Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8403-8404, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01921-1

A simple synthesis of 16-unsaturated corticosteroids.

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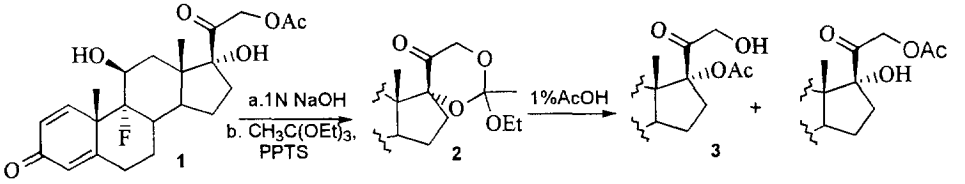
Abstract: A simple,direct procedure for the synthesis of 16-unsaturated corticosteroids is described. The route developed is shorter than currently used procedure and can be easily scaled up. Copyright © 1996 Elsevier Science Ltd

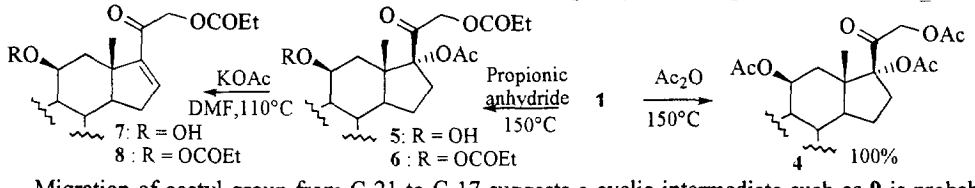
16-unsaturated corticosteroids are important intermediates in the synthesis of a variety of glucocorticoids[1-4]. Introduction of substituents such as alkyl, halo, etc., in the 16-position of glucocorticoids results in significant increase in activity[5-8]. Generally the double bond at C-16 is introduced by elimination of the 17-acyloxy group[6,9]. Acylation of 17α-OH involves initial synthesis of the 17α,21-orthoester **2**[9]. Hydrolysis of **2** yields the desired 17α-acetate[9-11]. This reaction also yields some 21-acetate which is subsequently separated. This makes the synthesis time-consuming and tedious.



1 **2** **3**

We herein report a simple, direct procedure for the synthesis of 17α-acyloxy compounds that eliminates the need to prepare the 17α,21-orthoester. This greatly reduces the length and time required for the synthesis of 16-unsaturated corticosteroids and simplifies the preparation and scale up.

We hoped to take advantage of the steric hindrance of 11β-OH to achieve a selective esterification of 17α-OH. However the 17-OH is itself quite hindered and its acetylation achieved only at elevated temperatures. Under the conditions, formation of 11-acetate is a major competing reaction. Thus reaction of 9-fluoroprednisolone-21-acetate **1** with acetic anhydride at 150°C gives exclusively the triacetate **4**. We postulated that use of a bulkier anhydride would disfavor reaction at the 11-position and might afford some selectivity in the esterification of 17α-OH over 11β-OH. Reaction of **1** with propionic anhydride gave the diester **5** and triester **6** in the ratio of 1:1.4. When a DMF solution of **5** or **6** were heated with KOAc deacetylation of the 17α-acetate occured giving the corresponding 16-olefins **7** and **8**.



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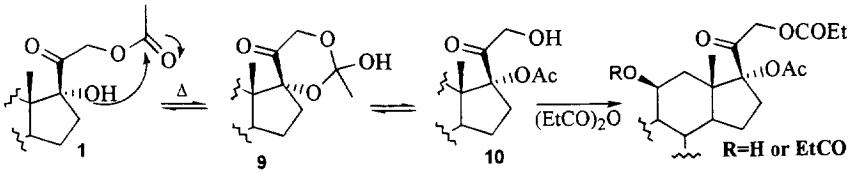
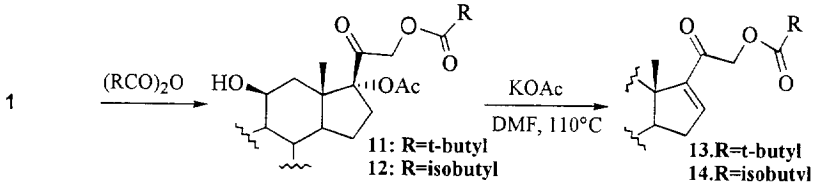
Migration of acetyl group from C-21 to C-17 suggests a cyclic intermediate such as **9** is probably involved. Under the reaction conditions **1** is in equilibrium with cyclic orthoester **9**. Ring opening of **9**

can occur in two fashions to afford **10** or **1**. In the presence of anhydride, **10** is rapidly esterified to the 21-ester shifting the equilibrium in its direction and thus driving the reaction to completion.



Since esterification of 11β-OH is determined by steric constraints alone it can be expected that use of bulkier reagents would disfavor reaction at this site. Formation of 17α-acetate is independent of this so we should observe greater selectivity in its formation. Indeed reaction of **1** with pivalic and isobutyric anhydrides gave diesters **11** and **12** respectively as sole products. **11** and **12** undergo deacetylation smoothly under standard conditions to give the corresponding 16-olefins[9]. Although **4** also undergoes smooth deacetylation to give the 11β,21-diacetate in good yield, this compound is quite insoluble in most common solvents. It is also not possible to selectively deprotect the 11β-acetate. Therefore our approach of selective acetylation of 17α-OH is very useful and provides an easy and direct access to 16-olefinic corticosteroids. Further chemistry using these olefins will be reported in due course.



To summarize, the present work takes advantage of steric hindrance around 11β-OH as well as the proximity of 17α-OH to the 21-acetate to synthesize the 17α-acetate directly. The method has considerable advantage over currently used procedures in that it is shorter, proceeds in higher yields, and gives no unwanted byproducts. The procedure can also be easily scaled up.

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(*Received in Japan* 9 *August* 1996; *revised* 17 *September* 1996; *accepted* 25 *September* 1996)