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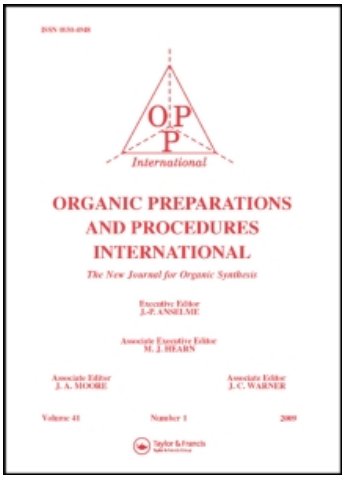

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THE BIRCH REDUCTION OF STEROIDS. A REVIEW

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THE BIRCH REDUCTION OF STEROIDS. A REVIEW

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INTRODUCTION

The aim of this review is to provide a classification of the Birch reductions of steroids according to the functional groups that they can bear. The selectivity of the reaction is emphasized since various functionalities present in the steroid can be preserved. References are given as superscripts for each equation.

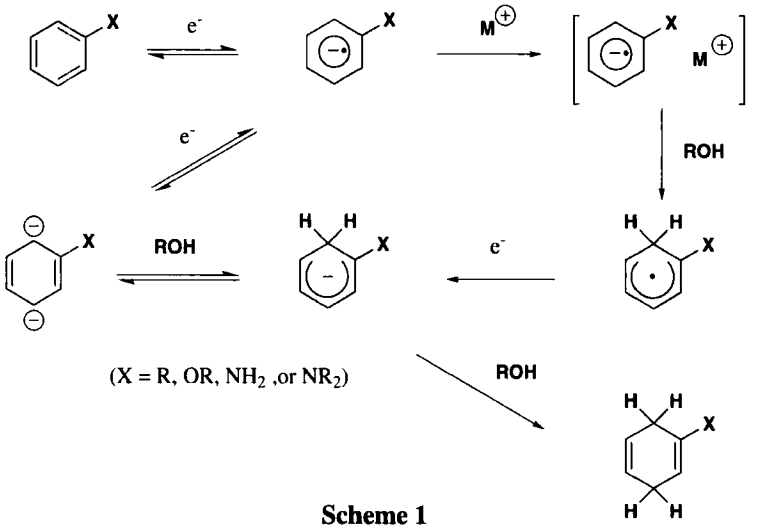
I. GENERAL CONSIDERATIONS

1. Historical of the Birch Process

The reduction of aromatic rings by solutions of alkali metals in liquid ammonia was first discovered by Wooster and Godfrey[1] who reacted toluene with sodium in ammonia followed by the addition of water. This reaction was actually developed by Birch more than five decades ago, providing one of the most powerful synthetic procedures available to organic chemists. Thus the reaction has come to bear his name although in some cases it is simply called metal-ammonia reduction. Actually, the term "metal-ammonia reduction" is best reserved for reductions in which ammonia is the only proton donor present. In recent years, many chemists have used the term "Birch reduction" to include all metal-ammonia reductions, whether an alcoholic proton source is present or not. By definition, a Birch reaction is one in which the metal, substrate, alcohol, and ammonia are present at the onset of the reaction.[2] The distinction in terminology emphasizes the importance of the acidity of the proton donor in the reduction process.

Metals of groups I and II of the Periodic Table dissolve readily in liquid ammonia. The resulting solution of solvated electrons are powerful reducing agents that may be used to perform highly selective reactions. The Birch reduction of a benzenoid compound involves the addition of two

electrons and two protons to the ring. The order in which these additions occur has been the subject of both speculation and study. Birch[3] and others[4] originally suggested that two electrons add to the aromatic ring affording a dicarbanion which is subsequently protonated. The preference for maximum separation of charge in dicarbanion provided a reasonable explanation for the formation of 1,4-dihydro compounds. This mechanism is incompatible with kinetic data and in addition, it cannot account for the failure of reduction to occur in the absence of an alcohol. Subsequently Birch[5] and Krapcho and Bothner-By[6] independently postulated the mechanism depicted in *Scheme 1*. Electrons are added in a reversible step to form a radical anion, which is usually protonated and reduced further



Scheme 1

to a pentadienyl anion.[7] Alternatively, the radical anion may be reduced further to a dianion,[8] which is then protonated to afford the same pentadienyl anion. Protonation of this intermediate occurs predominantly at the central carbon atom to form the unconjugated 1,4-diene, which is resistant to further reduction. With aromatic ethers, it is necessary to displace the initial equilibrium between the substrate and the radical anion through protonation by a stronger acid than ammonia. Alcohols (often ethyl, isopropyl, or *t*-butyl alcohol) are normally used to supply protons. In the absence of the alcohol, products arising from dimerization of the radical anion are frequently obtained. Recently, the kinetics of the Birch reduction of benzene derivatives have been reinvestigated by Greenfield *et al.*,[9] who proposed the formation of an intermediate ion pair whose protonation is rate determining. This was established by the observed acceleration of the reaction upon addition of alkali cations common to the dissolved alkali metal, and the observed deceleration of the reaction by addition of alkali cation complexing cryptands.

With substrates that bear electron-withdrawing groups (EWG), the radical anions are formed in sufficiently high concentrations to be protonated by the ammonia or then may be reduced further to dianions (*Scheme 2*). When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups such as alkyl decrease the rate of the reaction and are generally found on the

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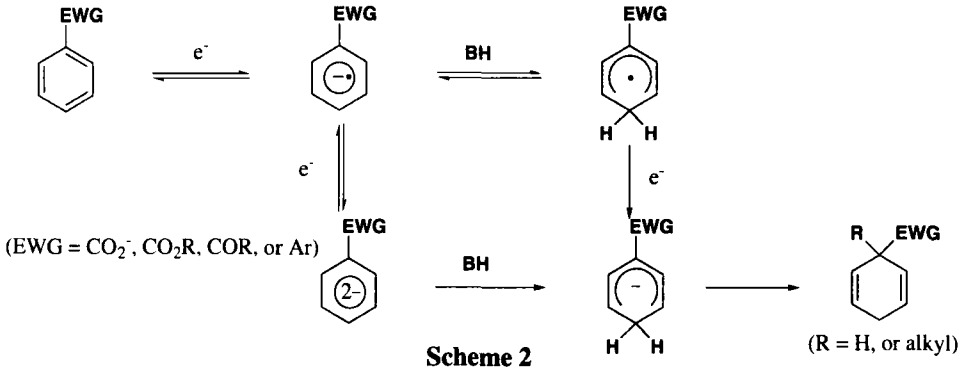
non-reduced positions of the product. On the other hand, electron-withdrawing groups such as CO_2H or $CONH_2$ increase the reaction rate and are found on the reduced positions of the products.



Scheme 2

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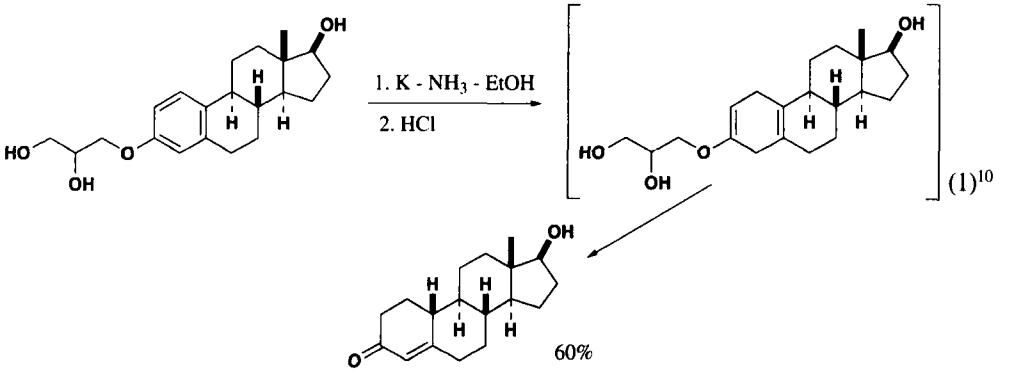
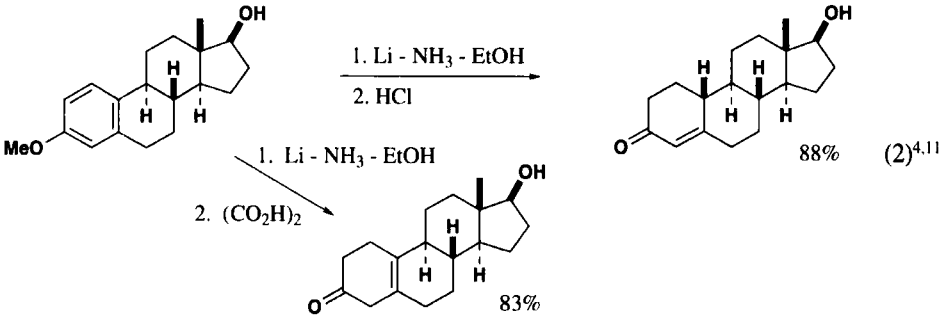
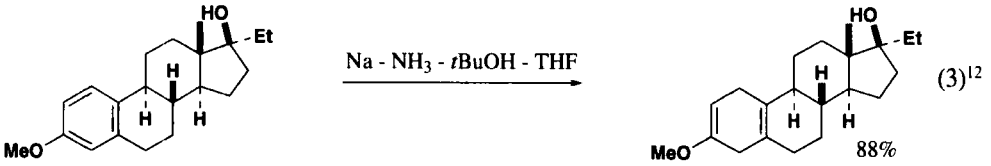
The synthetic approach to 19-norsteroid hormones was first achieved by Birch and Mukherji's method of reduction, in which the 3-glyceryl ether of estradiol (more soluble in liquid ammonia than estradiol) was reduced with sodium (or potassium) and an alcohol in liquid ammonia, and the dihydro-derivative so obtained hydrolysed to an unsaturated ketone.[10] This compound had 30% of the androgenic activity of testosterone and was the first active androgen to be obtained by synthesis. This success led to the 19-norprogestagens, including the first oral contraceptives. This method was improved by Wilds and Nelson by using lithium instead of sodium and they found another advantage in adding alcohol last, as opposed to having it present when the metal was added.[4,11] The lithium technique permitted the use of the easily prepared 3-methyl ether of estradiol, while Birch and his co-workers were forced to use the more soluble, but less available, glyceryl ether. Thus, excellent yields of the corresponding crystalline dihydro derivative were obtained. It was cleaved and rearranged in 88% yield to the α,β-unsaturated ketone 19-nortestosterone, using dilute methanolic hydrochloric acid. This facile shift of the double bond into conjugation was easily avoided however, with aqueous oxalic acid which gave the β,γ-unsaturated ketone in 83% yield.





