Pergamon

Tetrahedron Letters 42 (2001) 2639–2642

TETRAHEDRON LETTERS

A regioselective PCl_5 mediated dehydration for preparing $\Delta^{9,11}$ corticosteroids

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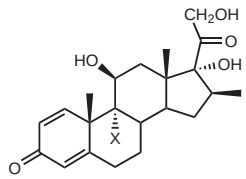
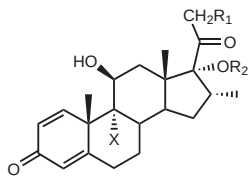
Received 21 December 2000; revised 1 February 2001; accepted 5 February 2001

Abstract—A regioselective PCl_5-induced dehydration of 11α-hydroxy corticosteroids was invented to provide the corresponding $\Delta^{9,11}$ double bond trienes in excellent yield (>90%) with 99:1 regioisomeric ratio to the $\Delta^{11,12}$ isomers. A *syn*-elimination mechanism was proposed for this reaction.

The pharmacologically important corticosteroid drugs such as betamethasone (I, X = F), beclomethasone (I, X = Cl), dexamethasone (II, X = F, R_1 = OH, R_2 = H), and mometasone (II, X = Cl, R_1 = Cl, R_2 = furoyl) have been well received since their introduction into the world-wide market. Corticosteroids continue to play major roles in dermatological and allergy practices.[1] The 9,11-halohydrin is crucial for biological activity.[2] Introduction of the $\Delta^{9,11}$ double bond is the key to functionalizing both the C-9 and C-11 positions. The existing manufacturing process involves conversion of the 11α-hydroxyl group into its corresponding mesylate and subsequent elimination to the desired 9,11 double bond. The elimination step, however, produces a considerable amount of a side product, the $\Delta^{11,12}$ isomer (15%). Both the yield and the purity suffer at this step. Minimizing or eliminating the $\Delta^{11,12}$ isomer formation has been a long standing challenge in order to boost the overall chemical yield and product quality. We wish to report a PCl_5 mediated elimination approach to selectively dehydrate the 11α-hydroxyl group to form the delta 9,11 double bond.



I



II

Keywords: dehydration; corticosteroids; betamethasone; mometasone; *syn*-elimination; phosphorous pentachloride.

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It is well understood that the problem in the elimination step is associated with the configuration of carbon C-11. With an 11β-OH,[3] the base catalyzed anti E_2 elimination works well to provide 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 exclusively form the $\Delta^{9,11}$ double bond. Although 11β-hydroxylation by fermentation is documented in the literature,[4] attempts to introduce the 11β-OH on the corresponding C-11 deoxy substrate through biotransformation have proved fruitless. Based on the above analyses, this situation could be resolved by a *syn*-elimination approach, or by converting the 11α-OH to an 11β-leaving group to conduct the anti-elimination.

Attempts to convert the 11α-mesylate into the 11β-Br analogue by refluxing the mesylate with NaBr in acetone were unsuccessful. Treatment of 11α-hydroxy (III) in THF with NaH followed by addition of CS_2 and CH_3I did not produce the desired 11-xanthate[5] for the proposed *syn*-elimination in a reasonable yield. Bernstein et al.[6] reported that reaction of a 3,17-bisketal-11α-OH-steroid with phosphorous oxychloride in pyridine gave the $\Delta^{9,11}$ double bond in 90% 'crude' yield. Indeed the desired $\Delta^{9,11}$ (VI) was formed with excellent ratio to $\Delta^{11,12}$ isomer (98:2 by HPLC area) by treatment of III under the Bernstein conditions. Although the solution yield of the desired product VI was less than 15% with remaining unidentified impurities, the $\Delta^{9,11}$ to $\Delta^{11,12}$ ratio was encouraging. Careful analysis of this reaction indicated that under the employed conditions, $\Delta^{9,11}$ (VI) was formed very slowly, and heating was required to push the disappearance of the starting material. Alternatives to $POCl_3$, such as PCl_5 were used in order to optimize the reaction yield. Shoppee et al.[7] reported that reaction of 5α-androstan-

