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Chemical Degradation of Steroid Side Chains. Efficient Conversion of Cholestanol to Corticosteroid Intermediates.

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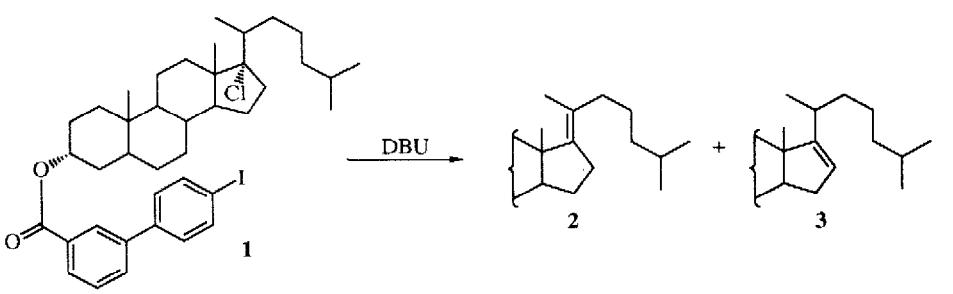
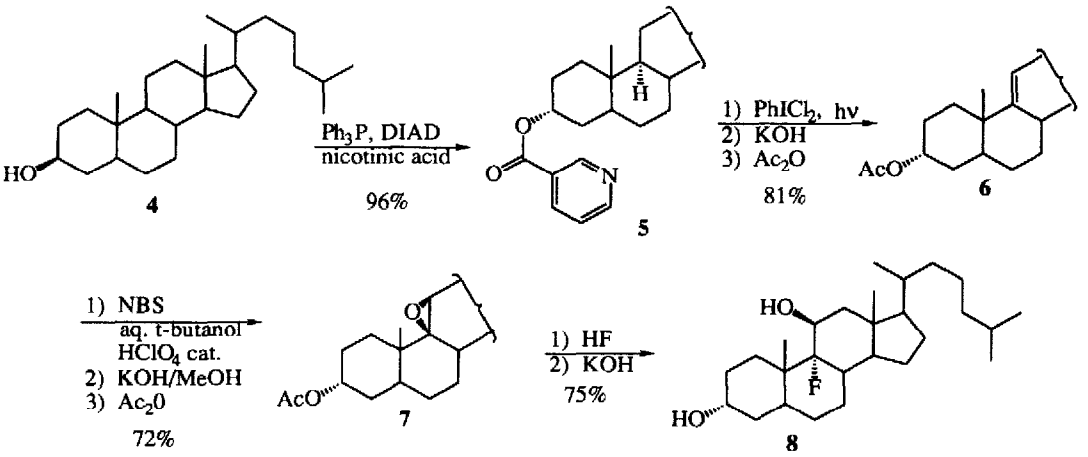
Abstract: 17-Chlorosteroids, produced by template-directed halogenation of 9-fluoro 11-oxygenated cholestanols that are themselves produced by template methods, are converted to their 17-keto analogs in high yields (85-91%) after HCl elimination with DBU, followed by ozonolysis.

The discovery of microbial degradations that convert abundant sterols to their 17-keto derivatives[1] by sidechain removal has spurred the invention of synthetic methods for the conversion of these keto groups to the corticosteroid side chains.[2] We had developed template-catalyzed and directed remote chlorination methods,[3] and used them for specific chlorination at C-17.[4] With most bases the resulting 17-chloro steroids (e.g. **1**) eliminate HCl to form the endocyclic 16 olefin **3**, which we converted by a multistep sequence to the dihydroxyacetone sidechain in a synthesis of cortisone.[4] However, Welzel reported that HCl elimination from a related 17-chlorosteroid using DBU as the base had a preference to form the exocyclic 17,20 olefin similar to **2**, and ozonolysis afforded the 17-keto steroid with a yield of 51%.[5] With **1** we saw that the DBU step demonstrated peculiar elimination patterns and at best gave only a 4:1 selectivity for the desired exocyclic **2** olefin over the endocyclic olefin **3**.[6] We have now found that the elimination is strongly promoted in the desired direction by the oxygen substituents at C-11 positions of the steroid that are required for anti-inflammatory activity, including cases with an additional fluorine substituent at C-9 that enhances medicinal potency.