(2)[4,11]

A few years later, Dryden and co-workers studied the experimental conditions of the Birch reduction carried out in presence of both sodium or lithium.[12] They concluded that the success of these conditions was due to the maintenance in solution of high concentrations of steroid, alkali metal, and proton donor for a sufficient period of time to allow the reduction to go to completion. Thus, 17-ethylestradiol 3-methyl ether was reduced with sodium to the corresponding 1,4-dihydro compound in 88% yield instead of 87% with lithium. Moreover, they suggested that Birch's low yields in some cases might be ascribed to iron contaminants in the ammonia.



(3)[12]

So, Dryden *et al.* concluded that the previously reported failures of sodium to reduce steroidal aromatic ethers in good yields were probably due not only to the insolubility of the steroid but also to the presence of iron in the reaction system.

2. Experimental Considerations

The rate of a given Birch reduction is strikingly controlled by the metal used, the nature and position of substituents on the aromatic ring, and the structure of the alcohol used as the proton donor. The choice of metal can have a profound effect on the outcome of the reduction:[13] lithium and sodium are usually the most satisfactory, but potassium may be superior, and sometimes essential for specialized applications.[14] Calcium metal is favored in the reduction of α-acetoxyketones, and magnesium appeared to offer advantages in some early reductions of aromatic amides, esters, and polycyclic hydrocarbons, but on the whole there appears to be little point to the use of metals other than the common elements of Group I.[15] In spite of small differences in their reduction potentials, lithium, sodium, potassium and calcium afford sufficiently high concentrations of the radical-anion so that all four metals can effect Birch reductions. However, lithium ion unlike sodium and potassium ions, can coordinate strongly with the radical-anion, and consequently equilibrium for lithium is shifted considerably more to the right than for sodium and potassium. This shift accounts for the greatly increased

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rate of reduction with lithium. Moreover, lithium has the highest solubility in ammonia and is the least sensitive to impurities. The choice of metal for a reduction depends upon the structure of the compound being reduced. For practical purposes, it is between lithium and sodium since neither potassium nor calcium offer any advantages.

Recent studies on the kinetics of the Birch reduction of benzene derivatives have shown that the rate of the reaction increases with the metals in the order K, Na, Li.[9] The authors recommended the general use of lithium because the yield of the Birch product is generally larger with lithium than with the other alkali metals. Moreover, the rate of the formation of hydrogen proceeding in competition with the Birch process decreases in the series of the alkali metals K, Na and Li. Sodium ions decelerate the rapid Li-Birch reduction while lithium ions accelerate the slow Na-Birch reduction.

$$2\,M + 2ROH \longrightarrow 2ROM + H_2$$

Electron-releasing groups direct reduction to unsubstituted 2,5-positions, and while alkyl groups retard reduction (*t*-butyl > isopropyl > ethyl > methyl), amino and alkoxy groups accelerate the rate of reaction slightly.[6] Phenols are rapidly ionized and are resistant to the addition of electrons, although reduction may be effected with high concentrations of lithium.[16] Groups which allow delocalization of electrons accelerate reduction and afford 1,4-dihydroderivatives, irrespective the presence of alkyl, alkoxy, and amino substituents. A major limitation on the choice of electron-withdrawing groups is the ease with which they themselves undergo reduction. In the absence of an electron-withdrawing group, it is usually difficult to reduce benzene rings which carry bulky substituents or which do not have two unsubstituted positions in a *para* relationship.

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The solubilities of ionic substrates, *e.g.* carboxylates salts, and their products depend very much on the metal counter-ion. Alcohols aid solubility, and it is common for insoluble substrates to dissolve as the reduction progresses. A co-solvent is usually necessary, however, and tetrahydrofuran is most commonly utilized, although other ethers may be employed. Tertiary alcohols react very slowly with the metal, but methanol or ethanol protonate the intermediate radical anions more rapidly and can suppress side-reactions.

It has been noted that the order of addition of reagents is the most important single variable to influence the distribution of products. A commonly employed procedure is that of Wilds and Nelson in which the steroid is stirred with ammonia, ether and lithium while ethanol is added gradually.[11] Alternatively, another procedure is based on the addition of small pieces of metal to a mixture of substrate, ammonia, solvent and alcohol at < -70° until the blue color persists for a reasonable period. Many published procedures employ low steroid concentrations (0.01-0.02M) and therefore are inconvenient for moderate scale preparative purposes. Efficient reductions on a larger scale are best realized by adjusting the solvent properties of the reaction medium with respect to the steroid. Aromatic steroids are virtually insoluble in liquid ammonia and a co-solvent must be added to solubilize them or reduction will not occur. Ether, ethylene glycol dimethyl ether, dioxane and tetrahydrofuran have been used and, of these, tetrahydrofuran is the preferred solvent. It is infinitely miscible

with liquid ammonia, but the addition of lithium to a 1:1 mixture causes the separation of two liquid phases. In general, a 1:1 ratio of ammonia to organic solvents represents a reasonable compromise between maximum solubility of steroid and dissolution of the metal with ionization. Many aromatic steroids submitted to the Birch reduction contain hydroxy groups which are deprotonated to the corresponding alkoxides during the reduction, particularly if a tertiary alcohol is used as the proton donor. The steroidal alkoxides and the one derived from the proton donor often precipitate and cause foaming of the reaction mixture. These alkoxides can be kept in solution by adding an excess of the proton donor alcohol to the mixture; the alcohol also assists in dissolving the starting hydroxylic steroid. A particularly useful reaction medium for hydroxylic steroids contains ammonia, tetrahydrofuran and *t*-butyl alcohol in the volume ratio of 2:1:1. This mixture is also useful with non-hydroxylic steroids that are readily soluble in tetrahydrofuran. The relatively slow reaction of the metals with *t*-butyl alcohol facilitates the maintainance of a reactant contact time of several hours, which assures virtually complete reduction of the starting material. Other alcohols may be used in place of *t*-butyl alcohol; however, methanol and ethanol react sufficiently rapidly with the alkali metals, especially lithium, to make it less convenient to obtain complete reduction of the starting material with them than with the slower reacting isopropyl or *t*-butyl alcohols.

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Temperature is often an important factor, and should be monitored with an internal thermometer or sensor, since the assumption that the temperature of the reaction mixture is the same as that of the external cooling bath is rarely warranted. Low temperatures (< -70°) are crucial for the ring-reduction of aromatic esters and ketones, and to help to suppress unwanted side-reactions with other substrates, *e.g.* hydrogenolysis of methoxy substituents.

It must be noted that oxygen should be rigorously excluded and, although ammonia at reflux provides quite good protection, it is advisable to employ an inert atmosphere. Nitrogen is usually satisfactory, but there is a potential for reaction with lithium, so the use of helium or argon has been recommended for reductions with this metal.[2f]

A variety of secondary reactions may reduce the yield of a desired product, and in some cases may prevent its formation altogether. For example, it is possible for both aryl and benzylic hetero substituents to undergo hydrogenolysis. Re-aromatization may occur readily, usually because oxygen is present, but in some cases by loss of hydride ion; tetrahydro-products often arise, as a consequence of base-catalysed conjugation of cyclohexa-1,4-dienes, or by initial protonation at C-1 or C-5 of the intermediate pentadienyl anions, or during quenching procedures which do not ensure complete consumption of metal before protonation of product anions; ammonia is an excellent solvent for alkylations but may prove to be too nucleophilic for very reactive electrophiles, such as benzyl iodides.

A competing reaction in any Birch reduction is the reaction of the alkali metal with the proton donor (*vide supra*). The more acidic the proton donor, the more rapid is the rate of this side-reaction. Alcohols possess the optimum degree of acidity for use in Birch reductions and react sufficiently slowly with alkali metals in ammonia so that efficient reductions are possible with them. On

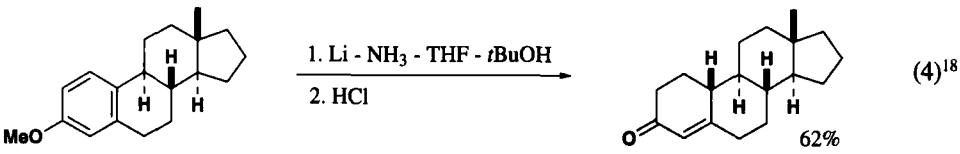
the other hand, most commercial liquid ammonia contains up to several ppm of colloidal iron compounds, possibly from the iron oxide catalyst commonly used in the manufacture of ammonia. Reduction converts these compounds to colloidal iron which strongly catalyzes the reaction between alcohols or ammonia and sodium and potassium. The reaction of lithium with alcohols is also catalyzed by iron but to a markedly lesser degree. The presence of trace amounts of iron also accelerates the destruction of metal by alcohols. Consequently, the ammonia should be carefully dried and distilled before carrying out any Birch reduction.

