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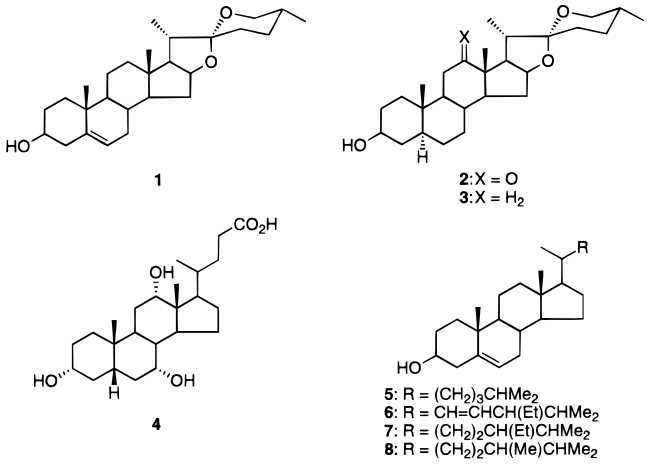
Improved Synthetic Route to Dexamethasone Acetate from Tigogenin

Tetsuo Ohta, Huyue Zhang, Yoshitaka Torihara, and Isao Furukawa*

Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-03, Japan

Abstract:

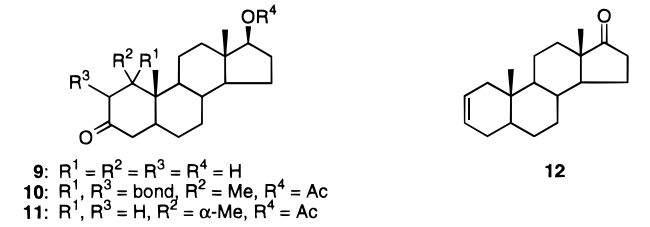
In the synthesis of dexamethasone acetate from tigogenin, the introduction of the 17α-hydroxy-16α-methyl and the 1,4-diene moieties was improved. For the introduction of the 17α-hydroxy-16α-methyl moiety, the key step, epoxidation, was accomplished in high yield with peracetic acid in a buffer solution of sodium acetate and acetic acid (overall yield from 17-ene substrate to 17α-hydroxy-16α-methyl intermediate: 95.3%). Then the introduction of the 1,4-diene in the A-ring was greatly improved by bromination−dehydrobromination, in which dehydrobromination proceeded smoothly in a solvent system that was a mixture of DMF and 6% of water (82.6% isolated yield of 1,4-diene based on 3-oxo compound).



Introduction

Steroidal hormones have a variety of pharmaceutical activities, and the demand for steroidal medicines increases 6−10% every year worldwide; of these compounds, estrin amounts to 20%, androgen and anabolic steroids amount to 5−10%, and corticosteroids amount to more than 60%.[1] The raw materials used in the production of these steroids come from natural plants and animals, for example, mainly diosgenin (**1**) and hecogenin (**2**), and successively tigogenin (**3**), cholic acid (**4**), cholesterol (**5**), stigmasterol (**6**), sitosterol (**7**), campesterol (**8**), etc.,[2] although some steroidal hormones, such as estrin, can be prepared by total synthesis.[3,4] In recent years, the improvement of the plant species has been changing the content of the above raw materials in plants. Formerly, the byproducts in a manufacturing process of hemp fiber contained a large quantity of **2** and a small quantity of **3**, so **2** was widely used as one of the main starting materials in the production of steroidal hormones. However, the content of **2** diminished considerably after the variety of hemp was improved; furthermore, the now widely used **1** is also becoming scarce. Therefore, the exploitation of **3** which is abundantly available in natural resources is an urgent necessity, even though the use of **3** is far more difficult than that of **1** and **2** in terms of the structure.

From 1984 to 1988, the synthesis of anabolic steroids such as stanolone (**9**) and methenolone acetate (**10**) and of androgens such as mesterolone acetate (**11**) and 5α-androst-2-en-17-one (**12**) from **3** were studied.[5] But the synthesis of corticosteroids is the most difficult among the syntheses of the various kinds of steroids.