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PII: S0040-4039(01)00274-X

Table 1. Solvent and temperature effects on the PCl_5 dehydration

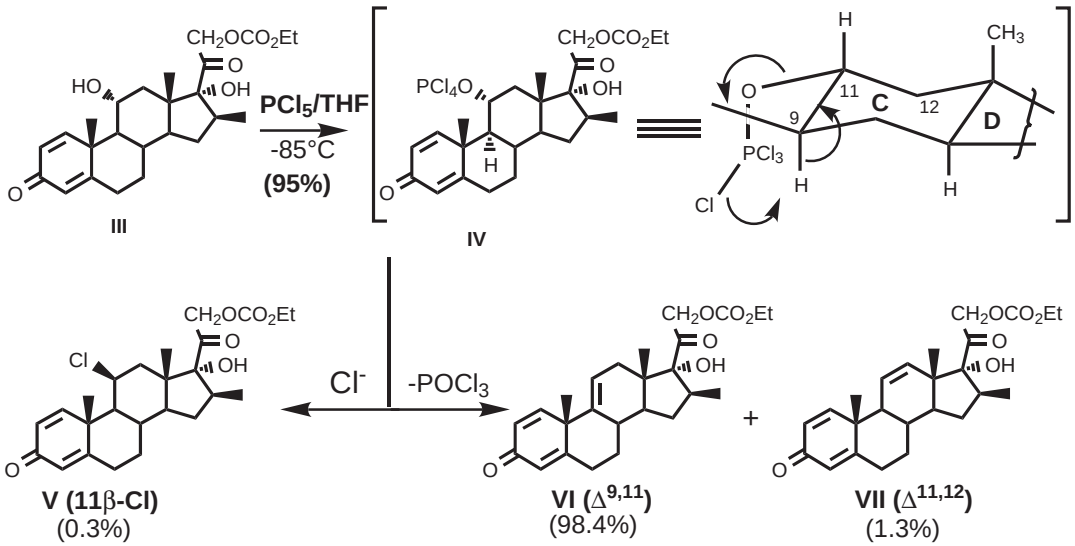
Solvent	Temp. (°C)	HPLC area (%)		
		$\Delta^{9,11}$	$\Delta^{11,12}$	11β-Cl
CH_2Cl_2/py	Rt	70.4	11.2	18.4
py	Rt	52.3	3.8	44.0
CH_2Cl_2	−20	74.4	14.5	11.0
THF	Rt	81.0	7.4	11.3
THF	−20	92.3	4.9	2.8
THF	−45	95.5	3.3	1.2
THF	−78	97.5	1.8	0.7
THF	−85	98.4	1.3	0.3

11α-ol with PCl_5 in $CHCl_3$ at rt gave 5α-androst-9(11)-ene in 65% isolated yield with a major by-product identified as 9α,11β-dichloride. Although the isomeric ratio of $\Delta^{9,11}$ to $\Delta^{11,12}$ was not analyzed by HPLC, the reported facile elimination was attractive. When 11α-hydroxy (III) was reacted with PCl_5 in CH_2Cl_2/py at rt, as expected, the starting material was consumed in less than five minutes and 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 compound (V) by mass spectrum and NMR experiments. The C-11 β configuration was determined by observation of only small coupling constants (<3 Hz) of 11α-H with H-9 and H-12. The corresponding 9α,11β-dichloride[7] was not detected under the conditions employed.

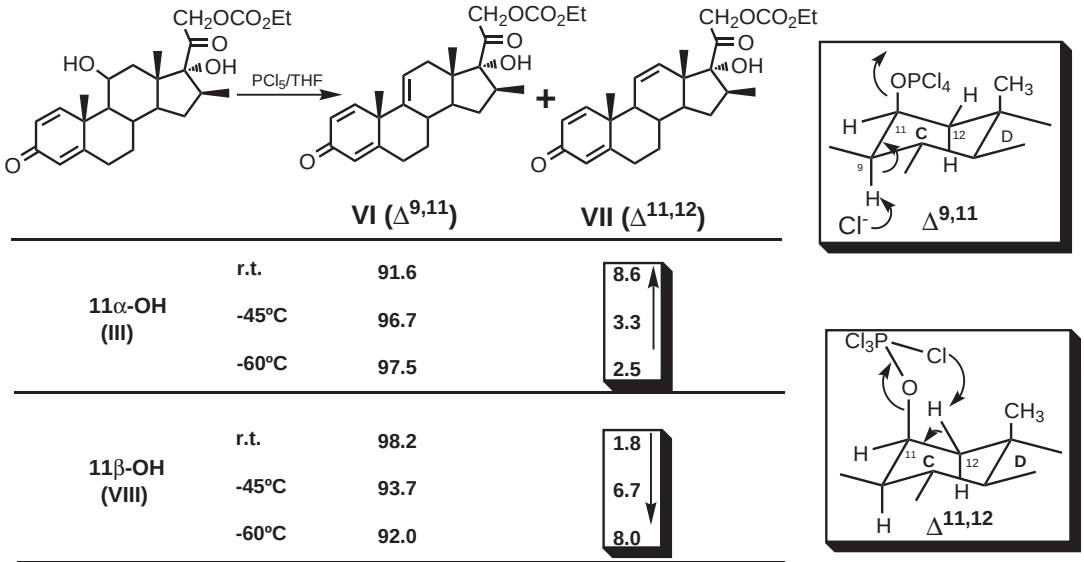
One can speculate that the $\Delta^{9,11}$ double bond is formed by the base catalyzed E_2 elimination via the 11β chloro intermediate since the latter compound was indeed detected in the reaction. In order to minimize the level of the 11β-Cl, the reaction was carried out in pyridine so that all of the 11β-Cl formed would be converted to the $\Delta^{9,11}$ (VI). However, a higher level of 11β-Cl was observed from this reaction than that detected from the reaction run in CH_2Cl_2/py. This result clearly suggested that the elimination did not go through the 11β-Cl intermediate.

