 was carried out in THF at −85 °C and generated $\Delta^{9,11}$ **23** in about 90% overall yield from **21** with a 99:1 ratio to $\Delta^{11,12}$ isomer (Scheme 7). The triene **23** was converted into bromoformate using DBH as reagent in DMF as described in the case of **3a**. Cyclization of the bromoformate followed by hydrolysis of 21-cathylate yielded the desired epoxide **3b** in a greater than 90% overall yield with an excellent purity (>98%). The material produced from this process was transformed into mometasone (**2**), and no new impurities were detected by HPLC analysis of the drug substance.

In conclusion, a significantly improved general process has been developed for the synthesis of *β*-epoxide **3** based on systematic studies of the deficiencies of the existing process. The overall yield from triol **6** to epoxide **3a** was improved to about 85% from 60%. The purity of the penultimate intermediate **3a** was enhanced to about 99% from 92% to meet all specifications. The new processes were implemented in commercial production. The drug substance betamethasone derived from **3a** showed a significant improvement in purity to meet all of the updated EP and USP specifications. A regioselective PCl_5-mediated 11α-OH dehydration process was invented to circumvent the 11α-mesylate elimination deficiency. A regiospecific dehydrochlorination process was also developed to eliminate a minor new impurity, 11*β*-chloride (**16**), so that the new chemistry could be implemented in the commercial process. Replacing the existing bromohydrin process with the bromoformate chemistry not only excluded the formation of dibromide impurity (**19**) but also increased the reaction yield. The

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versatility of the new process was demonstrated by the successful extension to the 16α-methyl series (**3b**).

Experimental Section

The starting materials triol **6** and **21** as well as all the reference compounds were provided by Mr. Luis Gil of Schering Plough Products, Manati, Puerto Rico. All other chemicals or reagents were purchased commercially. The ratios of $\Delta^{9,11}$ to $\Delta^{11,12}$ steroids and all of the purity percentages were determined by HPLC analysis (μ-Bondapak C-18 column, 1:1 CH_3CN/H_2O as mobile phase at 1−2 mL/min, UV detector at 254 nm) of the products or reaction mixtures. The product impurity profile comparisons were performed by gradient HPLC analysis (Beckman Ultrasphere C8 column, $CH_3CN/MeOH/H_2O$ as solvent system with a ratio of 15:20:65 and increment of CH_3CN by a gradient table, 2.5 mL/min. at 45 °C column temperature, UV detector at 254 nm). Molar yields were calculated based on the starting compound and product purities, as determined by HPLC using the above conditions. NMR spectroscopic data were recorded on a Bruker NMR spectrometer.

17α-Hydroxy-16β-methyl-21-ethoxycarbonyloxy-pregna-1,4,9(11)-triene-3,20-dione (9). The solid 16β-methyl-11α,17α,21-trihydroxy-pregna-1,4-diene-3,20-dione (**6**) (20 g, 97% purity) was suspended in a mixture of CH_2Cl_2 (80 mL) and triethylamine (30 mL) and cooled to about −15 °C. A solution of ethyl chloroformate (6.5 mL) in CH_2Cl_2 (10 mL) was added slowly over a period of 1 h, while maintaining the temperature at about −15 °C. The reaction mixture was allowed to warm to room temperature, and the progress was monitored by HPLC analysis. When the reaction was judged complete (<0.2% of **6**, about 2 to 4 h agitation at about 25 °C), THF (40 mL) and water (80 mL) were added to the reaction mixture. The pH of the mixture was adjusted to below 2 by careful addition of concentrated HCl (13 mL) at temperature below 25 °C. The resulting two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were concentrated, and the residual CH_2Cl_2 was replaced by azeotropic distillation with THF (KF < 200 ppm). The resulting THF solution was directly used for the dehydration step without further purification.