Investigation for synthesizing dexamethasone acetate (**25**) from **3** began in 1988, **25** being the most widely used as an anti-inflammatory and antiallergic high-effect corticosteroid and the annual demand for it being about 5 tons worldwide. The selected synthetic route[6−8] was as depicted in Scheme 1.

This route, which was established by Oliveto *et al.*[6] and followed by Ma *et al.*,[8] has some difficult steps, and the yields were inadequate. In particular, the introduction of the 1,4-diene into the A-ring by bromination, followed by dehydrobromination (**19** → **21**), was a key step (the yield was not available in ref 6 and a 52% yield was reported in ref 8).

Many methods for introducing the 1,4-diene into the A-ring of steroids have been reported, for example, the use of selenium compounds,[9−12] DDQ (2,3-dichloro-5,6-dicy-

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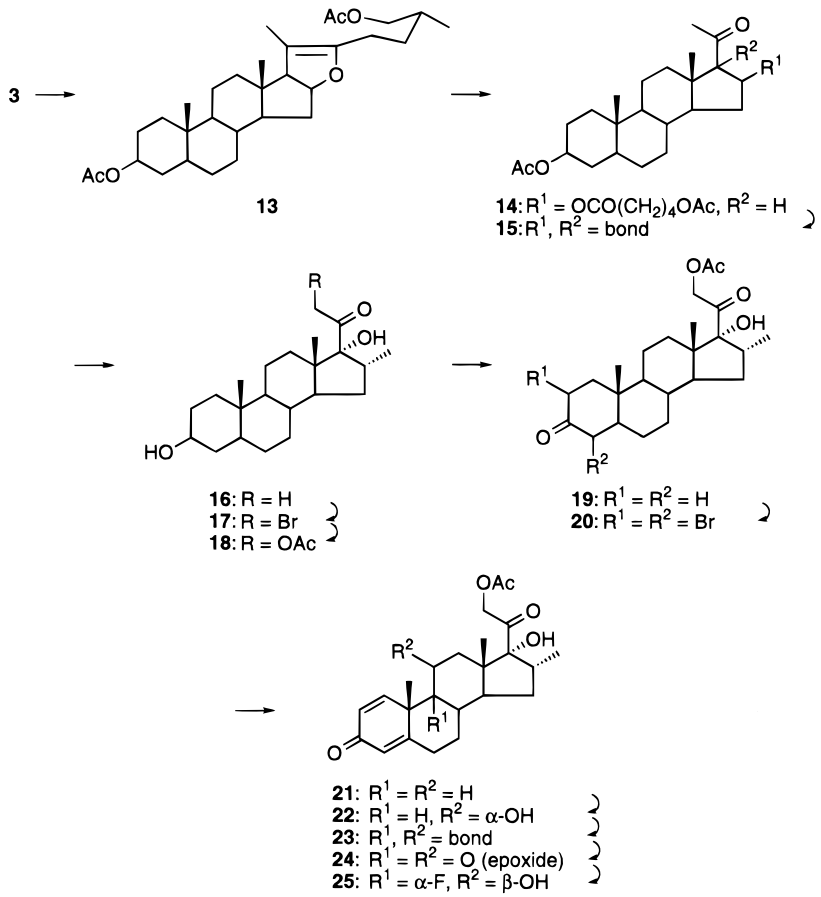
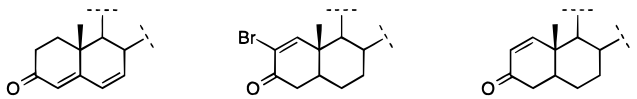
Scheme 1



anobenzoquinone) as an oxidizing agent,[13,14] fermentation,[15−17] and bromination−dehydrobromination.[18−26] Among these, selenium compounds and DDQ are toxic and even gave the products in moderate yield. Fermentation needs a low substrate concentration and a very long reaction time, even though in the course of the production of corticosteroids, such as androstanedione and androstadienedione, from stigmasterol (**6**) and sitosterol (**7**), fermentation is the method for introducing alkenes into the A-ring. Although bromination−dehydrobromination seems to be the best synthetic route to apply to industrial production, the reported yields were modest and the selectivities of the product were low, because the desired product **21** was accompanied by three or more byproducts **26**−**28** in the previous methods.[27]



