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DOUBLE FUNCTIONALIZATION OF CHOLESTANOL DIRECTED BY SELECTIVE BIFUNCTIONAL TEMPLATES

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Abstract: 3-α-Cholestanyl esters of bipyridine acids and of iodophenylpyridine acids can direct radical chlorination to both C-9 and C-17 of the steroid, with high efficiency. The reaction is quite sensitive to reaction conditions and precise geometry.

We have described the Radical Relay chlorination of substrates, directed by covalently attached catalytic templates.[1,2] The templates temporarily bind a chlorine atom and deliver it to specific hydrogen atoms of the substrate, with geometric control. Templates so far described include iodoaryl compounds,[2,3] thioethers of various types,[2,4] pyridine rings,[2,5] and pyridine N-oxides.[2,6] We also find that an imidazole ring can act as an effective template; an example is shown in Scheme 1, which illustrates the Radical Relay process. The substrates examined have chiefly been steroids, but functionalizations (with lesser selectivity) of flexible chains have also been observed.[7]

With appropriate templates the chlorination is directed to C-9 (cf. Scheme 1), and dehydrochlorination then furnishes the 9,11 olefin that is useful in the preparation of corticosteroids. With other templates yet other positions can be selectively functionalized,[2] including in particular C-17.[8] The resulting 17-chlorosteroid can be used in various schemes for the removal of the cholesterol or sitosterol sidechain.[8,9]

In the practical synthesis of corticosteroids functionalization at both C-9 and C-17 would be useful. Indeed, current fermentation methods for the degradation of sitosterol can produce compounds hydroxylated at both C-9 and at the sidechain. Thus we have examined the possibility of achieving a similar conversion with bifunctional templates covalently attached at C-3α, but designed to deliver chlorine atoms to both C-9 and C-17. With careful geometric control this proves to be possible.

An ester of bipyridinecarboxylic acid **1** has been prepared previously[10] by the Pd catalyzed coupling of 5-bromonicotinic acid methyl ester with pyridine-4-boronic acid, but we find that pyridine-4-trimethylstannane is superior. Acylation of 3α-cholestanol with the acid chloride of **1** afforded **2,** m.p. 161-162°, in 75% yield. Chlorination of **2** with $PhICl_2$ under our standard conditions[3] caused precipitation of hydrochlorides, but $PhI(OAc)_2$ proved to be an excellent HCl scavenger, converting the HCl back to $PhICl_2$. With 3 equiv. of $PhICl_2$ and 3 equiv. $PhI(OAc)_2$ in CH_2Cl_2, photoinitiated (275 W sunlamp) chlorination of 10 mM **2** for 30 min. afforded the 9,17 dichlorosteroid **3** in quantitative yield, as judged by tlc and ^{1}H-NMR. Compound **3** showed the C-18 methyl signal at δ 0.826 in the ^{1}H-NMR. Dehydrochlorination and saponification of **3** with 10% KOH in methanol/dioxane, then acetylation, afforded the diene acetate **4** as the only steroidal product. In the NMR **4** showed the expected vinyl peaks at δ 5.29 (H-16) and 5.34 (H-11); the C-18 peak was shifted to δ 0.686, as expected for the NMR effects of the two double bonds.

C-9 is chlorinated first. With 1.2 equiv. of $PhICl_2$ we obtained only **5** in 90% yield, with no evidence of C-17 chlorination or of double chlorination. The product was identified by conversion to the well known[3] 9,11 olefin. Apparently the C-9 chlorine does not prevent the template from packing under the steroid to deliver chlorine to the C-17 hydrogen; indeed it seems to help. We prepared the mixed iodophenyl nicotinate template ester **6** of 3α-cholestanol, m.p. 128-130°, which is related to the ester **7** that we first used[8] for the selective chlorination at C-17. The template in **6** was prepared by Pd coupling of 4-nitrophenyltributylstannane with the 5-bromonicotinic acid methyl ester, followed by standard transformations. Again with an excess of $PhICl_2$ **6** underwent quantitative chlorination at both C-9 and C-17; with only 1.2 equiv. of $PhICl_2$ we again observed selective chlorination at C-9, so this is chlorinated first. With the 3 equiv. of $PhICl_2$ that converts **6** quantitatively to the doubly chlorinated **8,** compound **7** is chlorinated (at C-17) to the extent of only 32%. The pyridine ring of monochlorinated **2** and **6** may interact with the C-9 carbon-chlorine dipole to promote a packed conformation that permits C-17 functionalization.