An analytical sample of 21-cathylate **7** was prepared by removing solvents under vacuum and recrystallizing **7** from a mixture of CH_2Cl_2 and THF. The HPLC retention time (∼4.5 min) and NMR spectrum were identical with that of a reference compound. ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 10.3 Hz, 1H), 6.20 (dd, J = 10.3, 1.9 Hz, 1H), 6.10 (s, 1H), 4.99 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 4.09 (dt, J = 10.4, 5.1 Hz, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H), 2.05 (m, 2H), 1.92 (m, 1H), 1.75 (m, 2H), 1.57(m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.32 (s, 3H), 1.15 (d, J = 7.3 Hz, 3H), 1.06 (m, 2H), 0.90 (s, 3H).

The reaction volume was adjusted to about 150 mL with THF and cooled to about −85 °C. Phosphorus pentachloride (PCl_5, 20 g) was charged slowly over a 30 min period while keeping the reaction temperature below −83 °C. The mixture was agitated at about −85 °C for about 1 h. When HPLC analysis indicated the disappearance of **7**, the mixture was slowly transferred into stirred water (800 mL). The slurry was filtered and washed with water (600 mL). The wet cake was dried overnight under vacuum at 60 °C to provide 22.56 g of triene **9** (90.7% purity with a ratio of 98.7:1.3 to **15**, 92% overall yield from **6**).

The HPLC retention time (∼10.5 min) and NMR spectra were identical with a reference compound. ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (d, J = 10.2 Hz, 1H), 6.31 (dd, J = 10.2, 1.9 Hz, 1H), 6.10 (s, 1H), 5.59 (m, 1H), 4.99 (d, J = 17.9 Hz, 1H), 4.92 (d, J = 17.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 1H), 2.69 (m, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 2.25 (m, 3H), 2.12 (m, 1H), 1.82 (m, 1H), 1.6 (m), 1.43 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.27 (m, 2H), 1.21 (d, J = 7.3 Hz, 3H), 1.19 (m, 1H), 0.85 (s, 3H). ^{13}C NMR (62.896 MHz, $CDCl_3$): 204.5, 186.5, 166.9, 154.8, 141.9, 127.2, 123.7, 120.8, 89.3, 71.6, 64.5, 49.6, 48.7, 47.0, 45.9, 36.4, 36.1, 35.0, 33.0, 32.2, 26.5, 19.6, 14.3, 14.2.

17α-Hydroxy-16α-methyl-21-ethoxycarbonyloxy-pregna-1,4,9(11)-triene-3,20-dione (23). Following essentially the same procedures as described for **9**, 16α-methyl triene (**23**) was prepared from 16α-methyl triol (**21**) via 21-cathylate (**22**) in an overall yield of 94%. The ratio of $\Delta^{9,11}$ to $\Delta^{11,12}$ was 99:1 by HPLC analysis.

22: ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 10.3 Hz, 1H), 6.30 (dd, J = 10.3, 1.9 Hz, 1H), 6.07 (s, 1H), 4.99 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 4.06 (dt, J = 10.3, 5.1 Hz, 1H), 2.50 (dt, J = 13.2, 4.6 Hz, 1H), 2.38 (m, 1H), 2.22 (m, 1H), 2.01 (m, 2H), 1.92 (dd, J = 12.0, 5.1 Hz, 1H), 1.75 (m, 2H), 1.58 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.02 (m, 3H), 0.89 (s, 3H). ^{13}C NMR (62.896 MHz, $CDCl_3$): 205.4, 187.8, 169.8, 160.6, 155.4, 124.9, 124.5, 89.3, 72.3, 68.2, 64.9, 60.7, 50.3, 49.5, 48.2, 44.6, 43.0, 35.5, 34.4, 34.3, 33.5, 20.0, 19.0, 16.1, 14.6.

23: ^{1}H NMR (400 MHz, $CDCl_3$): 7.18 (d, J = 10.1 Hz, 1H), 6.30 (dd, J = 10.1, 1.7 Hz, 1H), 6.08 (s 1H), 5.56 (br. d, J = 5.7 Hz, 1H), 5.03 (d, J = 17.7 Hz, 1H), 4.84 (d, J = 17.7 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.13 (m, 1H), 2.66 (m, 2H), 2.43 (m, 1H), 2.31 (m, 1H), 2.14 (m, 1H), 1.81 (m, 3H), 1.46 (m, 1H), 1.42 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.21 (m, 1H), 0.95 (d, J = 7.2 Hz, 3H), 0.79 (s 3H). ^{13}C NMR (62.896 MHz, $CDCl_3$): 205.2, 186.8, 167.4, 155.4, 155.2, 142.9, 127.6, 124.2, 121.1, 91.4, 71.0, 65.0, 48.5, 48.1, 46.3, 37.2, 35.2, 33.4, 32.8, 32.6, 27.1, 14.9, 14.8, 14.6.

