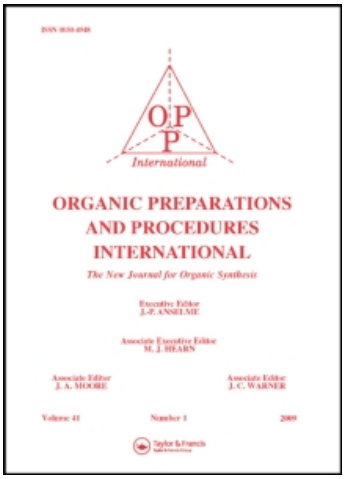

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FUNCTIONALIZATION OF THE 18-METHYL GROUP OF STEROIDS. A REVIEW

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FUNCTIONALIZATION OF THE 18-METHYL GROUP OF STEROIDS. A REVIEW

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INTRODUCTION

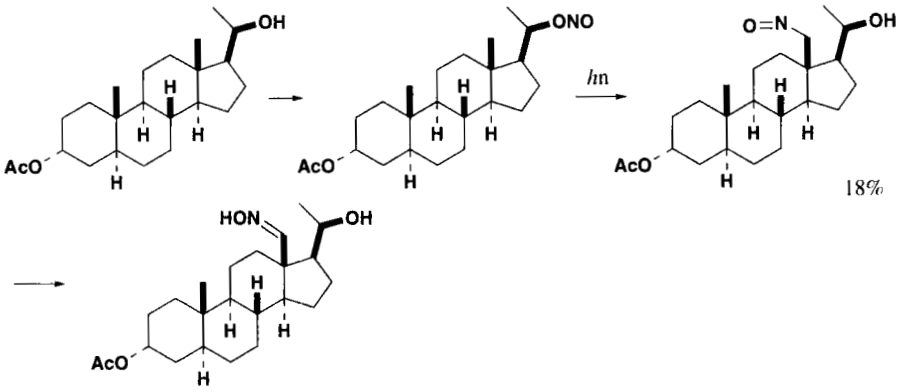
The selective introduction of a functional group in place of hydrogen atom at a carbon atom not directly joined to labilizing centers poses an interesting challenge in synthetic chemistry, a challenge which is magnified by the rife occurrence of such transformations in Nature under the influence of enzymes.[1] In the field of steroids the problem assumes a special urgency with regard to the C-18 angular methyl group because functionality at this position is a special feature of the important hormone, aldosterone, and of naturally occurring steroid alkaloids such as holarrhimine and conessine.[2] The literature discloses few methods which allow the direct functionalization of the 18-methyl group of steroids.[3] Among these are the Barton, the hypoiodite and the Hofmann-Löffler-Freytag reactions which will be discussed in this review along with several others

Functionalization of C-18 on the steroid nucleus has been largely achieved by intramolecular free radical reactions initiated by free radical formation at the 11-hydroxy or 20-hydroxy groups.[4] Photochemical attack of the 18-methyl group of steroids was first reported by Barton and co-workers, who synthesized 18-substituted steroids by a photochemical degradation of 11β- and 20-nitrite esters. Later, much work on the photochemical attack of angular methyl groups has been carried out by Heusler, Kalvoda and co-workers, who subjected secondary and tertiary steroid alcohols (including 20-cyanohydrins) to irradiation in the presence of lead tetraacetate and iodine to form 18-substituted steroids. These reactions are called hypoiodite reactions and constitute the most versatile methods for intramolecular substitution of non-activated centers.[5]

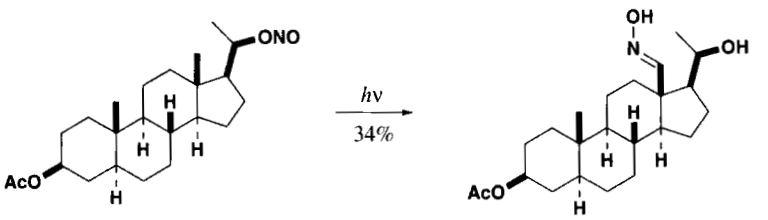
The third method to introduce a functionalization at the 18-angular methyl group of a steroid bearing a functional group located at C-20 is the Hofmann-Löffler-Freytag reaction.[6] Further methods have also been described such as microbiological hydroxylation, intramolecular photorearrangement of 17-nitrosteroids, photolysis of α-peracetoxynitriles or electrolysis.

I. THE BARTON REACTION

The new photochemical reaction described by Barton in 1960 allowed for the first time the direct functionalization of the C-18 angular methyl group.[7] These results have proven that the photolysis of suitably constituted organic nitrites triggered an intramolecular exchange of the NO of the nitrite residue with a hydrogen atom attached to a carbon atom in the δ-position. The C-nitroso compound thus formed, then isomerized into the corresponding oxime.[8]

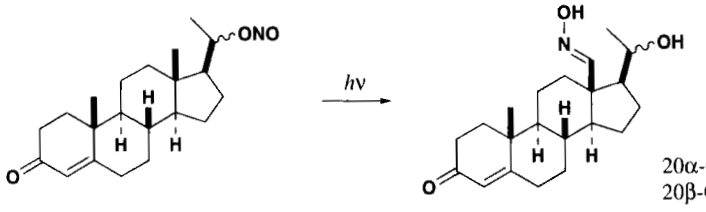


(1)



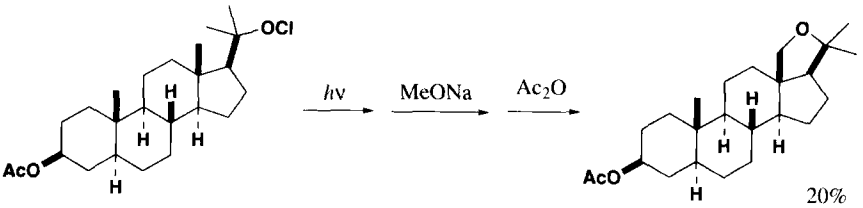
(2)

It was disclosed that the photolysis of a 20α-nitrite gave a much higher yield of the corresponding 18-oxime than did a 20β-nitrite.[9]



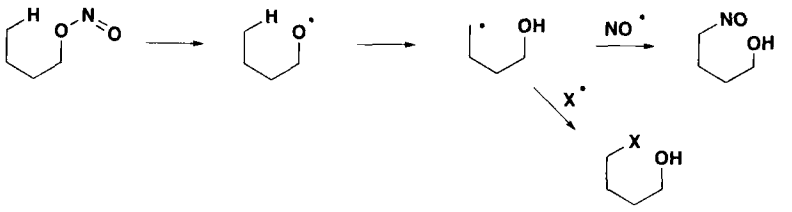
(3)