Geometry is quite important in these reactions. An analog of **6** with the iodine meta instead of para produces the same steroid dichloride, but even with 3 equiv. of $PhICl_2$ it is mixed with a lot of C-9 monochlorinated product, so the meta iodine is less effective. Compounds in which the benzene ring of **7** is replaced with a thiophene ring perform no chlorinations under these conditions, while replacement of the nicotinate pyridine ring of **2** with a thiophene ring leads to compounds that perform only limited C-17 chlorination. However, with the optimum geometries of **2** and **6** the quantitative double chlorinations of the cholestanol nucleus that we have achieved open promising pathways for the preparation of useful steroid derivatives.

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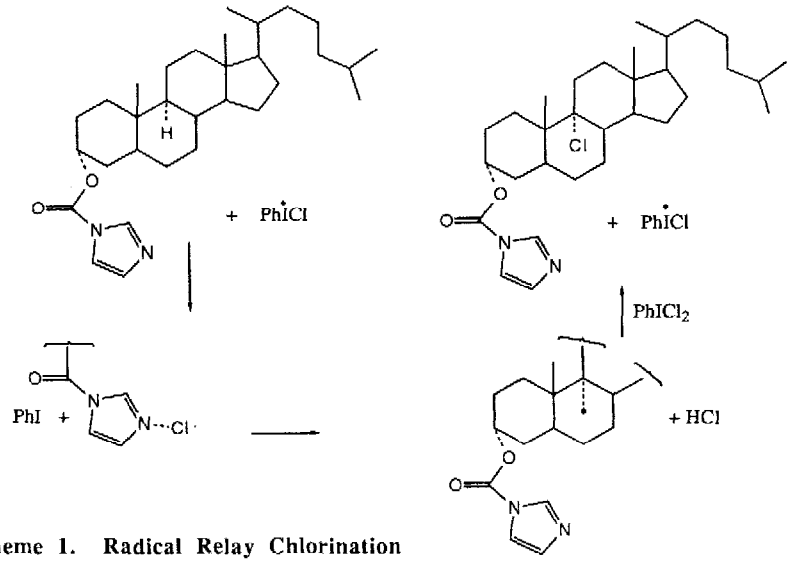
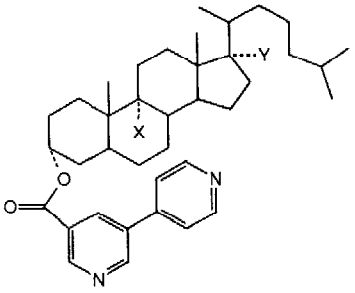


Scheme 1. Radical Relay Chlorination



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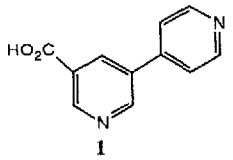
3: X = Y = Cl
5: X = Cl, Y = H



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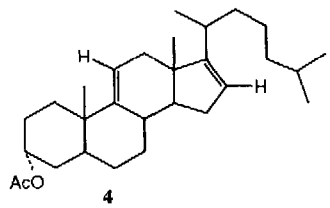

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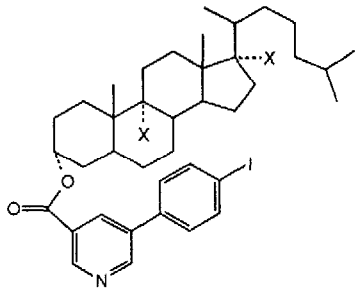
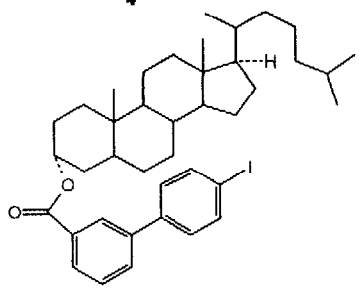


6: X = H
8: X = Cl



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