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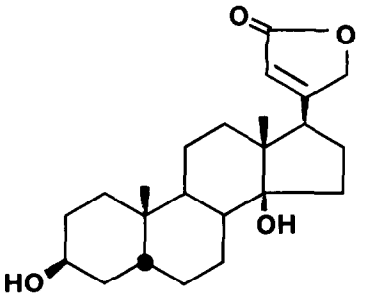
SYNTHESIS OF DIGITOXIGENIN BY REMOTE FUNCTIONALIZATION

Stephen F. Donovan, Mitchell A. Avery, and John E. McMurry*
Thimann Laboratories, University of California, Santa Cruz, California 95064

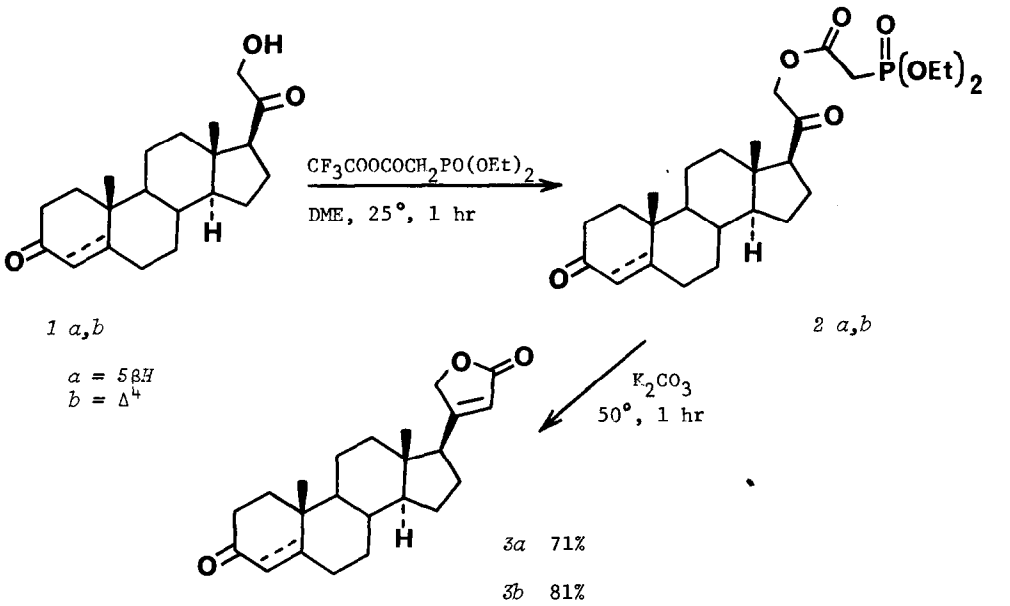
Abstract. Treatment of a 21-hydroxy-20-keto steroid with the mixed anhydride of trifluoroacetic acid—diethylphosphonoacetic acid leads directly to cardenolides by an intramolecular Horner-Emmons reaction. Photolysis of 3β-acetoxy-5β,14α-card-20(22)-enolide and iodobenzenedichloride in benzene solution then yields 3β-acetoxy-5β-carda-14,20(22)-dienolide (β-anhydrodigitoxigenin acetate).

The cardiac aglycones (cardenolides), exemplified by digitoxigenin, comprise a class of compounds of great medical utility. It is therefore not surprising that a considerable effort has gone into finding suitable synthetic routes to these compounds.[1] Two crucial aspects of cardiac aglycone synthesis are the construction of the butenolide side chain by mild methods and the introduction of the 14β hydroxyl. In this Letter, we describe some solutions to these problems.



Digitoxigenin

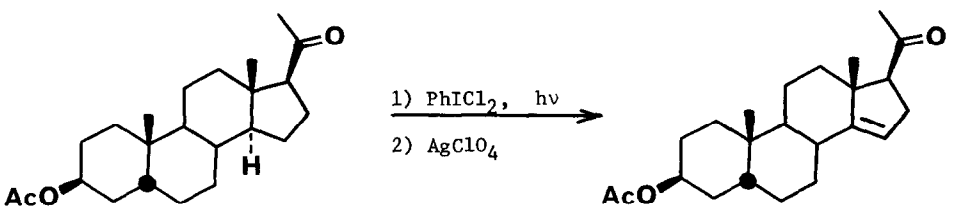
The last decade has seen a large amount of work aimed at butenolide synthesis, and numerous synthetic possibilities exist.[2,3] One particularly attractive idea is the intramolecular Wittig or Horner-Emmons reaction first reported by Lehman and Wiechert[4] in 1968. These authors, and others subsequently,[5] proceeded from an appropriate α-bromo or α-hydroxy ketone by a multi-step sequence involving esterification to a bromoacetate, Wittig reagent formation, and cyclization to product butenolide (51-67% yield for the cyclization step). We have simplified the scheme considerably by developing a mild and efficient one-flask synthesis of butenolides from α-hydroxy ketones. Treatment of a 21-hydroxy-20-keto steroid (*1*) with the mixed anhydride of trifluoroacetic acid and diethylphosphonoacetic acid yields directly the steroidal 21-diethylphosphonoacetate, *2*. This, without isolation, is cyclized by dilute carbonate at 50° to afford the cardenolide product *3* in good overall yield (Scheme I).