II. REDUCTION OF STEROIDS BEARING UNREDUCIBLE FUNCTIONS

Simple alcohols, phenols, ethers, and amines are not normally reduced by metal-ammonia solutions in the presence of an alcohol.

1. Reduction of Steroids with no Substituent at C-17

The Birch reduction of 17-deoxoestrone methyl ether reported in 1964, was carried out in presence of lithium and provided either corresponding 1,4-dihydro compound[17] or corresponding α,β-unsaturated ketone.[18]



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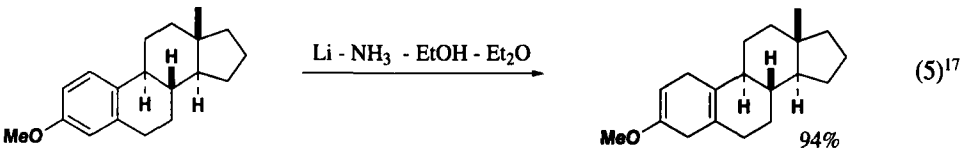
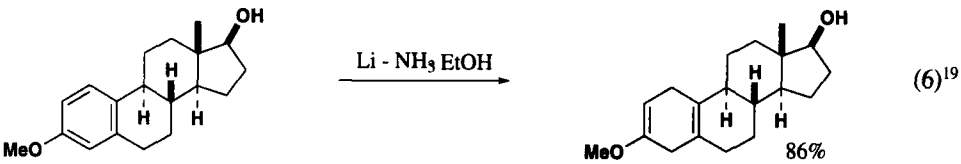


(5)[17]

2. Reduction of Steroids bearing a Hydroxy Group at C-17

a. Reduction of Steroids bearing a Hydroxy Group at C-17β

Many steroids bearing a hydroxy group at position C-17β have been subjected to the Birch reduction conditions. The equations are depicted below.



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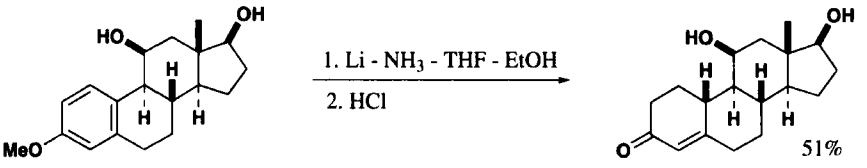

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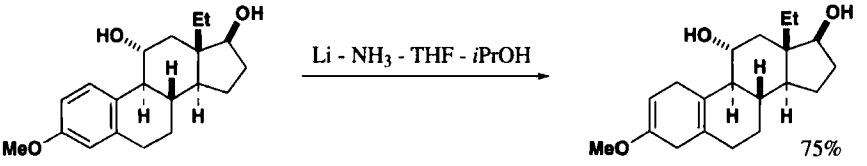

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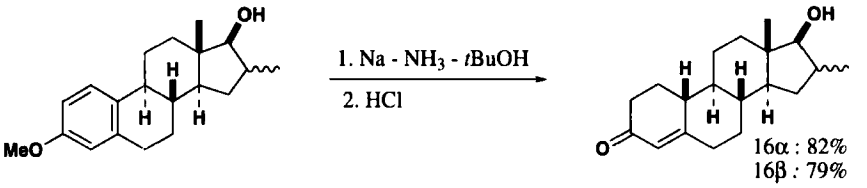

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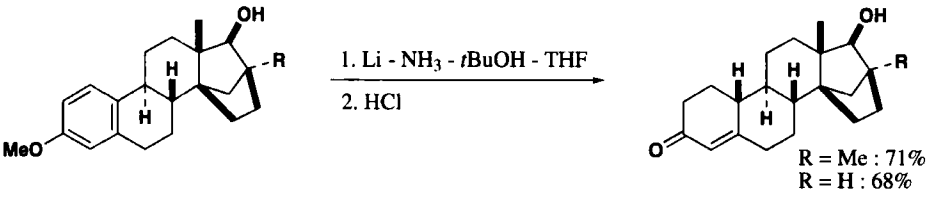

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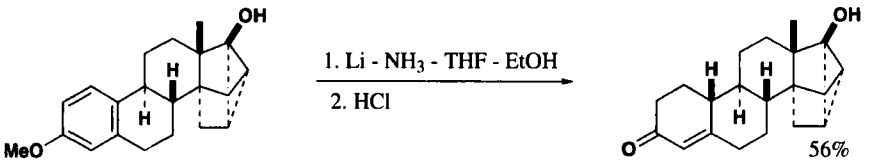

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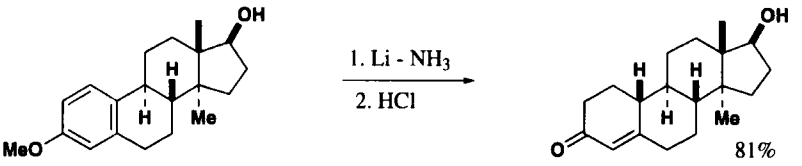

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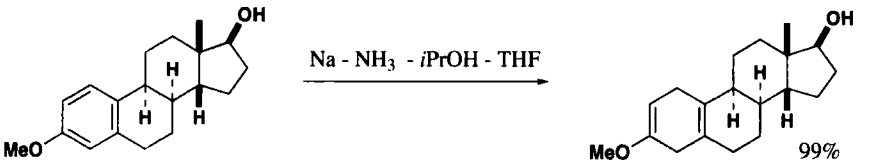

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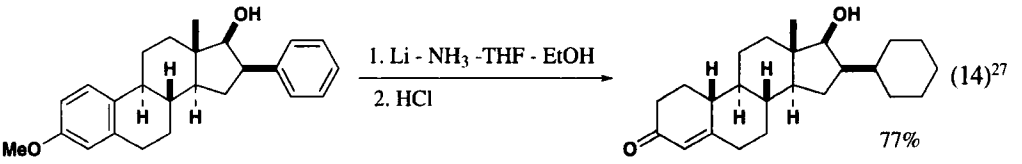

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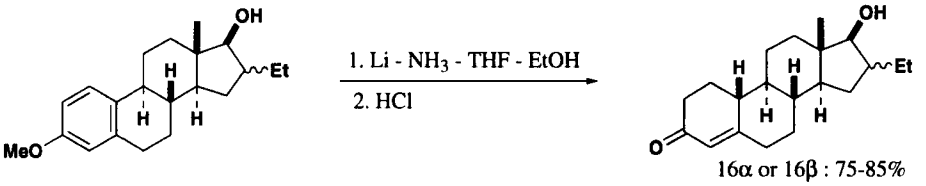

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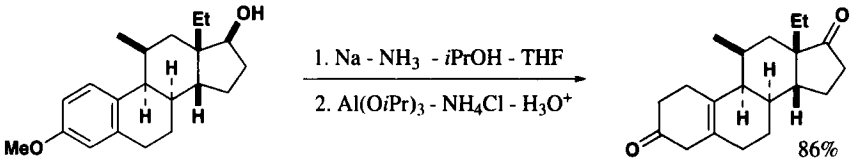

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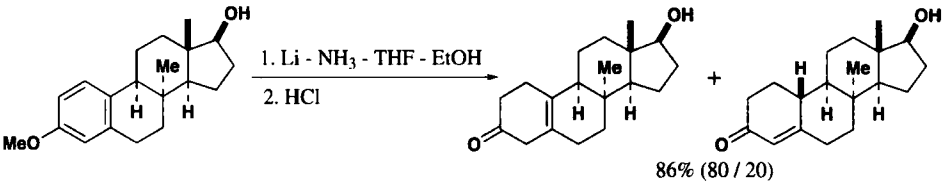

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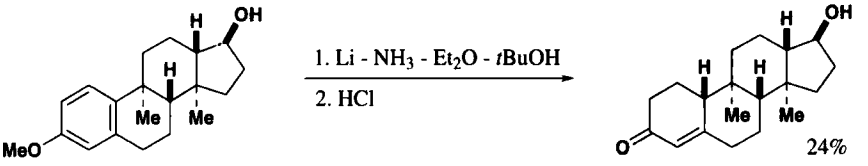

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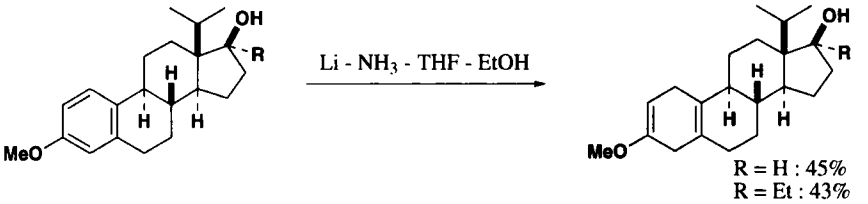

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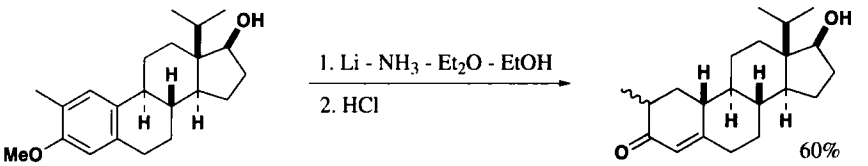

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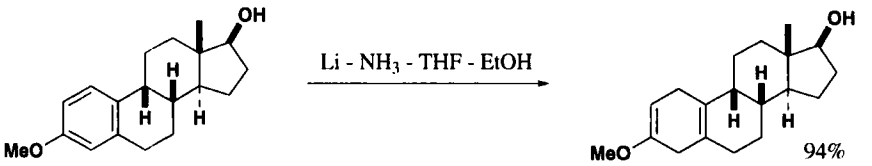