11β-Chloro-17α-hydroxy-16β-methyl-21-ethoxycarbonyloxy-pregna-1,4-diene-3,20-dione (16). The starting material (**7**, 2 g) was dissolved in a mixture of CH_2Cl_2 (30 mL) and pyridine (6 mL) at room temperature. To the stirring solution, PCl_5 (2 g) was added portionwise over a period of 15 min. The resulting mixture was stirred for an additional 30 min at room temperature, quenched with water (20 mL) and then diluted with CH_2Cl_2 (100 mL). The mixture was washed with aqueous HCl solution (6 N, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to provide a residue of **16** (0.15 g), which was purified by silica gel chromatography (30/70 then 50/

50 EtOAc/hexane). Mass spectrum (FAB): 467 ($M^+ + 3$), 465 ($M^+ + 1$), and 429 ($M^+ + 1 - HCl$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.25 (d, $J = 10.0$ Hz, 1H), 6.30 (dd, $J = 10.0$, 1.7 Hz, 1H), 5.99 (s, 1H), 5.00 (d, $J = 17.8$ Hz, 1H), 4.91 (d, $J = 17.8$ Hz, 1H), 4.66 (br s, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 2.58 (dt, $J = 13.4$, 4.5 Hz, 1H), 2.40 (dd, $J = 14.5$, 4.7 Hz, 1H), 2.34 (dd, $J = 13.1$, 3.6 Hz, 1H), 2.10 (m, 5H), 1.55 (m, 1H), 1.52 (s, 3H), 1.38 (dd, $J = 10.8$, 3.7 Hz, 1H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.23 (m, 2H), 1.18 (d, $J = 6.6$ Hz, 3H), 1.16 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 204.8, 186.8, 170.4, 155.6, 128.9, 122.4, 89.3, 72.1, 64.9, 59.8, 56.6, 51.1, 49.7, 49.4, 44.5, 40.9, 35.3, 34.4, 32.0, 30.9, 21.0, 20.2, 18.2, 14.6.

Dehydrochlorination of 11*β*-chloro-21-cathylate (16). 11*β*-Chloro-21-cathylate (**16**, 95 mg) was dissolved in DMSO (2 mL). The solution was heated to 90 °C for about 3 h. The reaction progress was monitored by HPLC analysis. The starting compound (retention time ~15.5 min.) was gradually converted into the triene product (retention time ~10.5 min.) over the course of the reaction. The triene **9** was formed in greater than 97% yield as determined by HPLC. Essentially no $\Delta^{11,12}$ was detected.

9*β*,11*β*-epoxy-17α,21-Dihydroxy-16*β*-methylpregna-1,4-diene-3,20-dione (3a). The crude 16*β*-methyl-triene-21-cathylate **9** (50 g, 90% purity) was dissolved in DMF (175 mL) at room temperature. The resulting solution was cooled to about 10 °C, and then 70% $HClO_4$ (6.25 mL) was slowly added. DBH (25.6 g) was slowly added to the mixture over a period of about a 15 min while keeping the reaction temperature below 20 °C. The reaction progress was monitored by HPLC analysis. When HPLC indicated that the reaction was complete (about 3 h), the mixture was diluted with MeOH (175 mL). The bromoformate **20** was precipitated in 1500 mL of water, and cooled to below 10 °C. The product was isolated by filtration and washed with water (about 1000 mL). The wet cake was used directly in the next step without further purification.