26 **27** **28**

We wish to report improved methods for introducing the 1,4-diene (**19** → **21**) and the 17α-hydroxy-16α-methyl (**15** → **16**) as well, and to discuss the reaction mechanisms of the dehydrobromination.

Experimental Section

Preparation of 3*β*,17α-Dihydroxy-16α-methyl-5α-pregnan-20-one (16). *Preparation of 16α-Methyl-5α-pregn-17(20)-ene-3β,20-diol 3,20-Diacetate (**15a**).* Into a three-necked flask were introduced 300 cm^3 of THF and 2.10 g (21.2 mmol) of copper(I) chloride, and the contents were kept below 0 °C until the addition of water. Then to this mixture was added 5.00 cm^3 of methylmagnesium chloride (3.0 M solution in THF) under argon, and the resulting mixture was stirred for 5 min. 3*β*-Acetoxy-16-pregnen-20-one (**15**) (50.0 g, 139 mmol) was rapidly added, and 65.0 cm^3 of methylmagnesium chloride (3.0 M solution in THF) was added dropwise within 30 min. After the reaction was finished, 20.0 cm^3 (212 mmol) of acetic anhydride was

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added, and the solution was further stirred for 15 min. Water (200 cm^3) was added at a temperature below 30 °C, and the solution was stirred for 30 min. After the reaction mixture was concentrated at 85 °C under reduced pressure, 1,2-dichloroethane was added, and the solution was concentrated at 85 °C again. Subsequently, the mixture of the resultant solution and an additional 250 cm^3 of 1,2-dichloroethane was stirred for 10 min. The mixture was treated with 250 cm^3 of 20% ammonium chloride. The separated aqueous layer was extracted twice with 25 cm^3 of 1,2-dichloroethane. The combined organic layer was washed with 500 cm^3 of water and concentrated to 300 cm^3. Insoluble materials were removed by filtration through 1 g of Celite and washed twice with 50 cm^3 of 1,2-dichloroethane. The solution was adjusted to 350 cm^3 with 1,2-dichloroethane and directly used in the following reaction.

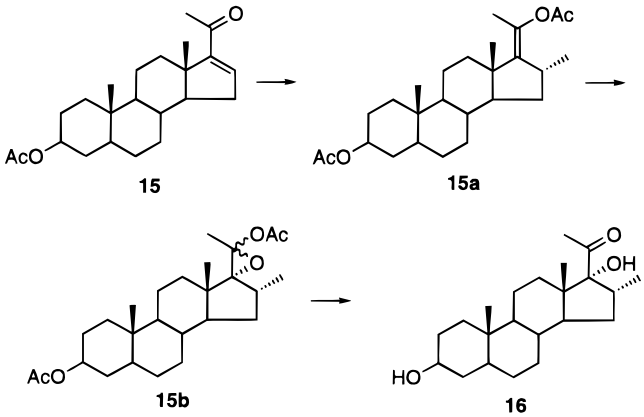
*Preparation of 17,20-Epoxy-16α-methyl-5α-pregna-3β,-20-diol 3,20-Diacetate (**15b**).* To the solution of **15a** obtained above were added 25.0 g of sodium acetate and 250 cm^3 of 16% (about 526 mmol) peracetic acid in acetic acid at 0−5 °C, and the mixture was stirred at room temperature for 24 h. The resulting mixture was washed twice with 350 cm^3 of 10% aqueous ferrous sulfate, twice with 315 cm^3 of 5% aqueous sodium bicarbonate, and twice with water. All aqueous layers were combined and extracted with 1,2-dichloroethane. The organic layer combined was concentrated in vacuo to 200 cm^3 and used in the next reaction.