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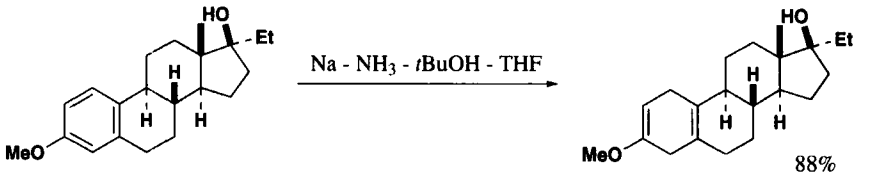

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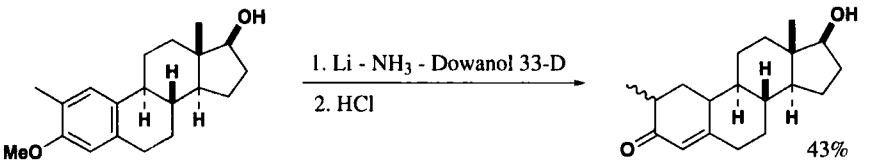

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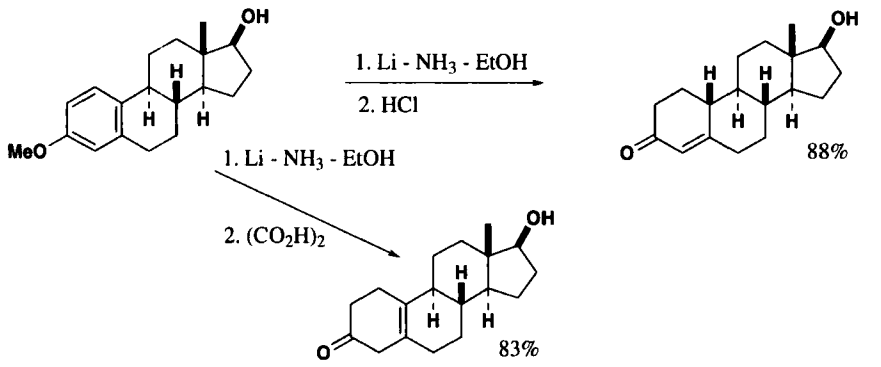

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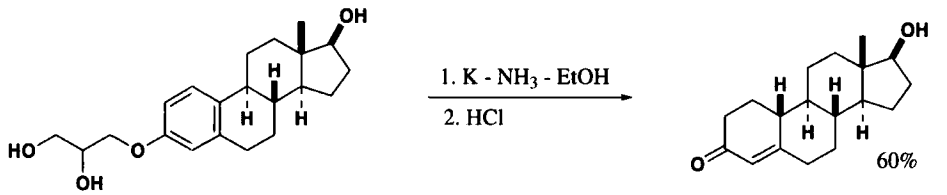
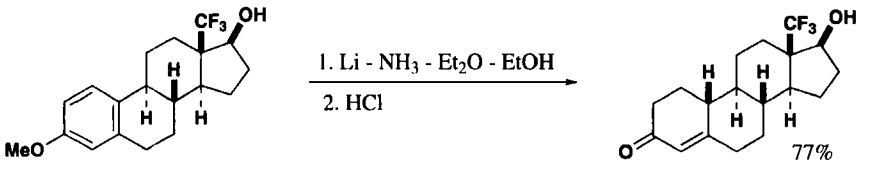


(25)[10]

It must be noted that fluorinated groups remain unaffected by the Birch conditions in agreement with their known high chemical inertness.[36,37]



(26)[36]

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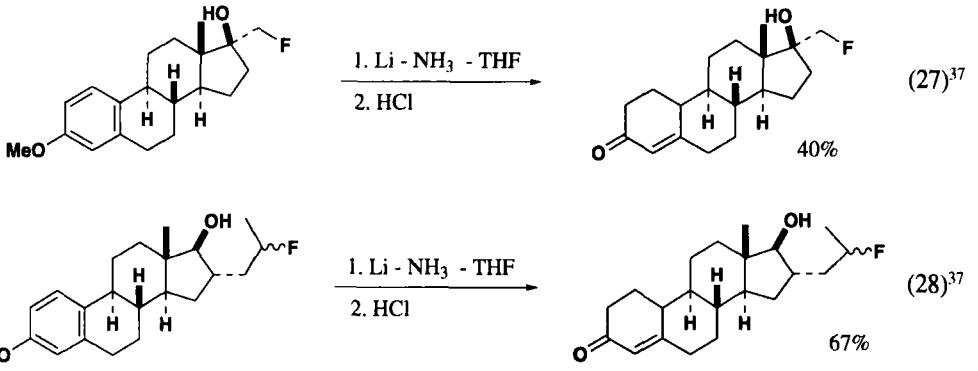
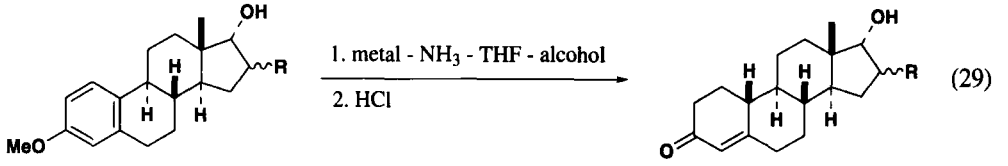


b. Reduction of Steroids bearing a Hydroxy Group at C-17α

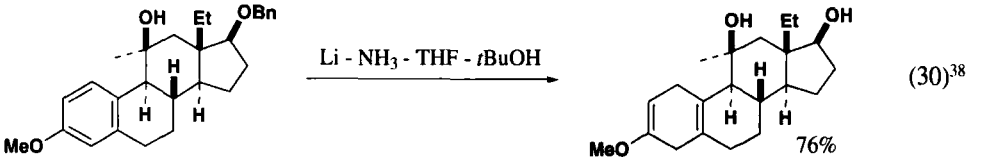
In contrast with 17β-hydroxy steroids, those bearing a hydroxy group at position 17α have been rarely subjected to the Birch reduction conditions. For instance, Goto[28] and Schneider[22] have reported the conversion of 3-methoxy-16-alkylestra-1,3,5(10)-trien-17α-ols into corresponding 17α-hydroxy-16-alkyl-19-nortestosterone derivatives *via* the Birch reduction.



metal	alcohol	R	Yield (%)	Ref
Na	*t*BuOH	16β	82	22
Na	*t*BuOH	16α	94	22
Li	EtOH	16β	75-85	28
Li	EtOH	16α	75-8	28

3. Reduction of Steroids bearing Hydroxy Groups at Positions other than C-17

Many steroids which have been subjected to the Birch reduction conditions bear hydroxy groups at various positions of their skeleton. The examples of steroids bearing hydroxy groups at positions other than C-17 are collected below.



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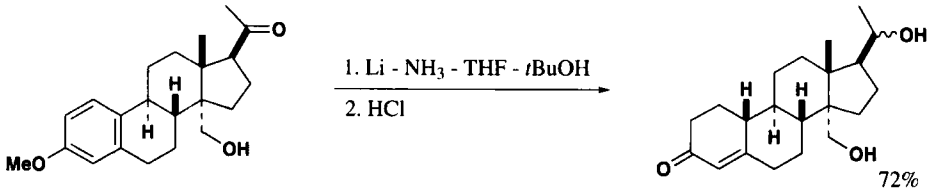
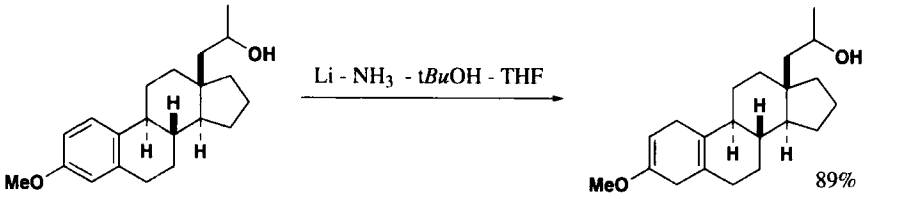
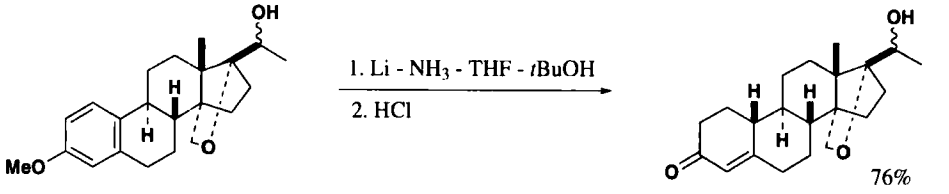


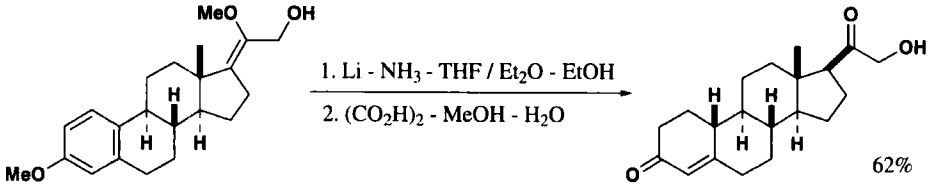
(31)[39]



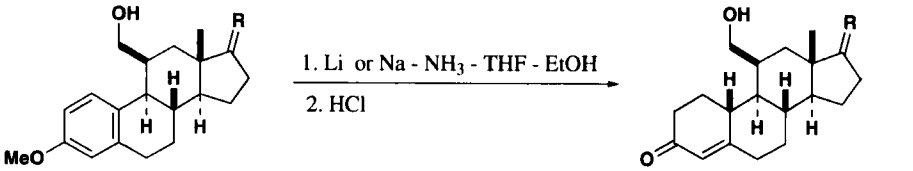
(32)[40]