A small sample of the wet cake was taken and dried under vacuum for NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (s, 1H), 6.85 (d, $J = 10$ Hz, 1H), 6.34 (dd, $J = 10$, 1.7 Hz, 1H), 6.10 (d, $J = 1.6$ Hz, 1H), 5.90 (br s, 1H), 5.02 (d, $J = 18$ Hz, 1H), 4.86 (d, $J = 18$ Hz, 1H), 4.22 (q, $J = 7$ Hz, 2H), 2.89 (dd, $J = 14.8$, 3.6 Hz, 1H), 2.60 (m, 1H), 2.40 (m 2H), 2.15 (m 3H), 1.95 (m, 1H), 1.75 (m, 2H), 1.58 (s 3H), 1.33 (t, $J = 7$ Hz, 3H), 1.25 (m, 1H), 1.19 (d, $J = 7$ Hz, 3H) and 1.00 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 204.8, 186.3, 165.4, 159.6, 155.2, 151.5, 130.1, 125.6, 89.2, 82.2, 75.1, 72.0, 64.9, 49.8, 49.7, 49.5, 44.6, 35.9, 34.5, 33.8, 31.0, 29.1, 25.1, 20.1, 17.9, 14.6.

The bromoformate **20** wet cake was dissolved in a mixture of CH_2Cl_2 (350 mL) and MeOH (325 mL). The resulting mixture was cooled to about −5 °C, vacuum degassed three times under nitrogen. A chilled solution of NaOH (15 g) in water (15 mL) was added slowly over about 1 h period while maintaining the reaction temperature between −5 and 0 °C. The resulting mixture was stirred for about 2 h. The reaction was quenched with acetic acid (40 mL). The solvents were removed by distillation and replaced with water (500 mL). The resulting slurry was cooled to about 0 °C and filtered. The wet cake was washed with water and dried under vacuum at about 50 °C to provide 41.2 g (purity 90.0% against standard) of the crude epoxide **3a** (97% overall yield from **9**).

The crude epoxide **3a** was heated in a mixture of CH_2Cl_2 (700 mL) and MeOH (200 mL) until dissolved. The resulting solution was filtered and concentrated to a volume of about 160 mL. The resulting slurry was cooled to about 0 °C, filtered, and washed with cold MeOH. The wet cake was dried under vacuum at about 50 °C to provide 36.0 g of purified epoxide **3a** (99% purity, 93% overall yield from **9**).

HPLC retention time and ^{1}H NMR of **3a** are identical to those of a reference compound. ^{1}H NMR (400 MHz, DMSO-*d*6): 6.62 (d, $J = 10$ Hz, 1H), 6.10 (br s, 1H), 6.09 (dd, $J = 10$, 1.8 Hz, 1H), 5.26 (s, 1H), 4.52 (t, $J = 5.8$ Hz, 1H), 4.37 (dd, $J = 19.4$, 5.9 Hz, 1H), 4.10 (dd, $J = 19.3$, 5.8 Hz, 1H), 3.19 (br s, 1H), 2.67 (m, 1H), 2.45 (m, 2H), 2.36 (m, 2H), 2.21 (m, 2H), 2.05 (m, 2H), 1.59 (m, 1H), 1.52 (m, 1H), 1.37 (s, 3H), 1.33 (m 1H), 1.01 (d, $J = 6.6$ Hz, 3H) and 0.86 (s, 3H).

9α,11*β*-Dibromo-17α-hydroxy-16*β*-methyl-21-ethoxycarbonyloxy-pregna-1,4-diene-3,20-dione (19). 16*β*-Methyl-triene (**9**, 2 g) was dissolved in $CHCl_3$ (20 mL) and cooled to 0 to 5 °C with an ice bath. Bromine (0.45 mL, 2 eq) was added slowly. The reaction was monitored by HPLC analysis for completion. The reaction was quenched with aqueous Na_2SO_3. The organic layer was separated and washed with water, dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to provide the crude dibromide **19** (greater than 92% by HPLC analysis), which was directly subjected to the next reaction. MS (FAB): 591 ($M^+ + 5$), 589 ($M^+ + 3$), 587 ($M^+ + 1$), 429 ($M^+ + 1 - 2Br$). ^{1}H NMR (250.1 MHz, $CDCl_3$): 7.3 (d, 1H), 7.4 (d, 1H), 6.0 (s, 1H), 5.1 (m, 1H), 4.9 (dd, 2H), 4.2 (q, 2H), 3.4 (m, 1H), 2.4 (m, 5H), 2.0 (m, 6H), 1.8 (s, 3H), 1.7 (m), 1.3 (t, 3H), 1.2 (s, 3H), 1.15 (d, 3H). ^{13}C NMR (62.896 MHz, $CDCl_3$): 204.0, 186.0, 166.0, 154.8, 151.2, 129.8, 124.2, 88.9, 87.1, 77.2, 71.6, 64.5, 50.9, 50.5, 49.3, 45.3, 38.7, 35.1, 34.1, 30.0, 29.4, 25.5, 19.7, 18.2, 14.2.