*Preparation of 3β,17α-Dihydroxy-16α-methyl-5α-pregnan-20-one (**16**).* To the above solution of **15b** were added 550 cm^3 of methanol and 11.2 g (280 mmol) of sodium hydroxide, and the mixture was refluxed for 1 h. Then the reaction solution was neutralized with acetic acid and concentrated in vacuo till crystals formed. After cooling of the suspension, the crystals were collected by filtration, washed twice with 30 cm^3 of methanol, and dried. **16**: 46.3 g, yield 95.3%; mp 244−246 °C; $[\alpha]^{25}_D$ +11.5 (*c* 1.00 in DMF) (lit.[8] mp 244−246 °C; $[\alpha]^{25}_D$ +11.5).

Preparation of 21-Bromo-3β,17α-dihydroxy-16α-methyl-5α-pregnan-20-one (17). Twenty grams (57.4 mmol) of **16** was dissolved in a solution consisting of 200 cm^3 of dichloromethane and 20 cm^3 of a 20% hydrogen chloride−ethanol solution. Then 9.20 g (57.6 mmol) of bromine dissolved in 40 cm^3 of dichloromethane was added dropwise. After the color of the bromine disappeared, the solution was neutralized with 20 g of sodium bicarbonate and concentrated in vacuo. To the resulting mixture was added 80 cm^3 of methanol, and then the mixture was concentrated in vacuo again. This was put into 400 cm^3 of water and allowed to stand for 2 h. The precipitate was subsequently filtered, washed with water, and dried in vacuo. The white solid of **17** was obtained in 99.1% yield (24.3 g): mp 212−213 °C (lit.[8] mp 210−211 °C).

Preparation of 3β,17α,21-Trihydroxy-16α-methyl-5α-pregnan-20-one 21-Acetate (18). To a solution of 23.0 g (53.8 mmol) of **17** in 575 cm^3 of acetone was added 21.2 g (216 mmol) of potassium acetate, and the mixture was refluxed for 2.5 h. The reaction solution was concentrated in vacuo and put into 460 cm^3 of water. After standing for 3 h, the solid materials formed were filtered, washed with water, and dried at 70 °C to give white solids of **18** (22.2 g): yield quantitative; mp 193−196 °C; $[\alpha]^{25}_D$ +23.5 (*c* 1.00 in dioxane) (lit.[8] mp 192−195 °C; $[\alpha]^{25}_D$ +23).