(33)[41]

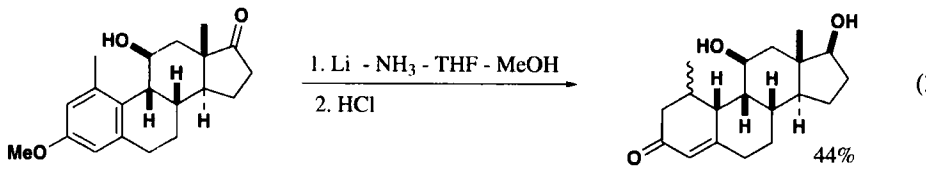


(34)[42]

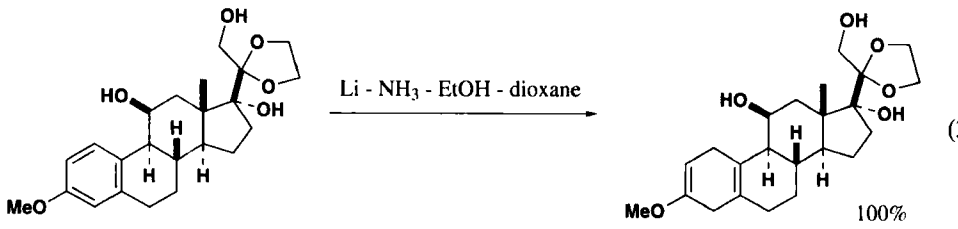


(35)[43]

R = O : 46% (Li)
R = O-CH_2-CH_2-O : 86% (Na)



(36)[44]



(37)[45]

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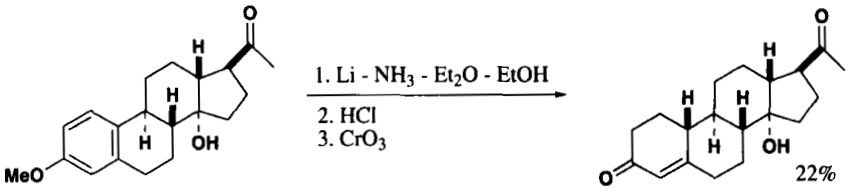


(38)[46]

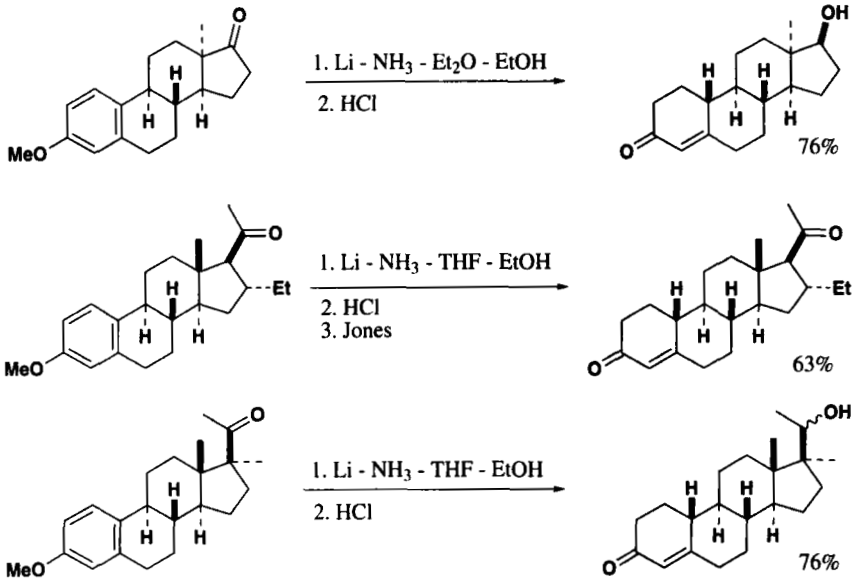
III. REDUCTION OF STEROIDS BEARING VARIOUS REDUCIBLE FUNCTIONS

The following functional groups or types of compounds are generally reduced by metal-ammonia solutions in the presence of an alcohol: aldehydes, ketones, esters, nitriles, certain amides, epoxides, organic halides, alkyl sulfides, alkynes, vinyl groups, olefinic bonds conjugated with other unsaturated groups, quaternary ammonium ions, benzylic and allylic alcohols and ethers, carbocyclic aromatic rings, and certain heterocyclic rings. However, in some cases such functional groups are not reduced during the course of the Birch reduction.

1. Reduction of Steroids bearing a Ketonic Function

Ketonic groups are commonly encountered in steroids and their reduction is facile. Various ketonic estra-1,3,5(10)-trien-3-methyl ether derivatives have been involved in the Birch process in order to prepare a wide range of 19-norsteroids.

In the following scheme, the steroid nucleus exhibits a simple internal or external ketone function which is obviously reduced during the reduction. Most of the time, the alcohols so formed may be reoxidized in a subsequent step.



(39)[47]

(40)[48]

(41)[49]

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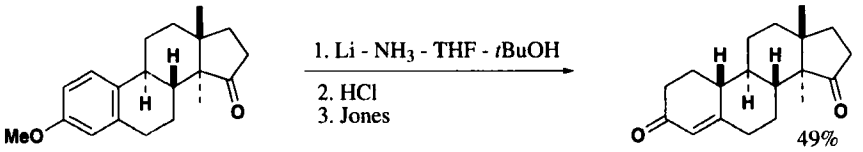
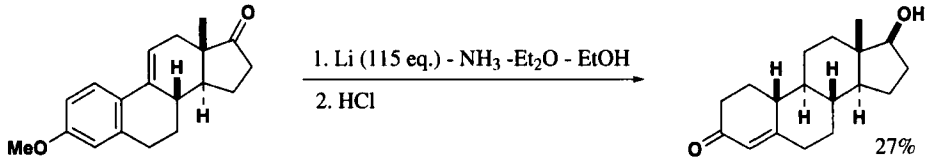
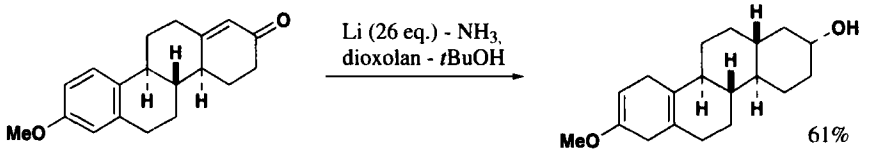


(42)[50]

In some cases, a concomitant double bond can be present on the steroid skeleton. In both the two following examples, the double bond was reduced during the course of the reaction.

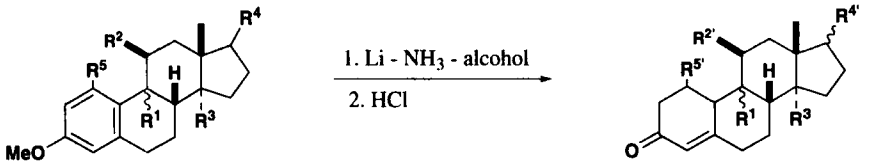


(43)[51]



(44)[52]

Frequently, the steroid bears an hydroxy group as a second functionality.

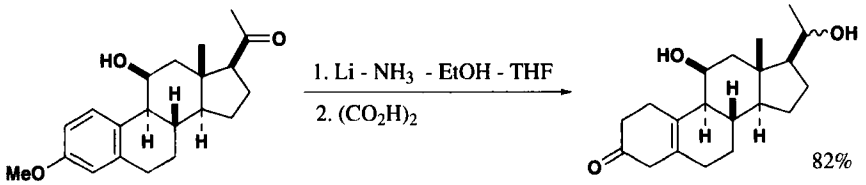


(45)

R^1	R^2	R^3	R^4	R^5	conditions	Yield(%)	$R^{2'}$	$R^{4'}$	$R^{5'}$	Ref
H_β	OH_β	H_α	=O	Me	MeOH/THF	44%	OH_β	OH	Me	44
H_α	H	CH_2OH_α	Ac_β	H	*t*BuOH/THF	72%	H	$CH(OH)(Me)_\beta$	H	39
H_α	H	OH_α	Ac_β	H	EtOH/Et_2O	22%	H	Ac_β*	H	46

(*: after reoxidation of the alcohol)

If the hydrolysis is carried out in the presence of oxalic acid, the unconjugated ketone can be obtained.[53]



(46)[53]

A novel reaction was encountered when 3-methoxy-11β-acetoxy-1,3,5(10)-estratrien-17-one

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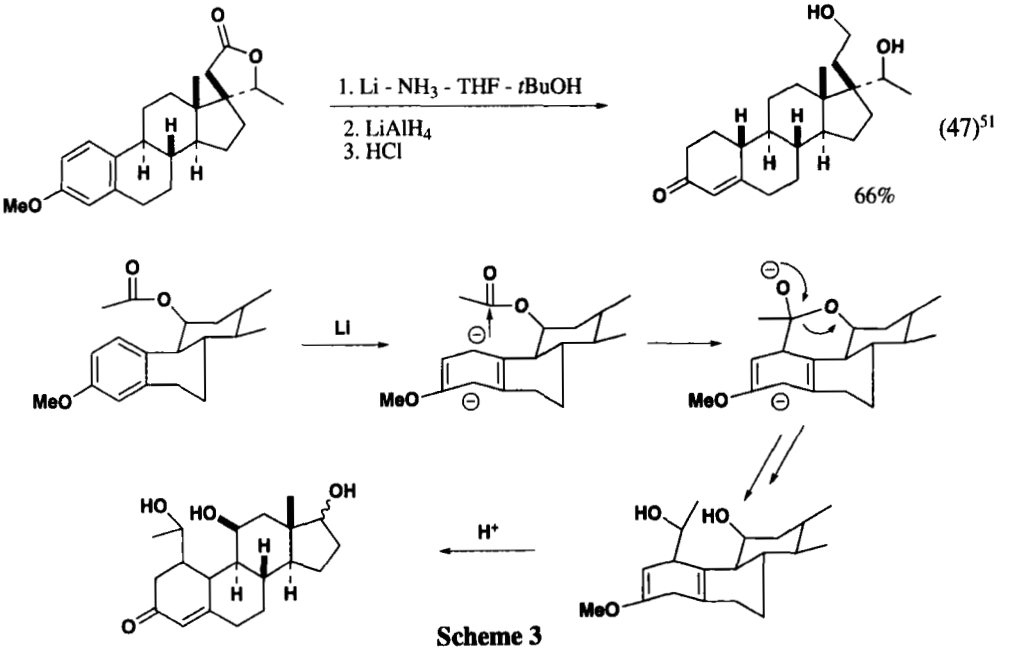
was submitted to the Birch conditions since an internal transfer of the acetate group from oxygen at 11 to the carbon at position 1 was observed.[51] The probable mechanism depicted below was proposed (*Scheme 3*).