In the same way, Barton reported the photochemical rearrangement of hypochlorites which led after base treatment to corresponding ethers.[10]



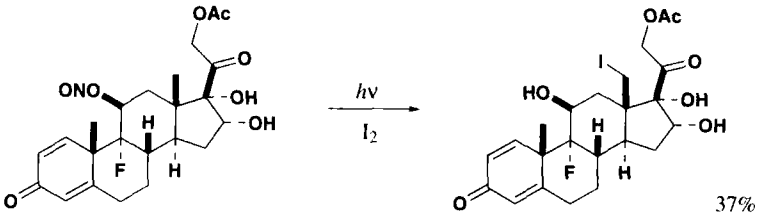
(4)

The mechanism of the Barton reaction has been clearly elucidated.[11]



(5)

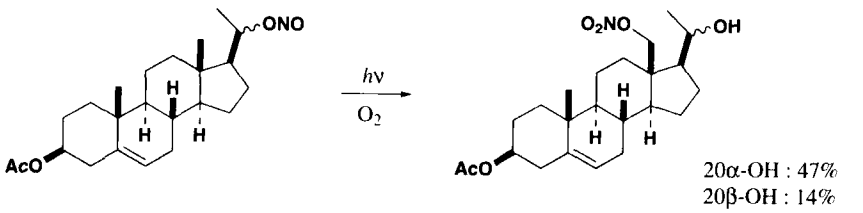
It was considered that competition for the resulting carbon radical between the nitric oxide and an alternative added radical source (X•) might be possible. Thus, photolysis of dexamethasone 21-acetate 11-nitrite in presence of iodine gave the expected 18-iododexamethasone 21-acetate in 37%



(6)

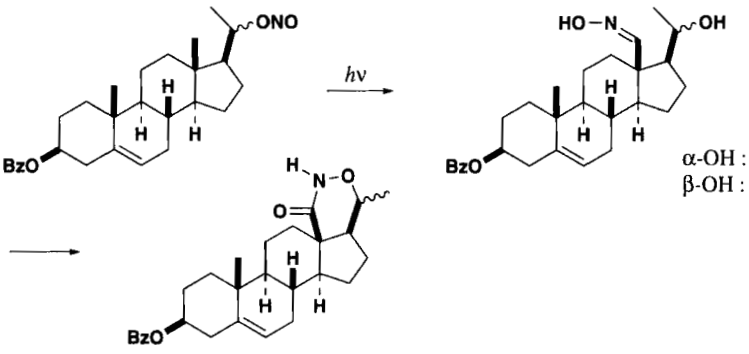
yield.[12] Moreover, bromine has been successfully introduced into the C-18 position of steroids.[13]

In 1975, Barton and his group described convenient syntheses of 11-deoxy-18-hydroxycorticosterone and 18-hydroxycorticosterone of which the key step was the obtaining of 18-nitrates by nitrites photolysis in the presence of dioxygen.[14] It was observed that some pregnane derivatives substituted by oxygen in position 18 possessed antimineralocorticoid activity.[15]



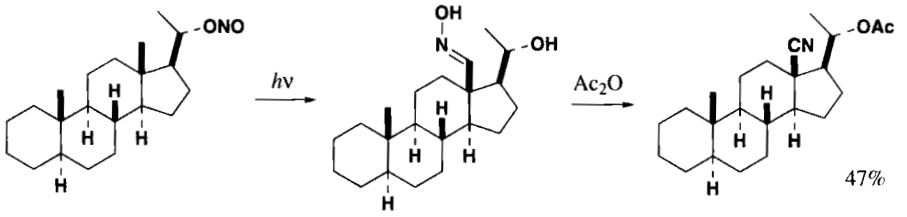
(7)

In order to study the influence of the nature of the functional group in position 18 on the biological activity, Hora[16] has prepared steroidal tetrahydro-1,2-oxazine-3-one derivatives starting from pregnenolone. In this way, he applied the Barton reaction to 3β-benzoyloxypregn-5-en-20-ol nitrites.



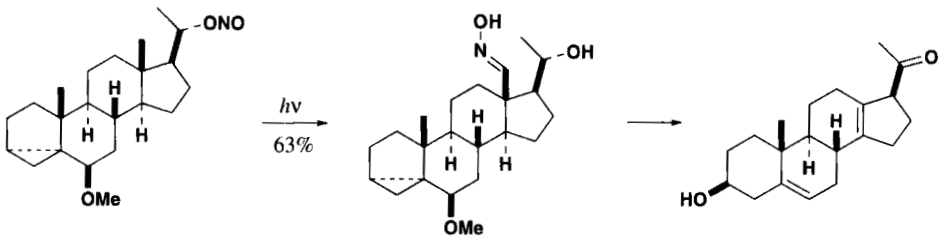
(8)

Various 18-nitriles androstane derivatives have been prepared by Wolff and Lee[17] by application of the Barton reaction.



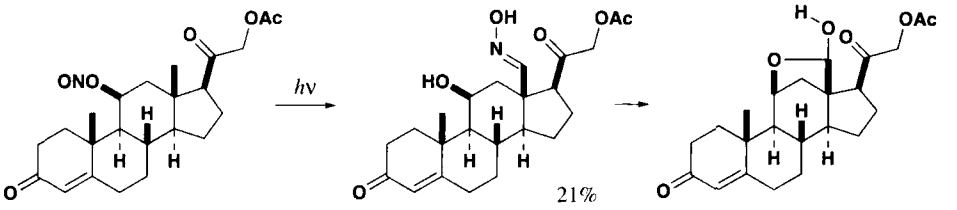
(9)

More recently, Suginome has prepared 18-norsteroids such as deoxofukujusonorone by photolysis of steroidal 20α-ol nitrites followed by deoximation.[18]



(10)