Scheme 2

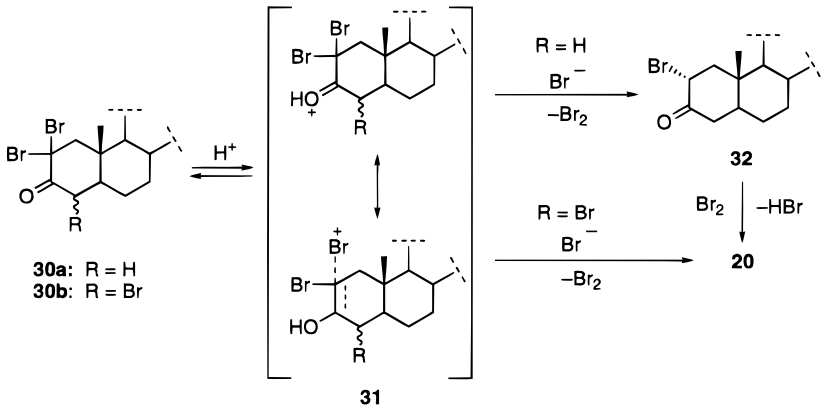


Preparation of 17α,21-Dihydroxy-16α-methyl-5α-pregnane-3,20-dione 21-Acetate (19). To a solution of 20.0 g (49.2 mmol) of **18** and 12.0 g (83.9 mmol) of calcium hypochlorite in 600 cm^3 of ethyl acetate was added 120 mL of acetic acid dropwise. The mixture was stirred at 25−35 °C for 3 h, concentrated in vacuo, and put into 400 cm^3 of water. After the mixture was allowed to stand for 2 h, the precipitate formed was isolated by filtration, washed with water, and dried at 70 °C to result in 20.7 g of **19** (crude material, mp 201.5−205 °C, $[\alpha]^{25}_D$ +45.5 (*c* 1.00 in dioxane)). Recrystallization from acetone gave 17.3 g of **19**: yield 86.6% based on **16**; mp 205.5−206.5 °C; $[\alpha]^{25}_D$ +50 (*c* 1.00 in dioxane).

Preparation of 2α,4ξ-Dibromo-17α,21-dihydroxy-16α-methyl-5α-pregnane-3,20-dione 21-Acetate (20). To a solution of **19** (10.0 g, 24.7 mmol) in acetic acid (21 cm^3) and dioxane (99 cm^3) was added at 10 °C a solution (50 cm^3) of hydrogen chloride (slightly over 7%) in acetic acid. After 5 min of stirring, a solution of bromine (8.28 g, 51.8 mmol) in acetic acid (10 cm^3) was added dropwise at about 10 °C. The resulting solution was stirred at 10−15 °C for 6 h and put into the water. The precipitate formed was filtered, washed with water, and dried in vacuo to give 13.9 g of white solids. This crude product of **20** was directly used in the next reaction.

Preparation of 17α,21-Dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-Acetate (21). To 100 cm^3 of DMF containing 6% (0.33 mol) of water were added 10.0 g (17.8 mmol) of the product **20** obtained in the above reaction, 10.0 g (99.9 mmol) of calcium carbonate, and 5.90 g (57.3 mmol) of sodium bromide, and this mixture was refluxed for 4 h. Then the resulting mixture was put into 140 cm^3 of water containing 66 cm^3 of concentrated hydrochloric acid. The solid material formed was collected by filtration, washed with water until neutral, and dried at 70 °C to give 6.90 g of **21**: yield 96.9% (from **19**); purity 84% by HPLC; $[\alpha]^{25}_D$ +61 (*c* 1.00 in dioxane). This material can be used in the following fermentation. Purification of 4.5 g of **21** was also carried out by column chromatography (silica gel (100 g), 38:62 ethyl acetate−hexane) and then by recrystallization from methanol to give 3.72 g of white crystals: yield 82.6%; mp 181−185 °C; $[\alpha]^{25}_D$ +62 (*c* 1.00 in dioxane); UV λ_{max} in MeOH (nm) 244.6 (15 100); IR ν_{max} (cm^{-1}) 3470, 1735,

Scheme 3

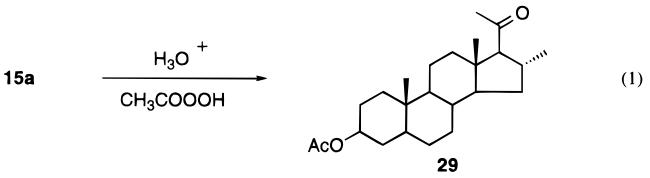


1720, 1655, 1620, 1600, 1239; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (3H, s), 0.91 (3H, d, J = 7 Hz), 1.0−1.1 (2H, m), 1.23 (3H, s), 1.2−1.3 (1H, m), 1.6−2.0 (8H, m), 2.17 (3H, s), 2.3−2.4 (2H, m), 2.48 (1H, td, J = 14 and 5 Hz), 4.80 (1H, d, J = 18 Hz), 4.99 (1H, d, J = 18 Hz), 6.07 (1H, s), 6.24 (1H, dd, J = 2 and 10 Hz), 7.05 (1H, d, J = 10 Hz). (lit.[8] mp 180−185 °C; $[\alpha]^{25}_D$ +58; UV λ_{max} in MeOH (nm) 245 (15 040); IR ν_{max} (cm^{-1}) 3470, 1735, 1720, 1645, 1610, 1590, 1230; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (3H, s, C_{18}-H), 0.93 (3H, d, J = 6.8 Hz, C_{16}-CH_3), 1.24 (3H, s, C_{19}-H), 2.2 (3H, s, O_2CCH_3), 3.0 (1H, s, C_{17}-OH), 4.94 and 5.16 (2H, ABq, J = 18 Hz, C_{21}-H), 6.22 (1H, s, C_4-H), 6.41 (1H, d, J = 10 Hz, C_2-H), 7.25 (1H, d, J = 10 Hz, C_1-H).