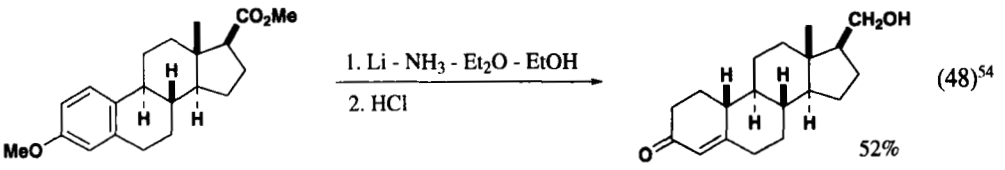


Scheme 3

Since selective reductions generally are not possible in the presence of a ketonic function, a ketone is usually protected by conversion to the ethylene ketal which is not reducible (see Eq. 37).

2. Reduction of Steroids bearing a Carboxylic Function

A Bouveault-Blanc reduction of the carboxymethyl side-chain was observed during the course of the Birch reduction of methyl 3-methoxy-1,3,5(10)-estratrien-17β-carboxylate.[54] C-17



steroidal 5- and 6-membered spirolactones are known to be potent aldosterone blockers. The Birch reduction was used by Cella *et al.*[55] and more recently by Bull and his group[56] for the synthesis of derived 19-nor-17-spirolactones. The spirolactone ring was previously converted into the corresponding disodium salt. The presumed intermediates of Birch reduction were not isolated, but were subjected to treatment with hydrochloric acid to give the corresponding methyl 21,17-carbolactones. In this reaction, the presence of the sodium salt of the hydroxy acid corresponding to the lactone leaves the carboxyl function intact whereas in such experimental conditions, both the lactone ring and

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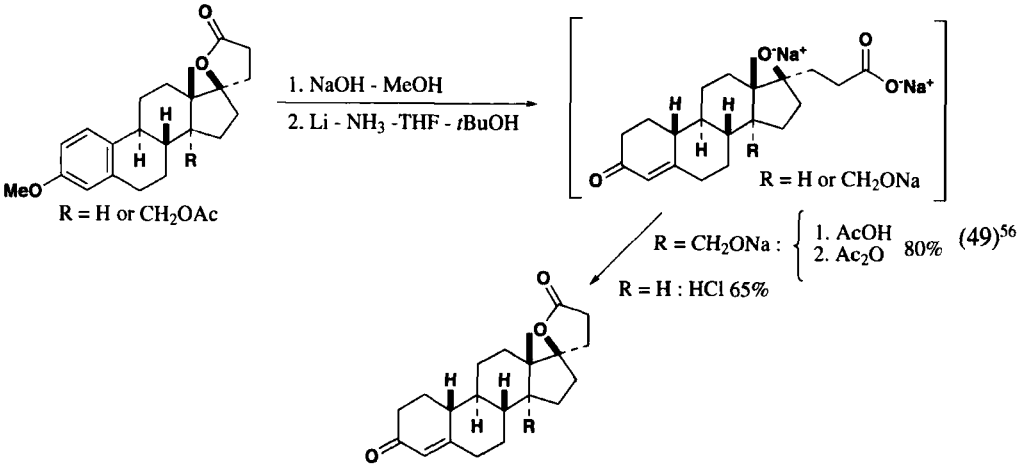
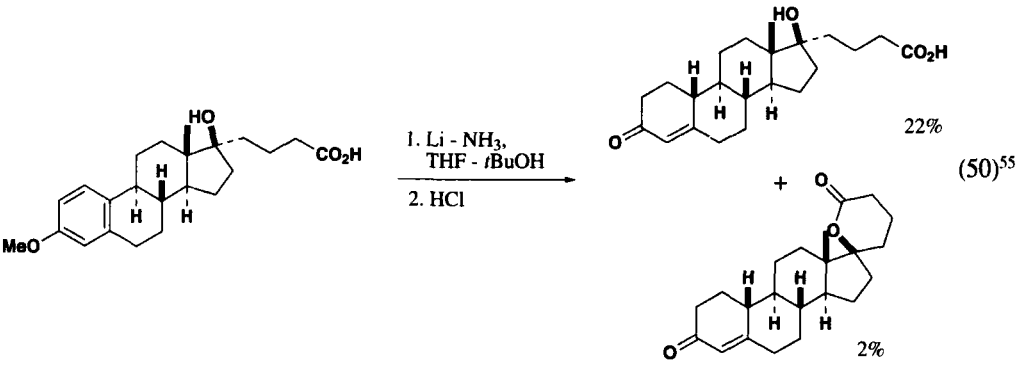
the aromatic ring would be reduced. The corresponding 6-membered spirolactone was prepared by reduction of the corresponding hydroxy acid along with corresponding reduced hydroxy acid.[55]

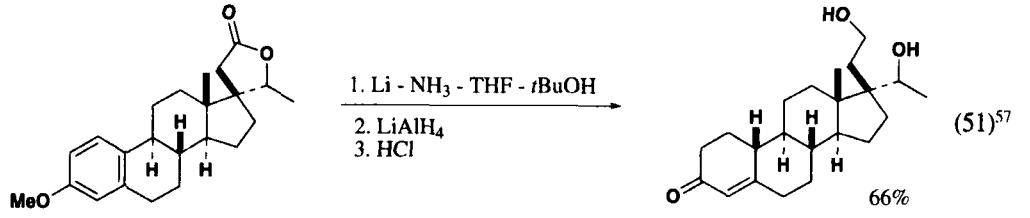


(49)[56]



(50)[55]

Another example of Birch reduction of a steroid bearing a lactone group was reported by Neef and co-workers.[57] In this case, a partial reduction of the lactone group was observed and the reduction was further completed by treatment with lithium aluminium hydride.



(51)[57]

In order to prepare inhibitors of steroid 5α-reductase, 17β-dialkylcarboxamides aromatic steroids were subjected to the Birch reduction.[58]

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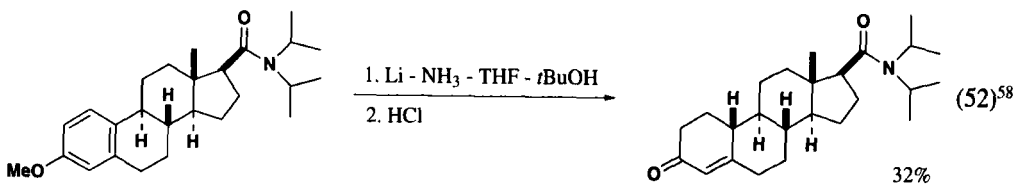
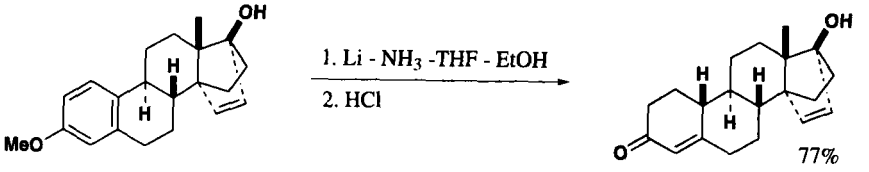


(52)[58]

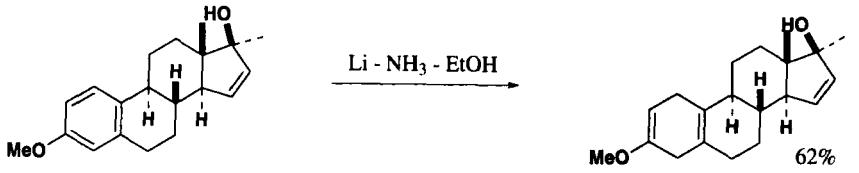
3. Reduction of Steroids bearing un Unsaturated Function

Ordinary olefins are usually unaffected by Birch reduction conditions, particularly if double bonds present on the molecule are not conjugated. For instance, 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl alcohol subjected to Birch conditions afforded the corresponding Δ^4-3-one.[24]

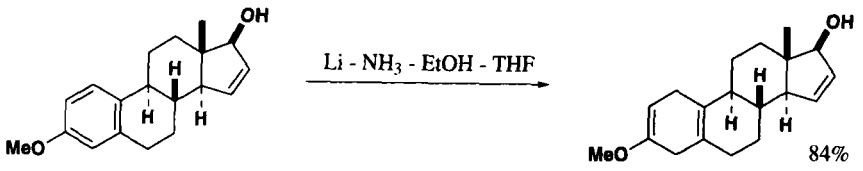


(53)[24]

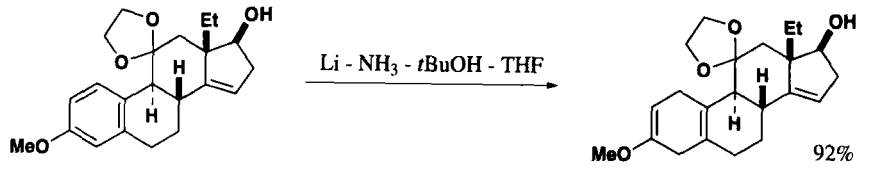
Other examples of Birch reductions involving steroids exhibiting a located double bond are depicted below.