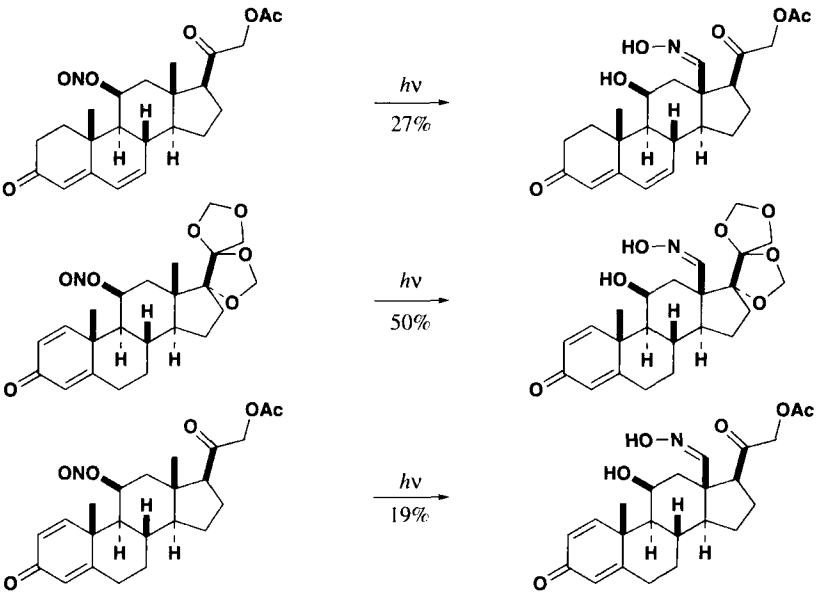
Efficient intramolecular hydrogen abstraction by an alkoxy radical normally requires a six-membered transition state in which the alkoxyl radical and the carbon atom bearing the hydrogen to be abstracted can approach to within 2.5-2.7 Å of each other. Thus, a second possibility to functionalize the C-18 angular methyl group by the Barton reaction involves a 11β-nitrite derivative. For



(11)

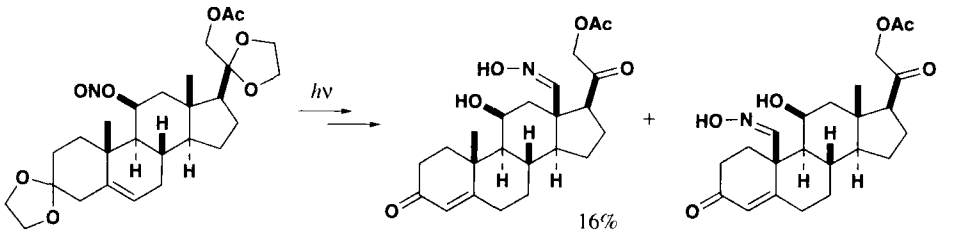
instance, a synthesis of aldosterone acetate described by Barton involves the photolysis of the 11β-nitrite of corticosterone acetate.[19]

Various substituted aldosterones have been obtained by the same procedure. In each case the angular 18-aldehyde grouping has been inserted by nitrite photolysis.[20]



(12)

In the case of 11β-nitrite steroids, the functionalization of the angular methyl group is frequently complicated by bifunctional attack at the C-18 or C-19 position. Thus, the photolysis of the 11β-nitrite of corticosterone 3,20-bis(ethyleneketal) led to the expected 18-oxime in 16% yield along with corresponding 19-oxime.[21]

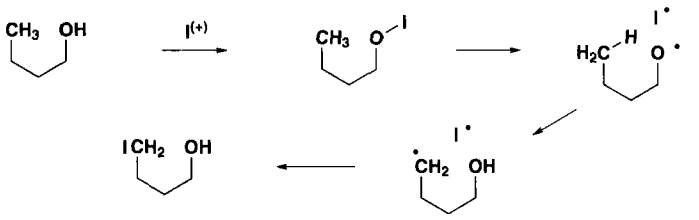


(13)

II. THE HYPOIODITE REACTION

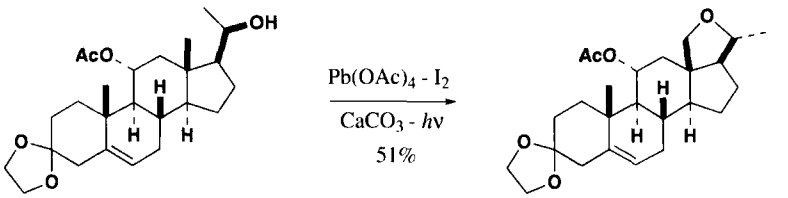
Alkoxy radicals can also be generated by reaction of alcohols with a variety of oxidizing reagents such as N-iodosuccinimide, mercuric oxide and acetates of Pb(IV), Hg(II), and Ag(I), usually in presence of iodine. Hitherto, the lead tetraacetate-iodine procedure has been the most frequently used and appears to give the best yields. The advantages of this method are easy handling of the reagents, compared with the nitrite method, and, in the case of 11β-hydroxy compounds, preferential attack at the 18-methyl group without concomitant functionalization at the 19-methyl group.

The general mechanism of the hypoiodite reaction can be summarized by the following scheme.[3]



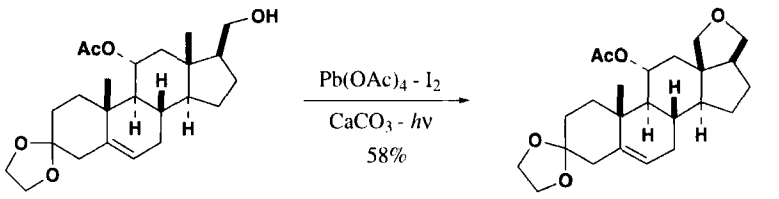
(14)

In 1961, the hypoiodite reaction first reported by Jeger[22] was used by Wettstein and his coworkers for a partial synthesis of aldosterone.[23]



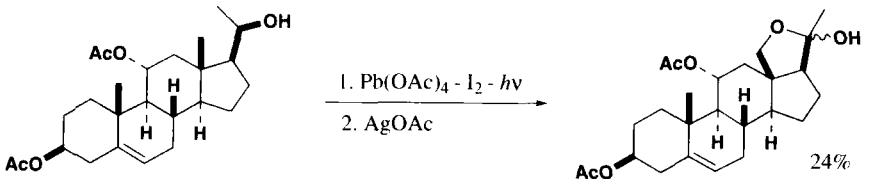
(15)

The influence of the environment of the hydroxyl group on the course of the oxidation of 20-hydroxy-steroids has been investigated by Jeger and his group.[24]



