Remote Functionalization of the Cholestane Side-chain by Chromyl Acetates†

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Edward J. Parish,[a] Nida Aksara,[a] Terrence L. Boos[a] and Edna S. Kaneshiro[b]

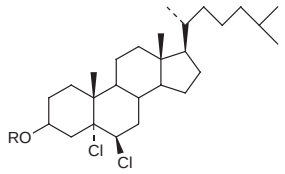
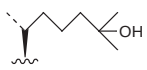
[a] *Department of Chemistry, Auburn University, Auburn, AL 36849-5312, USA*
[b] *Department of Biological Sciences, University of Cincinnati, OH 45221, USA*

Chromyl acetate and chromyl trifluoroacetate are effective reagents for the oxidation of C-25 on cholestane side-chains to the corresponding C-25 hydroxy derivative.

Chemical functionalization of the saturated side chain of steroids (*e.g.*, cholesterol) is a difficult problem for the organic chemist. The need to modify the saturated side chain of certain steroids may arise through the study of enzymatic transformations of the side chain and the requirement to have authentic standards for the identification of potential metabolites. Also, the synthesis of biochemical inhibitors would require introducing functionalities at selected positions on the side chain. Collectively, the necessity to modify the saturated side chain of steroids has been the driving force for developing facile methods to accomplish this goal.

An efficient approach to the functionalization of steroid side chains involves the direct introduction of a modification into the side chain in a single chemical reaction. This approach is termed 'remote functionalization' and represents a rapidly developing area in steroid chemistry which promises to streamline the synthesis of many difficult-to-obtain steroids. Through the earlier work of Breslow and colleagues,[1–5] methods for the remote functionalization of the steroid nucleus have become well known reactions. The functionalization of remote positions on the steroid nucleus and side chain represents some of the most important advances in the steroid field. Remote functionalization of a saturated steroid side chain usually involves oxidation on the tertiary carbon at C-25 to produce a 25-hydroxy steroid. In most studies, these reactions have been developed in the cholesterol series, and the end product of these reactions is cholest-5-en-3β,25-diol (25-hydroxycholesterol), owing to its interesting biological properties[6–8] and its ability to be dehydrated[9–12] to desmosterol which can be further chemically modified.

Table 1 The C-25 oxyfunctionalization of 3β-acetoxy- and 3β-benzoyloxy-5α,5β-dichlorocholestane

Substrate	C-25 hydroxy product	Yield (%)[a] CA (CTFA)[b]
		
1 R = Ac	**2** R = Ac	16 (51)
3 R = Bz	**4** R = Bz	18 (56)

[a] Yield of isolated product. [b] CA is chromyl acetate and CTFA is trifluoroacetate.

Early attempts to obtain 25-hydroxycholesterol directly from cholesterol included attempts to enhance the air- or autoxidation-process, these efforts only resulted in complex mixtures and low yields.[14,15] Later attempts, using chemical methods to protect the C-5 double bond, were more successful. These methods resulted in the direct synthesis of C-25 hydroxy steriods with varying degrees of success.[16–21]

We now report the successful use of chromyl acetate and chromyl trifluoroacetate as simple and convenient reagents in the C-25 oxyfunctionalization of **1** and **3** (Table 1). In these experiments the Δ^5 double bond is protected as the dichloride.[22] These reagents were prepared *in situ* from the reaction of acetic anhydride or trifluoroacetic anhydride and chromium trioxide, respectively.[23,24]

The success of this procedure depends on maintaining some starting material during the course of reaction to prevent further oxidation of the initially formed C-25 hydroxylated product. The accessibility of the relatively less hindered C-25 on the side chain allowed an initial selective oxidation at this position followed by partial oxidation of other tertiary carbons on the steroid nucleus which would result in complex oxidation products. The initial C-25 hydroxylated product may be treated with zinc in acetic acid to remove the 5α,6β-dichloride and restore the Δ^5 double bond.[22,25]

Chromyl acetate has previously been found useful for introducing a 14 α-hydroxyl group onto steroids devoid of a side chain and in the oxidation of hydrocarbons.[22,23,25] Chromyl trifluoroacetate also has been utilized in hydrocarbon oxidations.[24] Attempts to use chromyl trichloroacetate to bring about C-25 oxyfunctionalization of **1** and **3** were unsuccessful and no significant amount of products were detected.

In summary, the reactions reported herein expand the scope and utility of synthetic transformations known to be accomplished by chromyl acetates and offer an alternative method for the C-25 oxyfunctionalization of cholestane side chains.

Experimental

C-25 Hydroxylation: General Procedure.—Anhydrous chromium trioxide (10.8 g) was pulverized and added to a solution of acetic or trifluoroacetic anhydride (39.6 mmol) in carbon tetrachloride (42.8 ml), and the mixture was stirred at room temperature for 4 h. A solution of substrate **1** or **3** (2.5 mmol) in 14.4 ml of carbon tetrachloride was added and stirring was continued for 4 h in an ice bath (monitored by TLC analysis). The mixture was poured over ice, extracted with chloroform, washed with a saturated salt solution, then water, and evaporated to dryness at reduced pressure. The product was purified through column chromatography (using a gradient of diethyl ether in toluene as the eluting solvent) to give the yields presented is Table 1. The procedures used for column and thin layer chromatography (CTLC) have been described previously.[26] The purified products **2** and **4** were recrystallized from acetone water and were characterized by IR, MS, ^{1}H and ^{13}C NMR spectroscopy.

* To receive any correspondence.

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