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CONCERNING THE REGIOSPECIFICITY AND STEREOSPECIFICITY OF STEROID FUNCTIONALIZATION BY PHOTOLYSIS OF ATTACHED BENZOPHENONE ESTERS

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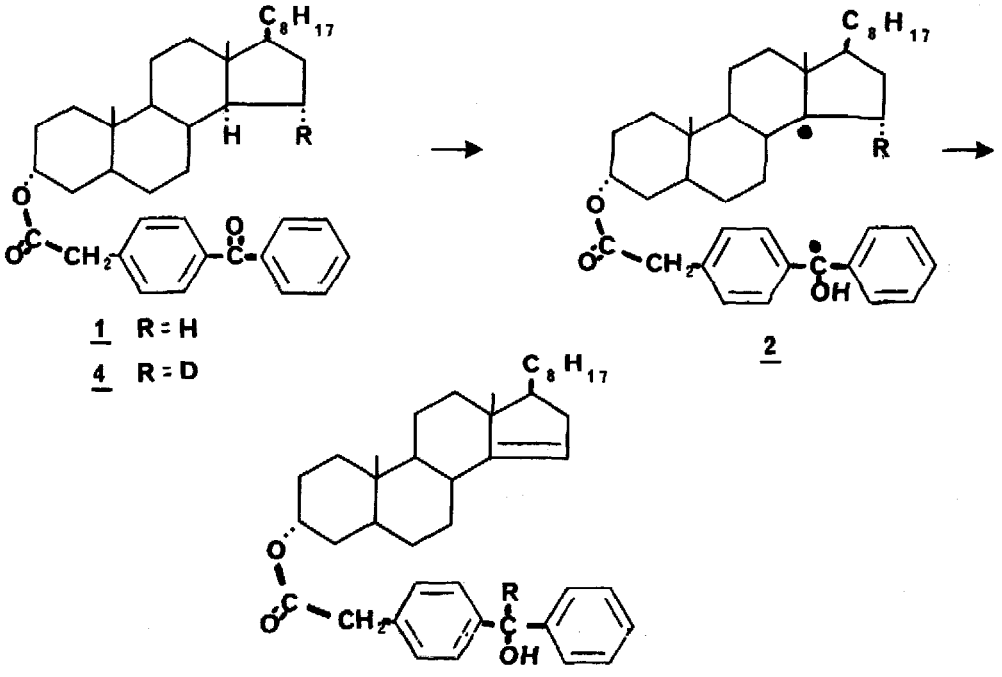
We have described the remote functionalization of steroids by photolysis of attached benzophenone groups.[1] The point of intramolecular attack is controlled by the geometry of the substrate; thus, for example, the benzophenoneacetic acid ester (1) directs photochemical dehydrogenation exclusively into ring D, affording the Δ14 olefin (3) in 55% yield.[1] We proposed that in this instance the oxygen of the excited benzophenone abstracts the axial hydrogen on carbon 14, and that the resulting diradical (2) then transfers the α-hydrogen from C-15 to the benzhydryl radical to complete the process. However, in the benzophenone carbonyl the oxygen is the distal atom; it was not obvious that it removes the proximal C-14 hydrogen and not the distal C-15 hydrogen. Although models suggested that the carbonyl oxygen could easily reach the C-14 hydrogen, the subsequent hydrogen transfer is strained in the original conformation and might well require configurational inversion of the C-14 radical, or at least substantial flattening in the transition state. We now report experiments which support our proposal and define the degree of stereoselectivity in the subsequent reactions of the intermediate diradicals.

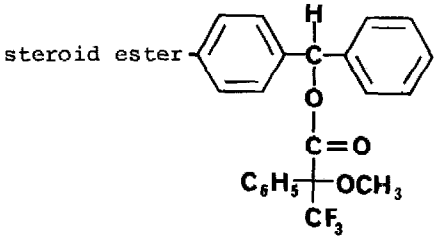
Treatment of Δ14-cholestenyl-3α-acetate with diborane, hydrolytic cleavage of the alkylborane intermediate with d_1-propionic acid in D_2O[2] and base hydrolysis afforded 3α-cholestanol with 83% incorporation of deuterium at C-15 (mass spectrum).[3] Esterification and subsequent photolysis of the deuterated benzophenoneacetic acid ester (4) in benzene in the manner previously described[1] was followed by isolation of the pure benzhydryl ester (5) by short column chromatography.[5] Base hydrolysis of (5) afforded the C-deuterated



benzhydrol acid in which the deuterium incorporation was found to be 78% (mass spectrum). The essentially complete transfer of deuterium from C-15 to the benzhydryl carbon in (5) confirms our suggested mechanism.[1]