1 **2** **3**

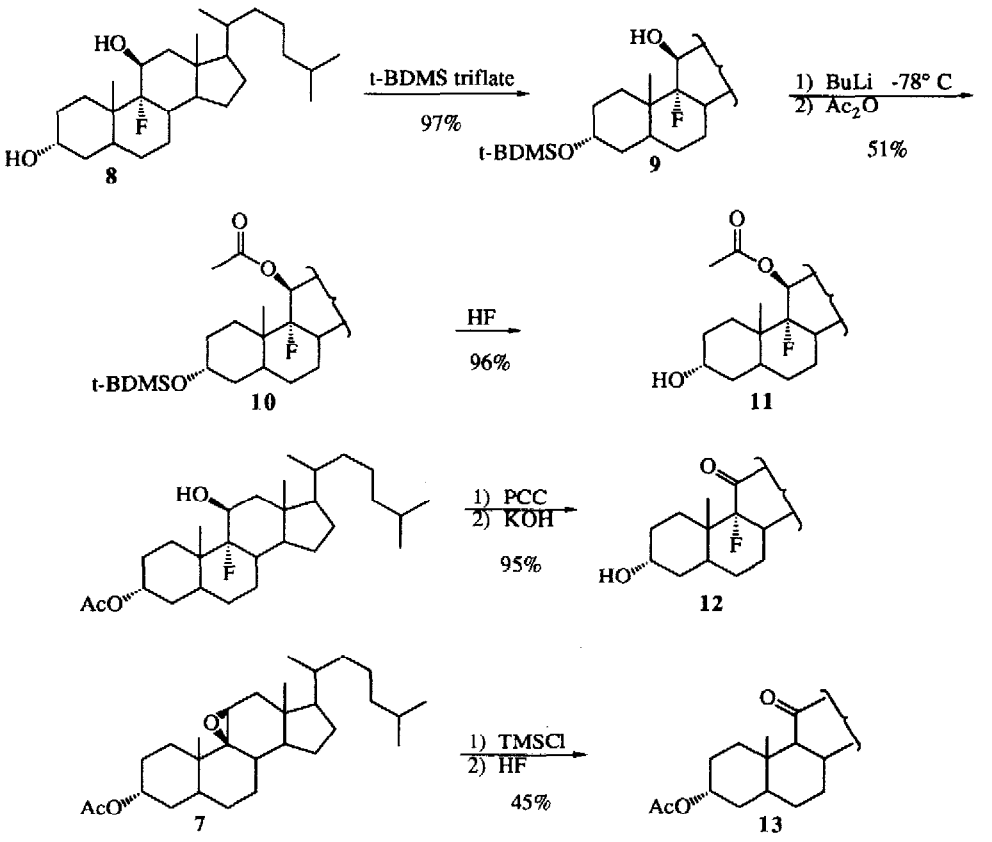
We have described a double-functionalizing template that directs two chlorinations to form 9,17-dichlorocholestanol,[7] but when this product was submitted to the DBU elimination conditions only the undesired endocyclic olefin was formed at C-17. The situation was quite different with 9-fluoro-11-oxygenated sterols. We synthesized 9α-fluoro-11β-hydroxy-3α-cholestanol using a simple template-directed 9-chlorination, as shown.



The 3α-cholestanol nicotinate **5** was made in excellent yield via a Mitsunobu inversion esterification process. Chlorination of **5** with $PhICl_2$ under our standard photolytic conditions[3], then concurrent elimination and saponification with 10% KOH in methanol/dioxane, followed by acetylation, afforded the 9(11) olefin **6**. The initial bromohydrin produced from olefin **6** decomposed to form the 11-keto steroid,[8] so the bromohydrin was not isolated but was closed immediately to β-epoxide **7** with methanolic KOH in overall yields of ca. 70%. Addition of HF to the epoxide[9] and hydrolysis of the acetate gave the fluorohydrin cholestanol **8.** Since the later DBU treatments caused the fluorohydrin to revert to epoxide, it was converted to the corresponding acetate **11** (the acetate group is easily removed later without fluoride loss by alkaline methanolysis at room temperature) and ketone **12**, as shown. We also prepared the non-fluorinated 11-keto compound **13** for our studies. The iodobiphenyl esters **14**, **15**, and **16** were formed quantitatively by reaction of the alcohols with the acid chloride in refluxing 10% pyridine/benzene with catalytic DMAP .

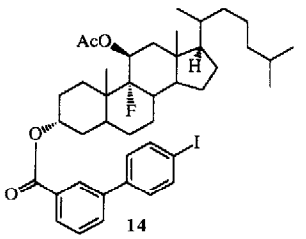
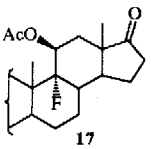
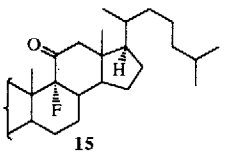
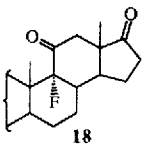
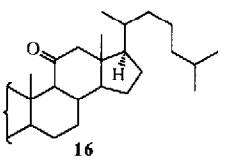
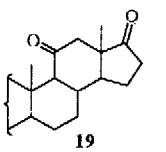
These new substrates were submitted to the degradation conditions: 1) chlorination in CH_2Cl_2 with 0.2 M t-butanol under photolysis conditions with 2.0 eq $PhICl_2$; 2) elimination of HCl with neat DBU; 3) ozonolysis of the crude product in CH_2Cl_2, followed by work-up with triphenylphosphine. The intermediate chloride and olefin were not isolated in these examples but carried on to the next step after crude purification by extraction. All products gave

satisfactory NMR, IR, and MS. The results are listed in the Table at the end of the paper.



In comparison to the unsubstituted cholestanol series, we find that in the new 11-oxygenated cases, particularly with 9α-fluoro-11β-acetoxy cholestanol template ester **14**, the product distribution in HCl elimination (exocyclic **2** vs. endocyclic **3**) is less dependent upon the base used.[5,6] However, DBU still gave a better olefin ratio than did Hünigs base, p-dimethylaminopyridine, imidazole, or 1,5,7-triazabicyclo[4.4.0]dodec-5-ene (TBD). C-13 NMR spectra of the crude olefins did show the presence of some Δ16 endocyclic olefins, and their ozonolysis products were detectable by mass spectroscopy, but always in very small quantities (1-3%). Thus the substituents in our most interesting compounds change the transition state for elimination, probably by a dipolar electron-withdrawing effect, to promote the direction that is most useful in the synthesis of corticosteroid derivatives.

Acknowledgment. This work has been supported by the NIH.

Substrate	Ketone	Isolated yield
 14	 17	85%
 15	 18	91%
 16	 19	86%

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