Results and Discussion

Introduction of 17α-Hydroxy-16α-methyl (15 → 16). Introduction of the 17α-hydroxy-16α-methyl moiety (**15** → **16**)[6−8,15] consists of four steps: methylation, acetylation, epoxidation, and hydrolysis (Scheme 2), and these steps are carried out sequentially.

In the previous investigations, the epoxidation (**15a** → **15b**) was carried out by use of peracetic acid (more than 40% concentration) in chloroform (yield of **15b** was usually 60−70%, except nearly 90%[8]). In this reaction, a byproduct (eq 1, **29**) observed might be due to the acidity of the reagent system.



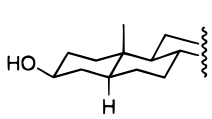
(1)

As a result of the improved epoxidation (**15a** → **15b**), the overall yield of the reaction product (**15** → **16**) reached 95.3%. Such a high yield has not been reported so far. In this step, a low concentration of peracetic acid (about 16%) in a buffer solution of sodium acetate and acetic acid was used, and the reaction was quickly performed at 30 °C in order to avoid the production of the byproduct (**29**).

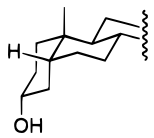
Introduction of 21-Acetoxy (16 → 18) and Oxidation of 3-Hydroxy (18 → 19). Bromination in the 21-position (**16** → **17**), the subsequent substitution (**17** → **18**), and the oxidation of the 3-hydroxy moiety to 3-oxo were carried out almost quantitatively carried out in each step. After the purification, the total yield was 86.6% (**16** → **19**), much better than reported before (72.5% in ref 8).

Introduction of 1,4-Diene (19 → 21). As purification of **20** is difficult because of its instability, conversion from **19** to **21** was performed without purification of **20**. Usually, several products, such as 2α-bromo **32**, 2,2-dibromo **30a**, 2α,4ξ-dibromo **20**, and 2,2,4ξ-tribromo **30b** were formed at beginning of the bromination of **19**, and then only **20** was shown on TLC as the reaction was prolonged. The best result was obtained at 10−15 °C for 6 h. This change of product distribution can be explained by the fact that the bromination in the A-ring of the steroid (A/B trans) takes place at the 2-position more easily than at the 4-position, because of the differences in electronic density and the tension of the A-ring. But dismutation has occurred in the course of the reaction (Scheme 3).

Dehydrobromination of 5β compounds was already well documented, and a very efficient method in anhydrous conditions was reported in the 5β series,[28] although insufficient results were obtained in the 5α-type steroids such as **20**.



5 α



5 β

As in the previous report, the products of the dehydrobromination of **20** were a mixture of **21** and **26**. First, dehydrobromination takes place at the 4,5-position prior to taking place at the 1,2-position, because a large quantity of 2α-bromo 4-ene compound **33** exists during the reaction. Next, dehydrobromination of **33** gives diene products. If the reaction proceeds through an E1 mechanism, the rearrangement of the carbonium ion (**34**) can easily take place (Scheme 4) and the products become a mixture of 1,4-diene (**21**) and 4,6-diene (**26**). So, we considered that the polarity of the solvent plays an important role for this selectivity.

We discovered that the addition of a small amount of water (2−8% in DMF) inhibited the formation of 4,6-diene **26**, but the proportion of **26** increased if the quantity of water was increased (Table 1).