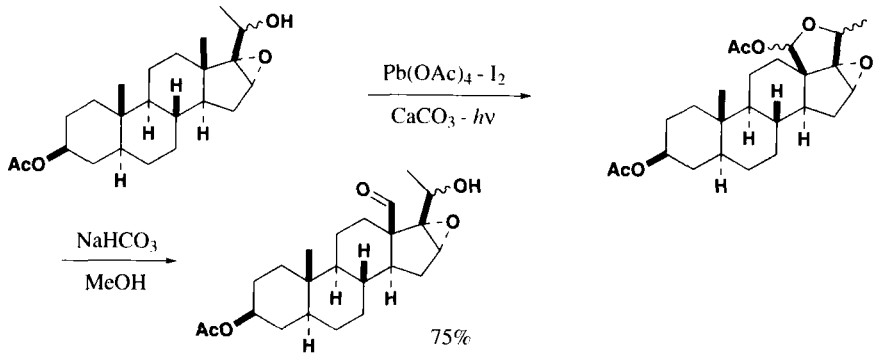
(16)

The same method was found to be the most suitable for the preparation of 3β-hydroxy-18-nor-13α-androst-5-en-17-one.[25]



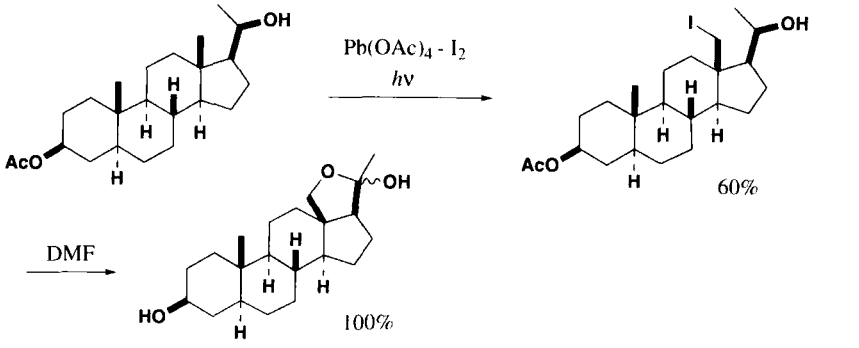
(17)

In 1973, Jeger and coworkers reported an original hypoiodite reaction of a 16α,17α-oxido-5α-pregnane which after treatment with base led to an unusual 18-oxo-derivative.[26]



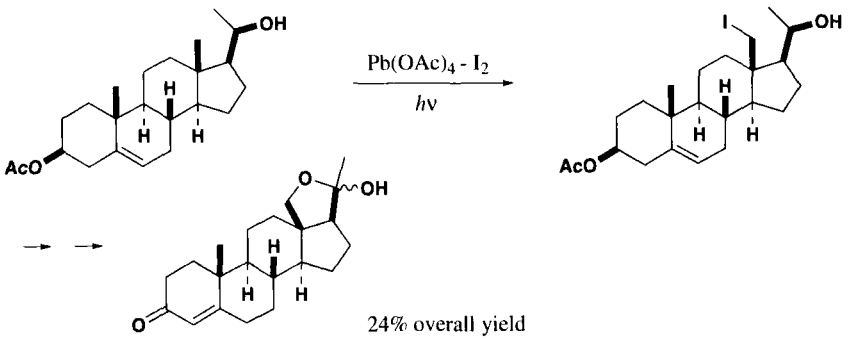
(18)

The intermediate 18-iodo-derivatives of the hypoiodite reaction were first isolated by Choay and coworkers[27] in the course of their synthesis of holantogenine.



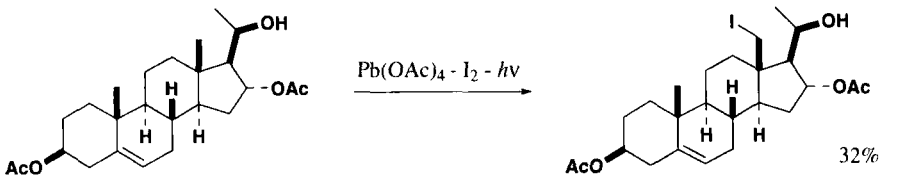
(19)

In 1975, Kirk and his group proposed improvements in the preparation of 18-hydroxydeoxy-corticosterone, an important hypertensive agent, based on the hypoiodite photolysis procedure.[28]



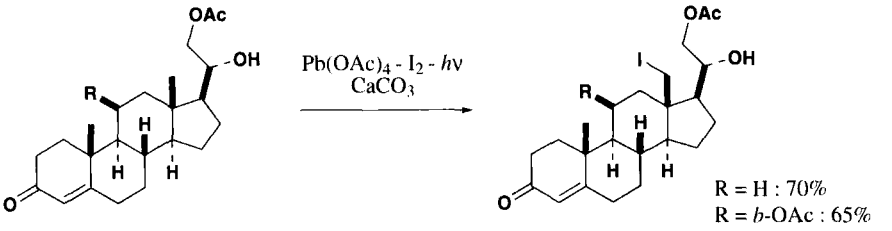
(20)

They applied the same strategy to prepare both 18-hydroxycorticosterone[29] and 16α,18-dihydroxy-11-deoxycorticosterone as depicted below.[30]



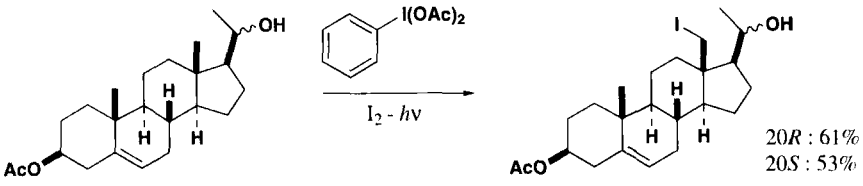
(21)

The synthesis of 18-hydroxycorticosterone has been reinvestigated very recently by Galons who has applied the hypoiodite reaction to 20-hydroxysteroids protected as acetates at position 21.[31]



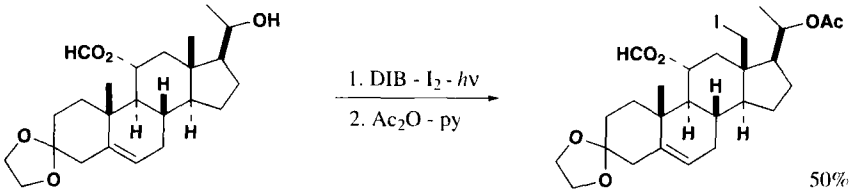
(22)

Suarez and coworkers introduced the use of the hypervalent iodine compound diacetoxyiodobenzene (DIB) in place of lead tetraacetate.[32] In practice, the reaction proceeds smoothly under mild conditions and the yields are usually better than those obtained with the heavy-metal derivative systems.[33]