The hydrogen transfer to form 3, with a new asymmetric center, might also be stereoselective if the transition state from 2 had a preferred conformation. Although the benzylic epimers of 3 are diastereomers, the interaction between the chiral steroid and this new asymmetric center is too weak to permit direct nmr analysis. Thus the benzylic epimeric mixture was analyzed from the relative intensities of the ^{19}F signals in the MTPA-esters (6) prepared[6] from 3. Photolysis of 1 in benzene afforded a 55/45 mixture of 3 epimers, which reversed to 47/53 when the photolysis was performed in t-butyl alcohol, and 45/55 in CH_3CN. The transition states for hydrogen transfer in 2 have either the phenyl group or the hydroxyl under ring D of the steroid. Thus the reversal in preference on changing from non-polar to polar solvents is reasonable, but the

overall effect is small. Similar small asymmetric inductions were observed on photolysis of 7, but 8 affords a mixture of Δ14 olefin and Δ16 isomers in which the epimeric benzhydrols are a 30/70 mixture. However, since 8 forms two olefinic products, a direct comparison is not possible. Our circular dichroism studies[1] indicated that the benzophenone in 8 was more extensively packed under the steroid than in 1, so it is expected that 8 exhibits a greater preference for one mode of packing during hydrogen transfer.



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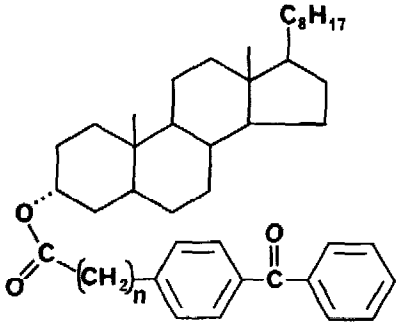
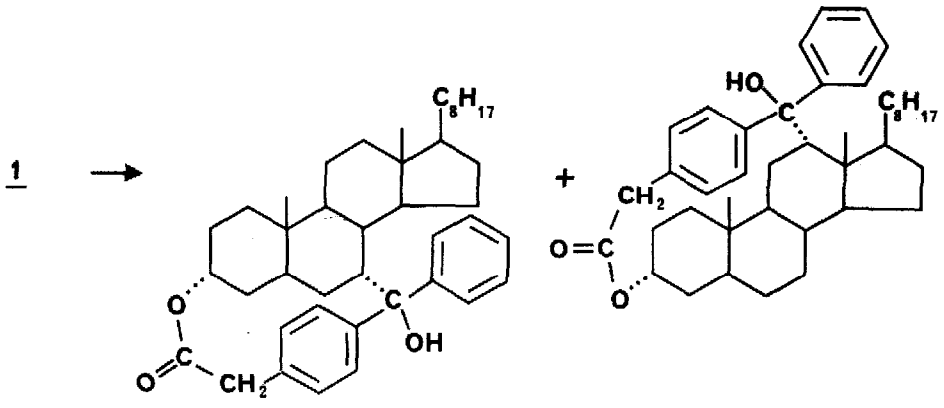


7 n = 2

8 n = 4

More stereochemical control is found in the other photoproducts derived from 1. Thus we obtain a single diastereoisomeric lactone[7] from insertion of the benzophenone into the C-7 α-H bond (17% yield), so this diradical coupling is stereospecific. By contrast, in the more flexible 7 insertion at C-7 produces both[7] diastereomers (22% and 23% yield) which are easily separated chromatographically and very different in the nmr. A single lactone[7] is also formed from 1 by insertion into C-12 (4% yield), while again 7 affords two such lactones[7] (9% and 10% yield). The other products from photolysis of 1 are the reductive pinacol dimer of 1 bearing an unchanged steroid ring (16%), the dimeric ether of 3 (4.5%), and a small amount (3.5%) of the benzophenone from oxidation of 3. Thus in contrast to our previous report[1] on the photolysis of 1, 21% of the product does arise from attack at positions other than C-14. Models show that these other positions, C-12 and C-7, are within reach of the ketone oxygen of 1.



each one formed as a single benzhydryl epimer

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3. We assign the deuterium an α configuration by analogy with other alkylborane functionalizations at C-15.[4]

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7. The lactone was identified by degradation[1] to the 7-ketosteroid or 12-ketosteroid.