The better ratio (Table 1) of $\Delta^{9,11}$ to $\Delta^{11,12}$ isomers might have resulted from a solvent effect. With this idea in mind, the PCl_5 mediated dehydration was carried out in different solvents and at different temperatures. After various experiments, THF was found to be the solvent choice and −78 to −90°C was observed to be the optimum reaction temperature (see Table 1 for results of solvent and temperature effects). With these conditions, $\Delta^{9,11}$ (VI) was isolated in greater than 90% yield with a ratio of $\Delta^{9,11}$ (VI) to $\Delta^{11,12}$ (VII) of about 99:1 (Scheme 1).

The mechanism of this reaction is not clear to us at this moment, however, it can be speculated (Scheme 1) from experimental observations. Reaction of 11α-hydroxyl group with PCl_5 produces an 11α-chlorophosphate intermediate. The phosphorous function should be a facile leaving group to provide a partial positive charge at position C-11. At the same time, the chloride would abstract the proton at C-9 since the two groups can be arranged in the proximity of the same face. This would, in return, increase the elimination rate to provide a $\Delta^{9,11}$ double bond. It is known that the $\Delta^{9,11}$ (VI) is more stable than the $\Delta^{11,12}$ (VII) isomer because the former is a tri-substituted double bond. Furthermore, hydrogens attached to tertiary carbons have weaker C–H bonds, which preferentially undergo intramolecular elimination. However, the activation energy difference may not be large enough for the $\Delta^{9,11}$ to be a dominating product at high temperature. But at lower temperature, the ratio of the two olefins can be dramatically increased to favor the desired product. This is clear from the results of the reactions from room temperature to −85°C in THF (Table 1). On the other hand, identification of the 11β-Cl impurity (V) provides



Scheme 1.



		VI ($\Delta^{9,11}$)	VII ($\Delta^{11,12}$)
11α-OH (III)	r.t.	91.6	8.6
	-45°C	96.7	3.3
	-60°C	97.5	2.5
11β-OH (VIII)	r.t.	98.2	1.8
	-45°C	93.7	6.7
	-60°C	92.0	8.0

*The above data are HPLC area% ratios for **VI** and **VII** only. The 11-β-Cl from **III** is left out for comparison.

Scheme 2.

good evidence to exclude the possibility of the formation of a free carbonium ion at C-11. The attack of a chloride ion on the carbonium C-11 would be mainly from the sterically less hindered α-face to furnish the corresponding 11α-Cl. However, there is no evidence for the formation of 11α-Cl from the PCl_5 dehydration reaction.

Furthermore, if the carbonium ion were indeed the reactive intermediate, the product distribution from the 11β hydroxy analogue would be similar to that from the 11α hydroxy under the same reaction conditions. However, treatment of the 11β-OH compound with PCl_5 in THF at −60°C furnished $\Delta^{9,11}$ (VI) with a ratio of 92.0:8.0 to its $\Delta^{11,12}$ isomer. While reaction at room temperature, as expected from its anti-coplanar orientation of H-9 with the leaving group, generated $\Delta^{9,11}$ as the dominant product. These results clearly suggest that in the case of the 11β-OH there are two competing elimination pathways. At higher temperature, the E_2 elimination mechanism dominates the reaction. The main pathway rate is slower at lower temperature, and the competing *syn*-elimination on the other hand generates more $\Delta^{11,12}$ isomer, as depicted in Scheme 2. These experimental results are also contrary to the hypothesis of the formation of a free carbonium ion at C-11 (Scheme 2).

Extension of the new chemistry to the 16α methyl series would provide an efficient synthesis for the mometasone triene intermediate. The reaction of the 16α analogue of 11α-hydroxy (III) with PCl_5 was carried out in THF at −85°C. The corresponding dehydrated product $\Delta^{9,11}$ was isolated in greater than 90% yield with a 99:1 ratio to the $\Delta^{11,12}$ isomer. The scope of this reaction seems to be limited to the C-11-hydroxy, the most sterically hindered site in the steroid nucleus. Treatment of the corresponding 12β-hydroxy with PCl_5 did not produce any elimination product. Reaction of menthol with PCl_5 in THF failed to generate an olefinic signal by NMR study.

In summary, a regioselective PCl_5-induced dehydration reaction has been discovered and successfully implemented in the manufacturing processes of betamethasone and mometasone. The solvent and temperature effects on the selectivity have been studied. The new processes produced the corresponding products in higher yields and superior quality, resulting in increased manufacturing efficiency.

Acknowledgements

The authors wish to thank Dr. Derek Walker and Mr. Luis Gil for helpful discussions. The authors are also indebted to Dr. Birendra Pramanik for providing mass spectra and Dr. Tze-Ming Chan for NMR analysis.

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