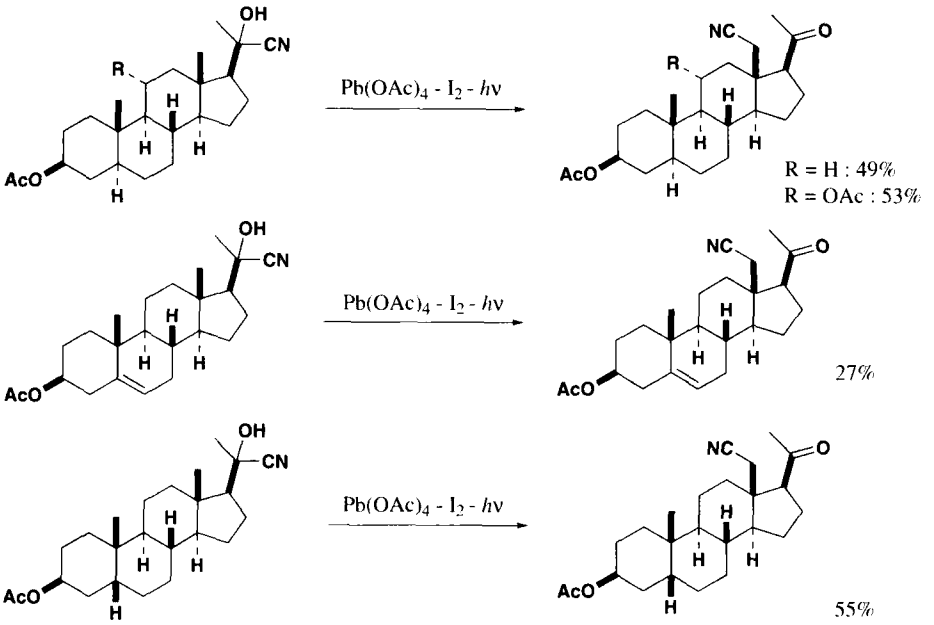
(23)

Moreover, the presence of $Pb(OAc)_4$ in either the Barton or the hypoiodite reaction limits the functional groups that may be present in the precursor molecule. Thus, iodination of the 18-methyl group of a steroid bearing a formate could be obtained in the presence of DIB.[34]



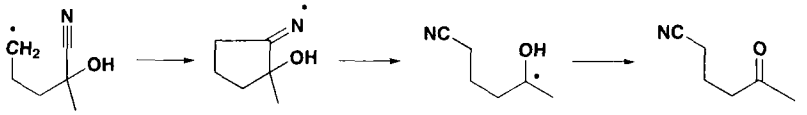
(24)

In 1966, Kalvoda showed that treatment of steroid 20-cyanohydrins under conditions of the hypoiodite reaction generated 18-cyano-20-oxo compounds by a 1,4-migration of the cyano group.[35]



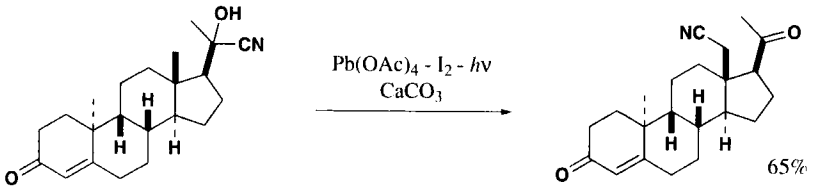
(25)

Cross experiments using ^{14}C-labelled compounds demonstrated the formulation of a reaction mechanism involving an internal addition of a carbon radical centre to the triple bond of a cyano group.[36]



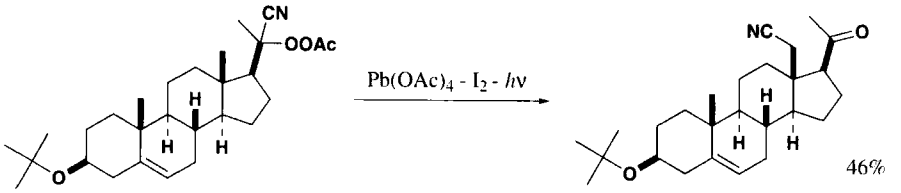
(26)

In order to prepare progestational agents, van Moorselaar and Halkes converted the 20-cyanohydrin of 9β,10α-progesterone into 18-cyano-9β,10α-progesterone by the hypoiodite reaction.[37]



(27)

In 1977, Watt proposed a new photochemical reaction which involves 20-peracetoxy-20-cyanosteroids, and compared this synthetic approach to 18-cyano-20-ketosteroids to the cyanohydrin-ketonitrile reaction developed by Kalvoda.[38] This latter reaction was improved by Neef in 1980[39] since the yield was increased to 80% in presence of $CuCl_2$ in pyridine at reflux.



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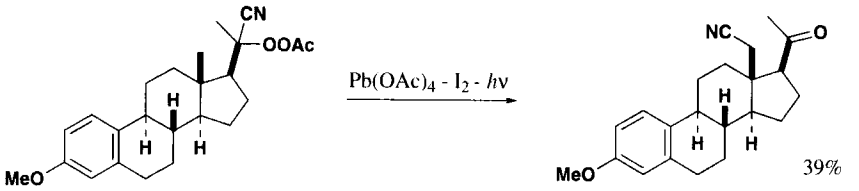
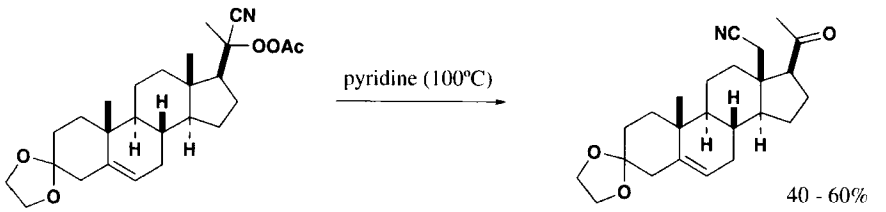


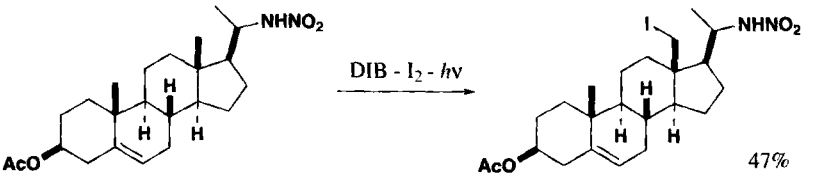
(29)