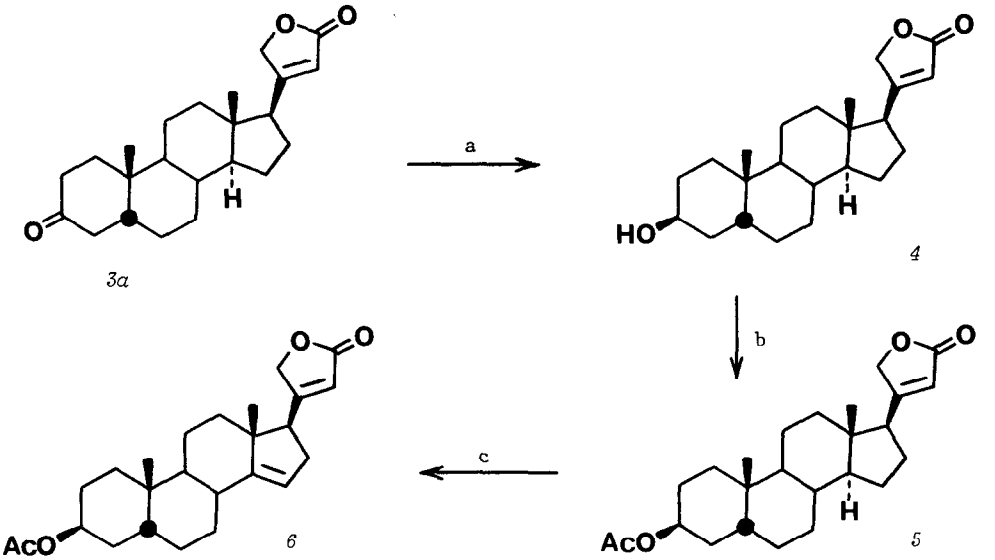
Scheme I

In a representative procedure, diethylphosphonoacetic acid was stirred for 30 min at room temperature with excess trifluoroacetic anhydride to generate the mixed anhydride. After removal of volatiles by rotary evaporation, a solution of 21-hydroxy-5β-pregnane-3,20-dione[6] (*1a*) in dimethoxyethane was added, and the reaction was stirred for 1 hr at room temperature. Although the intermediate phosphonoacetate *2a* could be isolated at this point if desired, it proved more convenient to proceed directly to butenolide. Thus, solid potassium carbonate and several ml *t*-butanol were added to the crude solution of *2a*, and the reaction was warmed to 50° for 1 hr. After aqueous workup and recrystallization, 3-oxo-5β,14α-card-20(22)-enolide (*3a*), mp 240-242° (lit.[7] 241°), was isolated in 71% yield. 3-Oxo-14α-carda-4,20(22)-dienolide (*3b*), mp 241-243° (lit.[7] 243-245°) was similarly prepared in 81% yield. With the butenolide side chain thus prepared, introduction of the 14β hydroxyl was our next goal.

Over the past few years, the Breslow group at Columbia has carried out an elegant series of researches concerned with remote functionalization of specific sites within the steroid nucleus.[8] One particularly interesting result was the recent report that photolysis of 3β-acetoxy-5β-pregnan-20-one and iodobenzene dichloride in benzene solution yields a chloride which, after treatment with silver perchlorate, gives the Δ^{14} olefin in 52% yield.[8,9]



Based on this precedent, we decided to examine the remote functionalization of 5β,14α cardenolides. Our sequence of reactions is shown in Scheme II.



3a 4 5 6

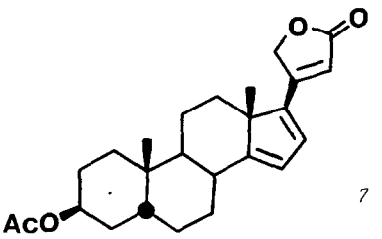
Scheme II

a) $Li(sec\text{-}Bu)_3BH$, THF, -78°, 98%; b) Ac_2O, pyridine, catalytic 4-dimethylaminopyridine, 91%; c) $PhICl_2$, PhH, hν, 55%.

3-Keto-5β-steroids such as *3a* are normally reduced to the 3β alcohols (axial) by the Henbest procedure[10] or, more recently, by catalytic hydrogenation over a rhodium catalyst.[11] We found, however, that *3a* underwent selective and stereospecific reduction in 98% yield on treatment with $Li(sec\text{-}Bu)_3BH$[12] to give 3β-hydroxy-5β,14α-card-20(22)enolide (*4*), mp 231-233° (lit.[13] mp 226-228°). The result of this reduction is not surprising but has not, to our knowledge, been reported previously. Acetylation of *4* using 4-dimethylaminopyridine as catalyst[14] proceeded normally to give *5*. Photolysis of a mixture of *5* and iodobenzene dichloride according to Breslow and Corcoran's procedure[8,9] took place exactly as desired to give β-anhydrodigitoxigenin acetate (*6*) in a crude yield of 76%. Chromatography on $AgNO_3$ impregnated preparative layer plates, followed by crystallization, gave the pure material which was identified by comparison with an authentic sample[15] (55%, mp 180-182°; lit.[16] mp 182-185°). Since *6* has previously been converted into digitoxigenin by a well established route,[1c] our work represents a synthesis of that material from a readily available steroid precursor.

Two points about the photolysis reaction deserve comment. The first is that the Δ^{14} olefin is produced *directly* in the reaction without need for a separate dehydrohalogenation step. NMR examination of the crude reaction mixture prior to workup verified this fact which is at variance with the results of Breslow and Corcoran. The second point worthy of comment is the fact that the butenolide ring survived the reaction and, more surprisingly, that the tertiary allylic C17 position was not oxidized to an appreciable extent. Careful examination of the mother liquors yielded only a small amount (10%) of a product which we believe on the basis of spectro-

scopic evidence to be the trienolide *7* (uv λ_{max} 338 nm; lit.[17] 337 nm; mass spectrum, M^+=396).



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