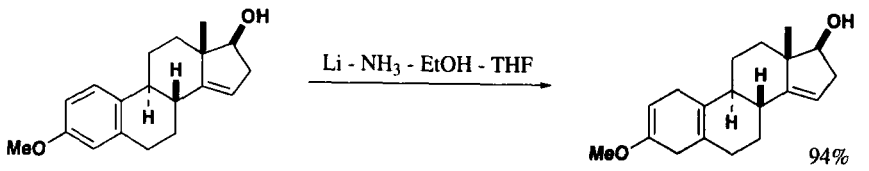
(54)[59]



(55)[59]



(56)[60]



(57)[61]

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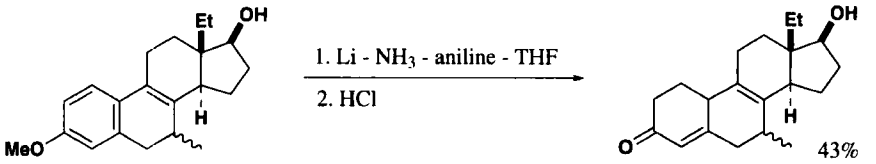
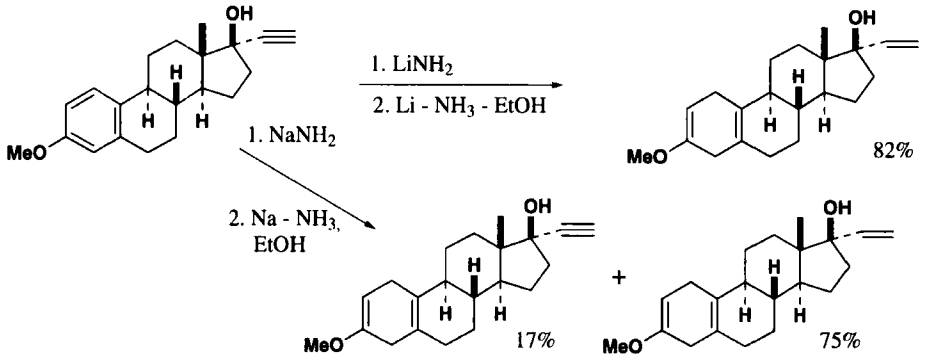


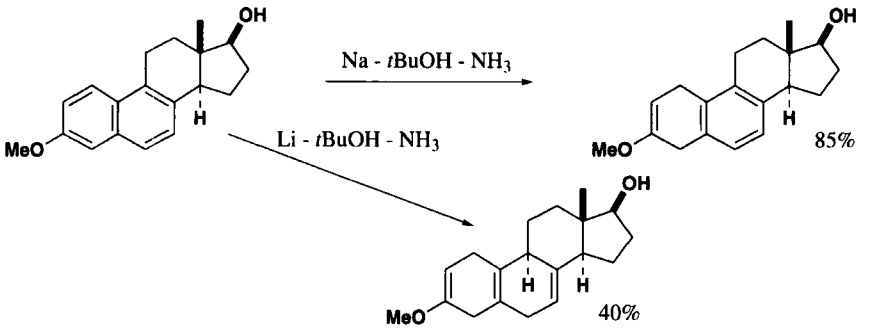
(58)[62]

Ruggieri *et al.* attempted to protect the 17-ethynyl group of 17-ethynylestradiol 3-methyl ether by stirring it with a large excess of lithium amide to form the salts of the ethynyl and hydroxyl functions prior to reduction, so that the A-ring could be reduced selectively.[63] However, only the ethylenic derivative was isolated. When sodium amide was used for salt formation and sodium metal for the reduction, a 17% yield of the desired acetylenic compound was obtained along with a 75% yield of corresponding ethylenic derivative.



(59)[63]

Treatment of the 17-ol derived from equilenin 3-methyl ether with sodium and *t*-butyl alcohol in ammonia reduced only the A-ring to afford the corresponding 1,4-dihydro compound.[64] The use of lithium instead of sodium led to reduction of both the two rings, since reductions with lithium are known to be more rapid than those with sodium.



(60)[64]

An inexplicably low yield was obtained for the reduction of 21,21-ethylenedioxy-3-methoxy-19-norpentara-1,3,5(10),16-tetraene.[65]

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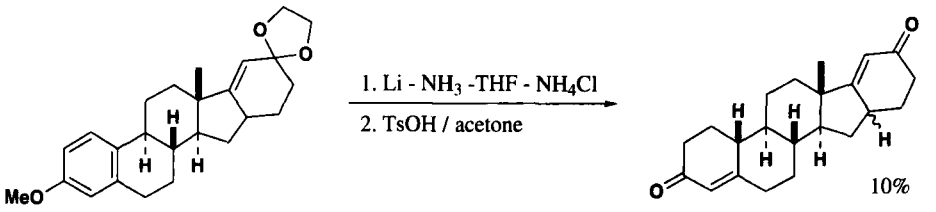
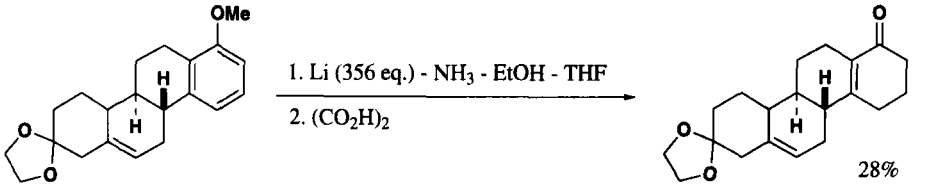


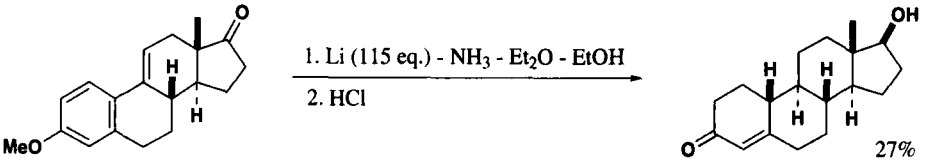
(61)[65]

In order to prepare 18-*D*-homo-19-bisnorsteroids, Birch *et al.* reported the reduction of 10-ethylenedioxy-1,2,7,8,10,11,12,13,14α,17β-decahydro-3-methoxychrysene to corresponding ethylenedioxydecahydromethoxychrysene.[66]

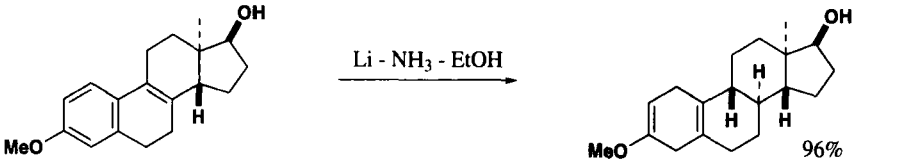


(62)[66]

Most of the time, the reduction of a double bond conjugated with the aromatic ring has been observed.[51,67,68]



(63)[51]



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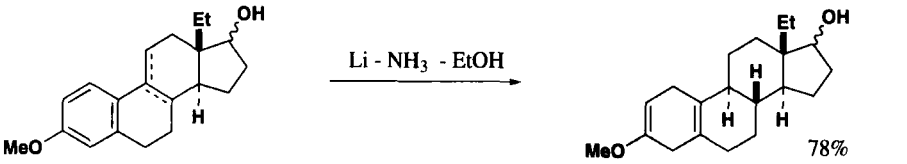
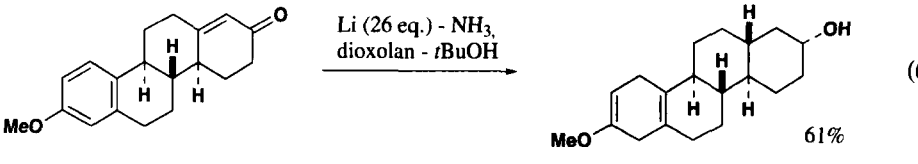


mixture of $\Delta^{9,10} + \Delta^{10,11}$

(65)[68]

Olefins conjugated with C=O are generally reduced under Birch-reduction conditions.[52,69]