The same methodology was applied to the synthesis of 11β-hydroxy-18-ethynylprogesterone which is an inhibitor of aldosterone biosynthesis. The expected C-18 nitrile was obtained by thermolysis of the corresponding C-20 cyanohydrin peracetate.[40]



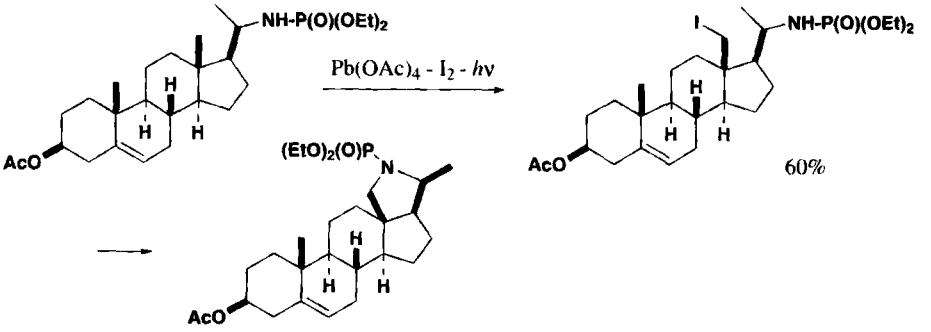
(30)

In 1980, Suarez showed that intramolecular functionalization of C-18 steroidal methyl group was also possible from suitably located N-nitramines.[41]



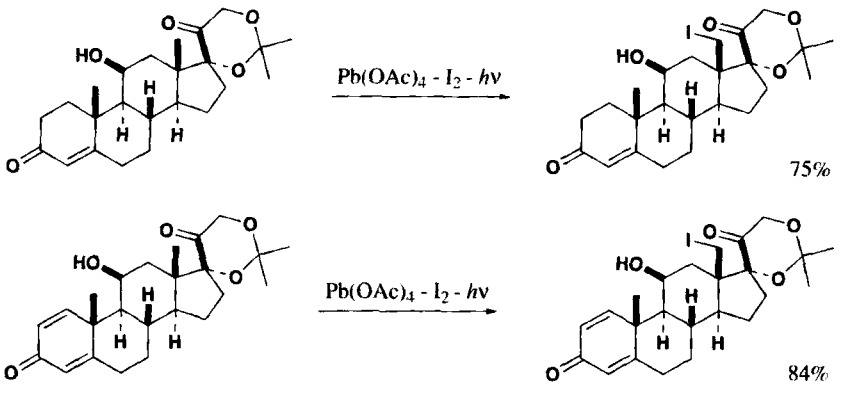
(31)

A 20(*S*)-phosphoramidate has been converted into the corresponding iodide in the presence of $Pb(OAc)_4$ and iodine[42] which provided an effective synthetic method for pyrrolidines.



(32)

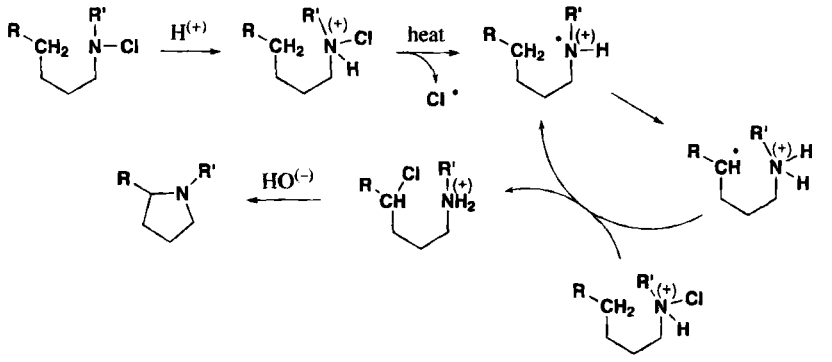
Similarly to the Barton reaction, it is possible to obtain 18-functionalized steroids by subjecting 11β-hydroxy steroids to the hypoiodite reaction. In this case, the reaction is frequently complicated by bifunctional attack at the C-18 or C-19 position to form 11,18- and/or 11,19-ether linkages.[43] Hydrogen abstraction by hypohalite reaction in saturated steroids with the 11β-hydroxyl group occurs almost exclusively at position C-19, whereas that in ring A unsaturated steroid favorably takes place at position C-18.[44]



(33)

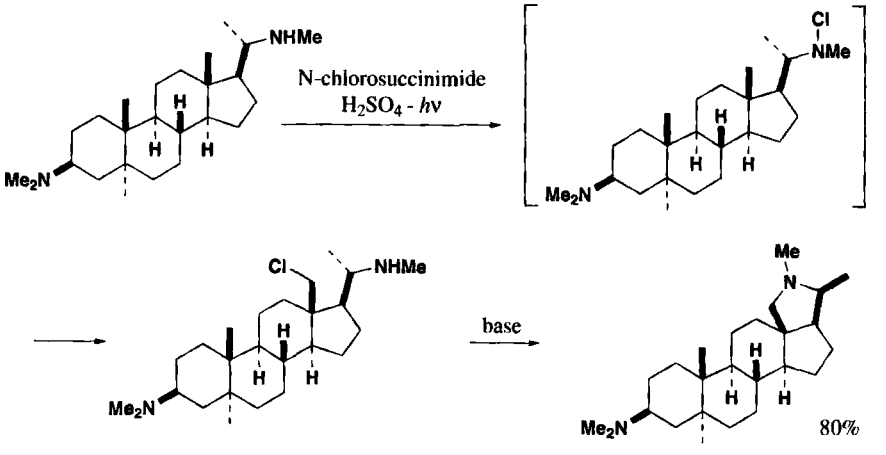
III. THE HOFMANN-LÖFFLER-FREYTAG REACTION

The general definition of the Hofmann-Löffler-Freytag reaction is the conversion of suitable N-halogenated amine derivative to a heterocyclic product in which the nitrogen function is incorporated into the newly created pyrrolidine or piperidine ring.[5]



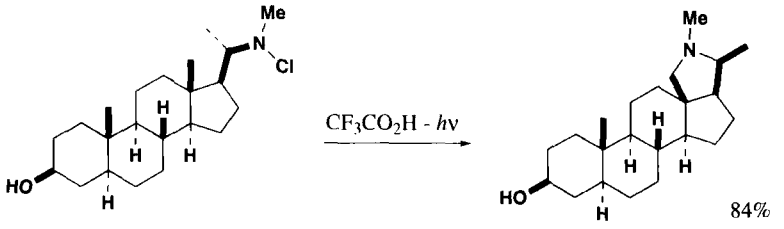
(34)

In 1958, Kalvoda and Jeger developed a new way of functionalizing the C-18 methyl group of steroids by the Hofmann-Löffler-Freytag reaction.[45] At the same time, Corey[46] described the free radical chain decomposition of an N-chloro-20-aminosteroid in acid solution and its application for the synthesis of dihydroconessine.