The 9,11-dibromide **9** was dissolved in a mixture of THF (15 mL), MeOH (15 mL) and water (2 mL). The solution was cooled to about 3 °C with an ice bath. A chilled solution of NaOH (0.85 g) in water (7 mL) was slowly added. The mixture was agitated overnight while the reaction temperature was allowed to warm to room temperature. HPLC analysis indicated that the major peak (53%) had the same retention time as a reference sample of **11**.

9*β*,11*β*-Epoxy-17,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (3b). The 16α-methyl-triene-21-cathylate **23** (50 g, 86.9% purity) was suspended in DMF (175 mL) at room temperature. Then 70% $HClO_4$ (6.5 mL) was added in the mixture, which was followed by addition of DBH (25 g) at room temperature over about a 10 min time period. The resulting mixture was agitated for about 1 h. MeOH (150 mL) was charged, and the resulting solution was slowly transferred into a water solution (4000 mL) that contained

MeOH (500 mL) and Na_2SO_3 (6 g). The slurry was cooled to about 5 °C with agitation. The bromoformate **24** was filtered and washed with water.

The bromoformate **24** wet cake was dissolved in a mixture of CH_2Cl_2 (300 mL) and MeOH (25 mL). The water layer was separated and extracted with CH_2Cl_2 (100 mL). The organic layers were combined with MeOH (100 mL). The chilled and degassed solution was reacted with NaOH (15 g) solution in water (30 mL) following the same procedure as described for **3a**. The reaction was quenched with an aqueous acetic acid solution (20 mL, 50%). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 125 mL). The combined organic layers were concentrated to remove CH_2Cl_2 and replaced with MeOH to a final volume of 150 mL. The slurry obtained was cooled to about −2 °C, filtered, and washed sequentially with cold MeOH (30 mL) and a mixture of MeOH and water. The wet cake was dried under vacuum at 60 °C to yield 35.5 g epoxide **3b** with a purity of 99.2% (93.3% overall yield from **24**).

The HPLC retention time and ^{1}H NMR spectrum are identical with those of a reference compound. ^{1}H NMR (400 MHz, DMSO-d_6): 6.47 (d, J = 10 Hz, 1H), 5.96 (br s, 1H), 5.93 (dd, J = 10, 1.7 Hz, 1H), 4.89 (s 1H), 4.54 (t, J = 5.9 Hz, 1H), 4.31 (dd, J = 19.3, 6.4 Hz, 1H), 3.88 (dd, J = 19.3, 6.4 Hz, 1H), 3.05 (br s, 1H), 2.74 (m, 1H), 2.51 (m, 1H), 2.32 (m, 1H), 2.10 (m, 3H), 1.61 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.22 (s, 3H), 1.14 (m, 1H), 1.05 (m, 1H), 0.60 (d, J = 6.8 Hz, 3H), 0.59 (s, 3H).

Acknowledgment

We thank Dr. Derek Walker for his helpful discussions and support, Mr. Luis Gil for providing all of the reference samples as well as converting the epoxides to betamethasone and mometasone for impurity profile comparison. We are also indebted to Mr. Danny Angeles for experimental assistance, Dr. Birendra Pramanik for providing mass spectra, and Dr. Tze-Ming Chan for NMR analysis.

Received for review January 4, 2001.

OP0102013