(28) Joly, R.; Warnant, J.; Nominé, G.; Bertin D. *Bull. Soc. Chim. Fr.* **1956**, 366.

Scheme 4

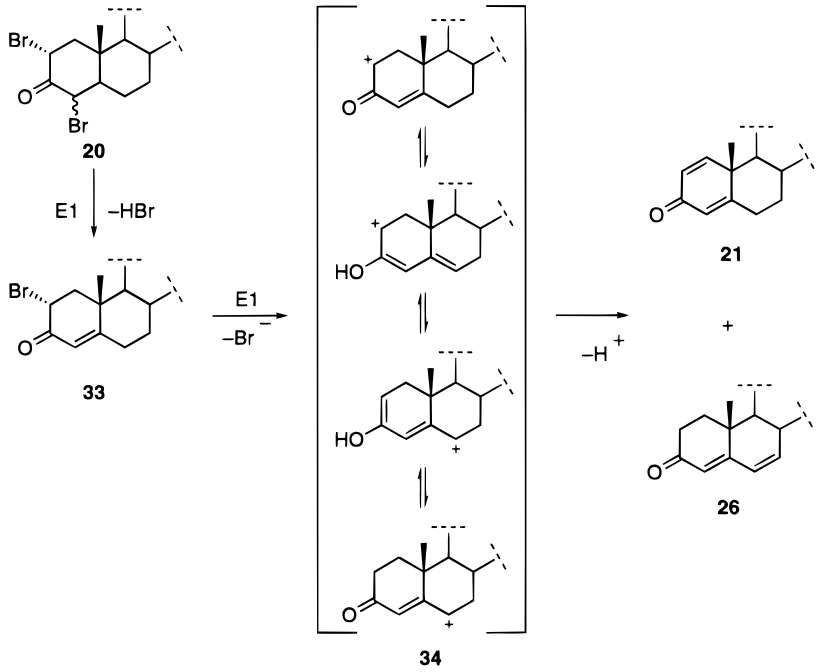
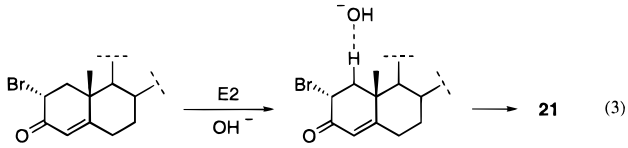


Table 1. **Effect of adding water on dehydrobromination of 20**[a]

run	H_2O (%, v/v)	yield[b] (%) 21	26
1	0	71.5	7.9
2	2	82.4	1.7
3	4	81.6	1.7
4	6	84.0	1.7
5	8	80.0	1.9
6	10	73.7	3.4

[a] See Experimental Section. [b] Determined by HPLC.

$$CaCO_3 + 2H_2O \rightleftharpoons Ca^{2+} + 2OH^- + H_2CO_3 \quad (2)$$



(3)

These observations can be explained as follows. First, some water was necessary for dissolving $CaCO_3$ in the reaction medium and for producing hydroxide anion to make an E2-type reaction effective (eqs 2 and 3). Second, water (dielectric coefficient: 78.3 at 25 °C) is more polar than DMF (dielectric coefficient: 37 at 25 °C) and stabilizes the high polar intermediate in the E1 mechanism but does not do so at the transition state in the E2 mechanism, because the polarizability of the intermediate in the E1 mechanism is higher than the polarizabilities of the starting material and the product, but the polarizability of the transition state in the E2 mechanism is lower. That is to say, the water accelerates an E2-type reaction, while an excessive amount of water encourages an E1-type reaction.

As shown above, it has been evidenced that the optimal condition for introducing the 1,4-diene moiety by debromination from 5α type **20** is to reflux a solution of **20** in DMF containing 2−8% of water in the presence of calcium carbonate.

In summary, after the introduction of 17α-hydroxy-16α-methyl (**15** → **16**) and of 1,4-diene (**19** → **21**) was improved, the total yield of dexamethasone acetate (**25**) synthesed was also raised.

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