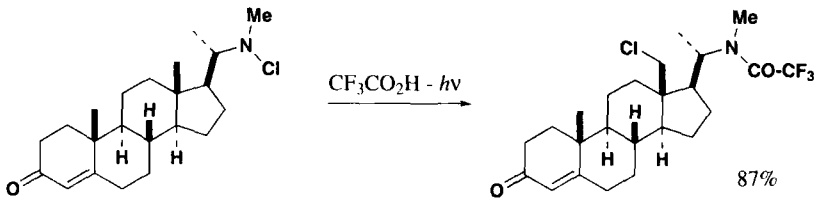
(35)

A number of 20-methylamino steroids have been prepared *via* reductive amination of the corresponding 20-keto steroids by Wolff and Georgian.[47]



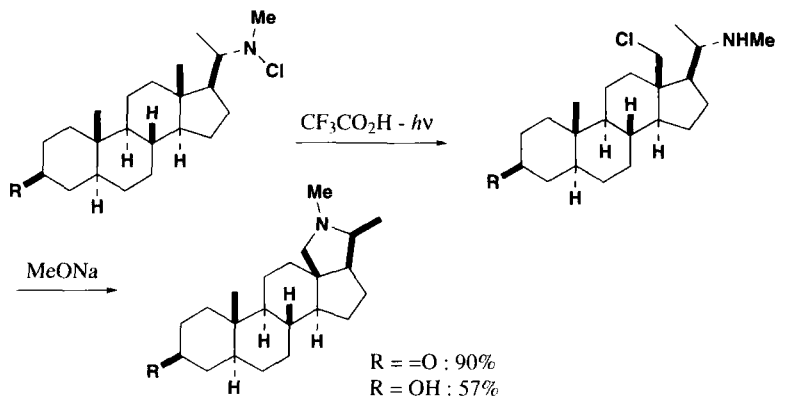
(36)

Wolff has shown that when trifluoroacetic acid was employed, the intermediate alkyl halide could be isolated.[48] Thus, irradiation of 20α-N-chloromethylaminopregn-4-en-3-one afforded 18-chloro-20α-N-methyltrifluoroacetamidopregn-4-en-3-one in 87% yield.



(37)

van Hove and co-workers prepared various heteroconanine derivatives.[49] They observed, like for other functionalizations of the 18 angular methyl group, that the Hofmann-Löffler-Freytag reaction proceeded easily especially when the configuration at C-20 was α.

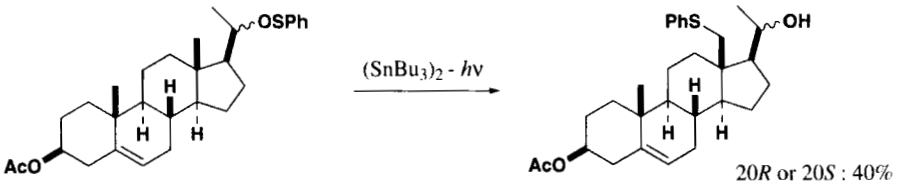


(38)

IV. OTHER C-18 FUNCTIONALIZATIONS

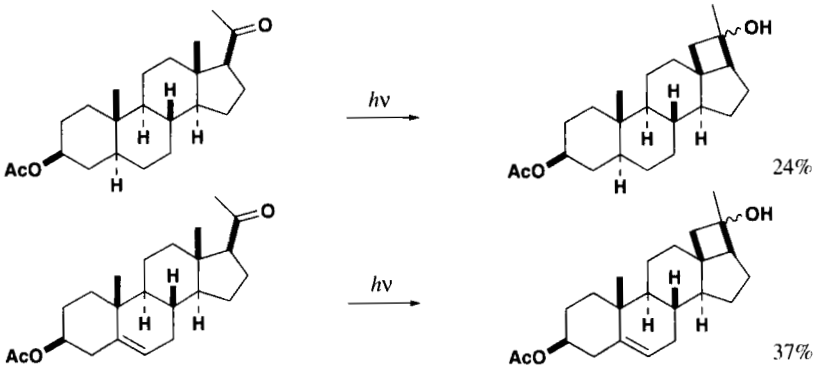
In 1997, Cekovic *et al.* reported the free radical phenylthio group transfer to nonactivated δ-carbon atom in the photolysis reaction of alkyl benzenesulfenates.[50] The reaction was carried out in

presence of 15 mol% of hexabutylditin and provided 18-phenylthio steroids.



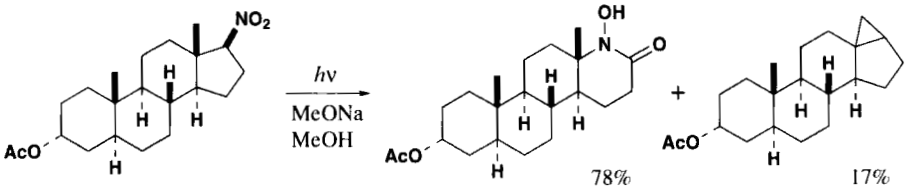
(39)

(5α)-3β-Acetoxy-20α-hydroxy-18,20-cyclopregnane was prepared by Jeger and his group by photolysis of 3β-acetoxy-20-keto-5α-pregnane in 1959.[51] The same reaction was applied to the 5-ene derivative in order to prepare 18-oxoprogesterone.[52]



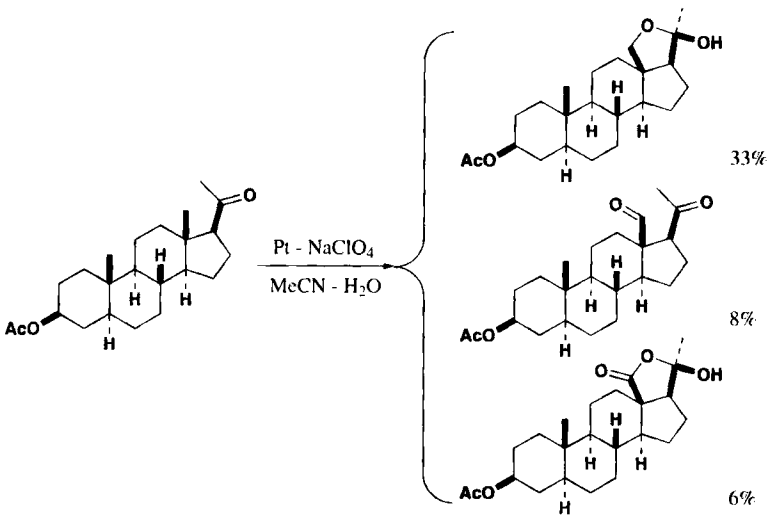
(40)

After preliminary results published by Marples in 1977,[53] Yamada has described the photorearrangement of nitronate anion which led mainly to the corresponding hydroxamic acid along with 17,18-cyclosteroid.[54]



(41)

In 1992, an oxygen-functionalization of the C-13 angular methyl group in 3β-acetoxy-5α-pregnan-20-one has been effected by means of an anodic oxidation mediated by the C-20-carbonyl

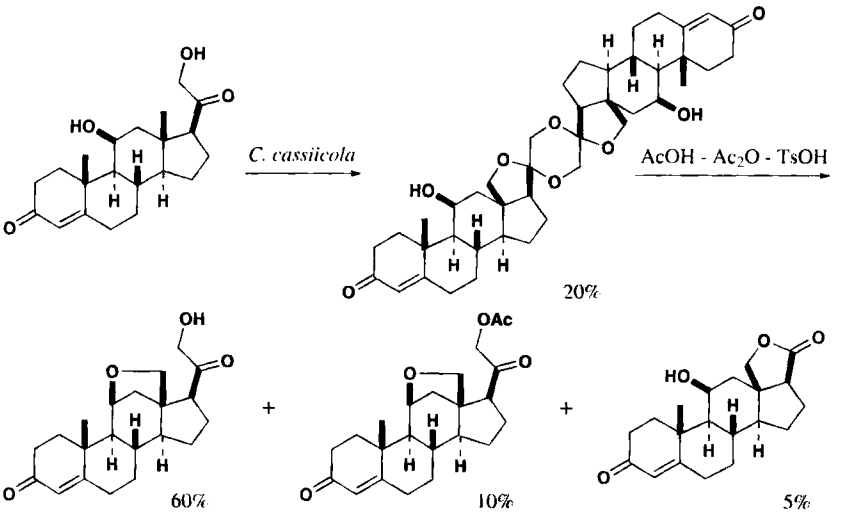


(42)

residue in the steroid skeleton.[55] The electrolysis led to a mixture of three products along with 51% of recovered starting material. Although the yield of the conversion was not satisfactory, this reaction is the first example of the oxidation of an angular methyl group in a steroid by carbonyl-mediated electrochemical reaction.

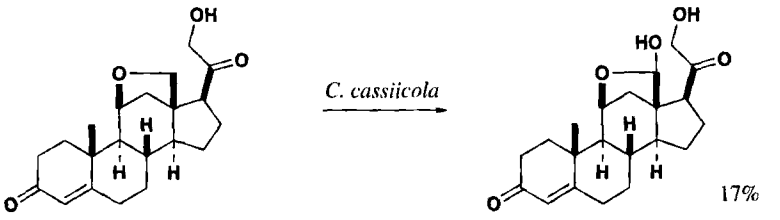
Microbiological 18-hydroxylation is unusual; it occurs in the case of certain steroids using *Cercospora melonis*[56] or *Corynespora cassiicola* .

In 1965, Kondo and co-workers[57] reported a partial synthesis of aldosterone from corticosterone through only three steps containing two transformations by microorganisms capable of introducing a hydroxyl group into the C-18 position of the steroid nuclei. Thus, transformation of corticosterone with the resting mycelium of *Corynespora cassiicola* afforded mainly 18-hydroxy-corticosterone which was isolated as a dimer, which latter was then treated with aqueous acetic acid to give three products.



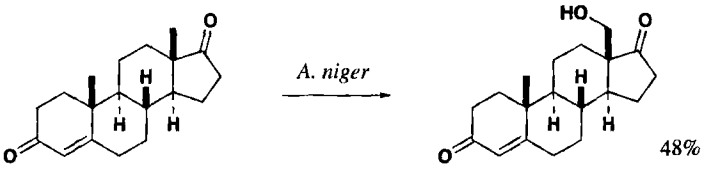
(43)

Finally, incubation of the major compound with *Corynespora cassiicola* produced aldosterone as the main product.



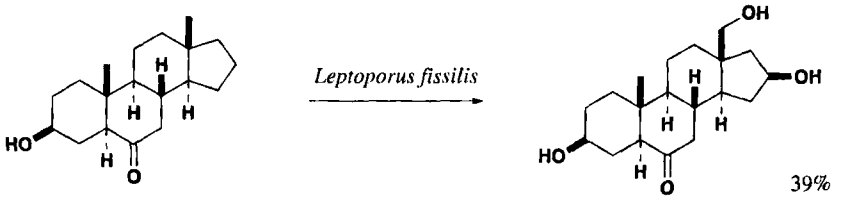
(44)

In 1971, Auret[58] showed that incubation of androst-4-ene-3,17-dione with a two-day growth of *Aspergillus niger* in Czapeck Dox medium gave 18-hydroxy androst-4-ene-3,17-dione.



(45)

However, 16β,18-dihydroxylations are much more common processes than simple hydroxylations at C-18. For instance, Meakins and Coworkers.[59] have reported various incubations with *Leptoporus fissilis* of dioxygenated 5α-androstanes leading to corresponding 16β,18-dihydroxylated derivatives.



(46)

V. CONCLUSION

In summary, we have shown that C-18 angular methyl functionalization in steroids is usually achieved by photochemistry. Intramolecular hydrogen abstraction from hetero radicals which leads to the remote functionalization of nonactivated carbon centers is an important target for organic chemists. The direct introduction of a substituent into the intact tetracyclic steroid molecule is also possible by several reactions such as the Hofmann-Löffler-Freytag reaction. More generally, the use of covalently attached templates to catalyze the remote functionalization of steroids was introduced by Breslow over 20 years ago.[60]

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