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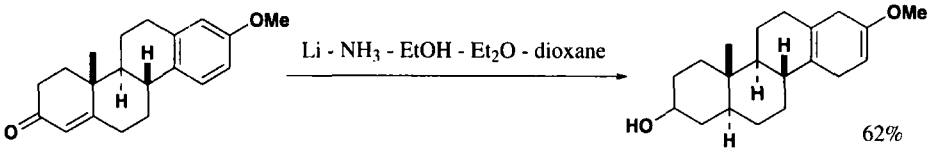
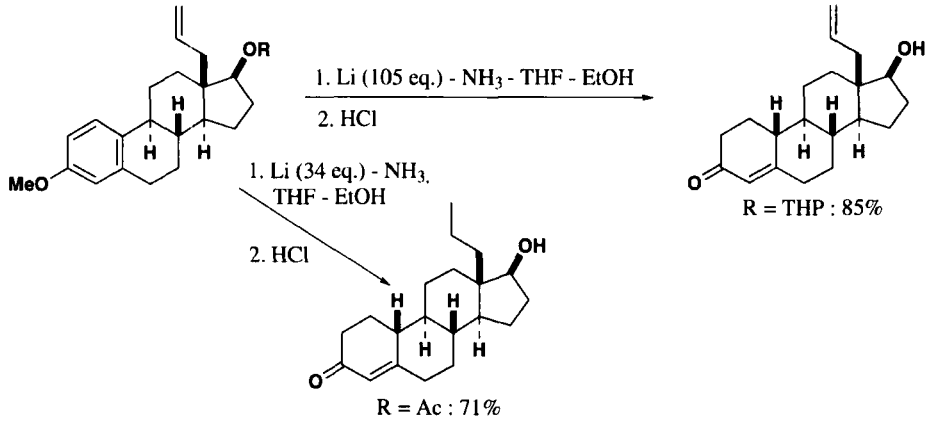
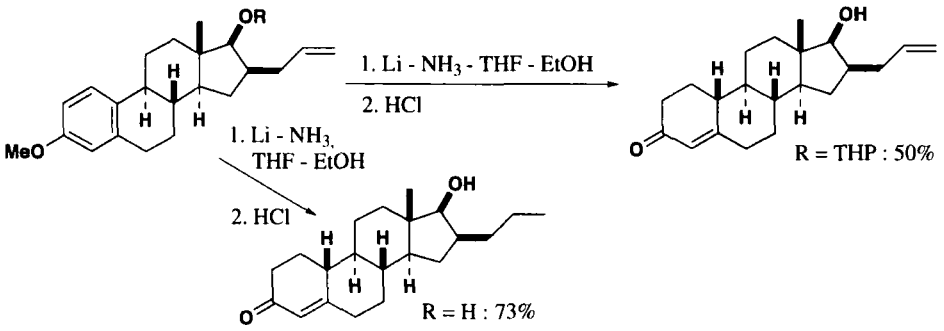


(67)[69]

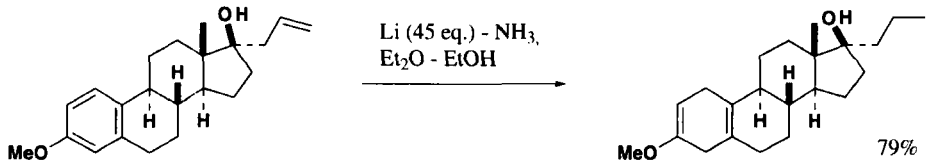
When the steroid exhibits an allyl group, the result of the Birch reduction seems to depend on the nature of the other substituents present on the molecule. For instance, it seems that when a tetrahydropyranyl ether group is present in the molecule, the allyl group is not reduced. In contrast, when an acetate group or an hydroxy group is present, concomitant reduction of the allyl group is generally observed. The greatly enhanced reduction of the allyl group may be due to an intramolecular participation by the hydroxyl group in a reduction intermediate. In the same context, arylated olefins are not systematically reduced under the Birch conditions.



(68)[70]



(69)[27]



(70)[71]

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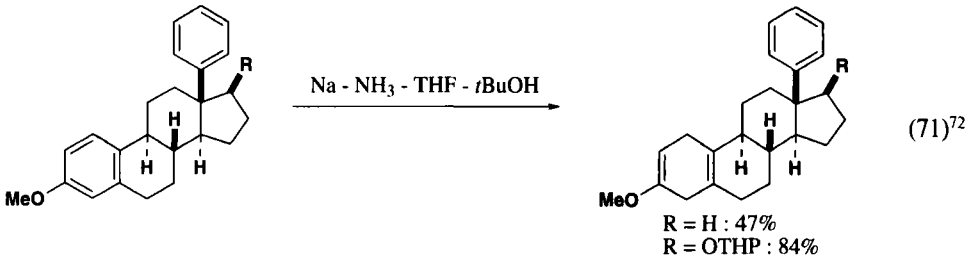
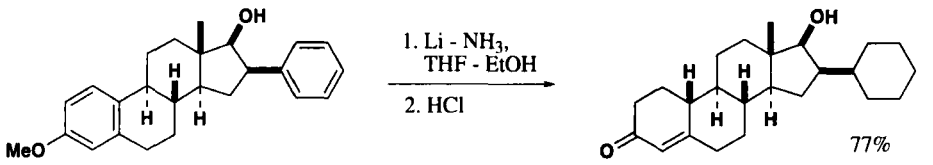
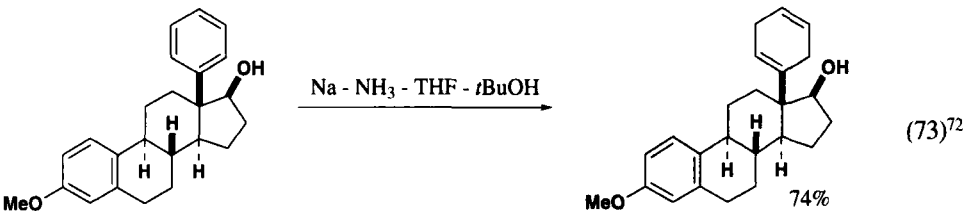
The presence of a hydroxy group in the vicinity of the phenyl group seems to involve the concomitant reduction of the phenyl group through an intramolecular participation by the hydroxyl group. Thus, a comparable reduction (Eq. **73**) of the corresponding alcohol depicted in Eq. **71** with about 2.8 equivalents of sodium (instead of 4 equivalents) unexpectedly afforded the product of angular phenyl reduction and intact aromatic A-ring in 74% yield.[72] This greatly enhanced rate of reduction of the angular phenyl group confirms the sterically favored intramolecular transfer of a proton from the 17β-hydroxyl group in this case to the radical-anion of the angular phenyl group.



(71)[72]

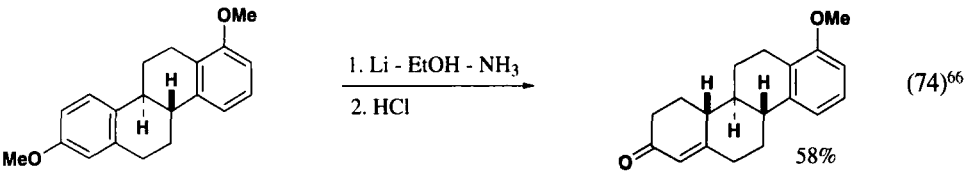


(72)[27]



(73)[72]

Birch *et al.*[66] found that the dimethoxyhexahydrochrysene which contains both the 5-methoxy and 6-methoxytetralin ring systems, undergoes reduction primarily in the 6-methoxytetralin ring when treated with lithium and ethanol in ammonia.[70] The modest yield suggests that some reduction of the less reactive 5-methoxytetralin system was also occuring. Actually, when a very large excess of lithium (250 equivalents instead of 60 equivalents) and a longer reaction time were employed in the reduction, both aromatic rings were reduced.



(74)[66]

On the other hand, the reduction of a benzyl group during the course of a Birch reduction has been reported.[38]

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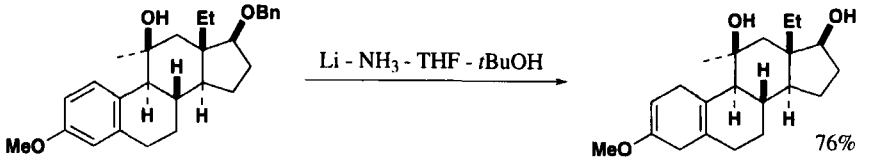
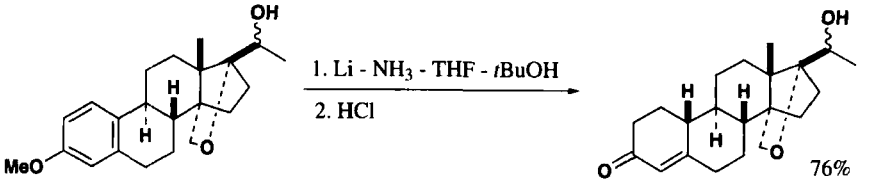


(75)[38]

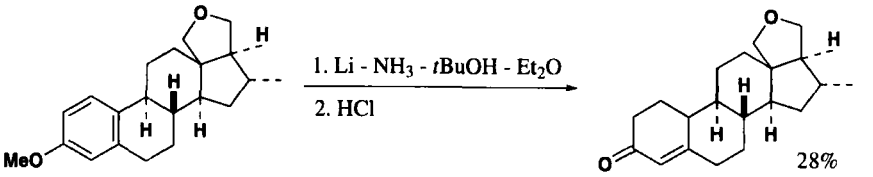
4. Reduction of Steroids bearing an Ether Linkage or a Ketal Group

In order to prepare new 14,17-hetero-bridged hormone analogues, Bull *et al.* treated a mixture of (20*R*)- and (20*S*)-17α,14-epoxymethano-3-methoxy-19-norpregna-1,3,5(10)-trien-20-ols under the Birch reduction conditions.[41]



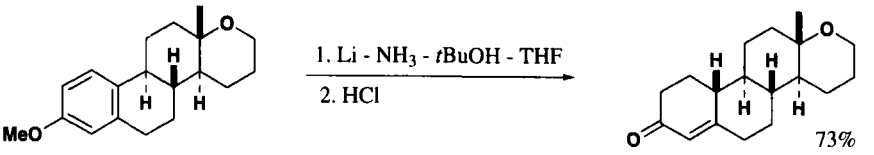
(76)[41]

Similarly, the Birch reduction of a 13,17-hetero-bridged steroid has been described.[73]



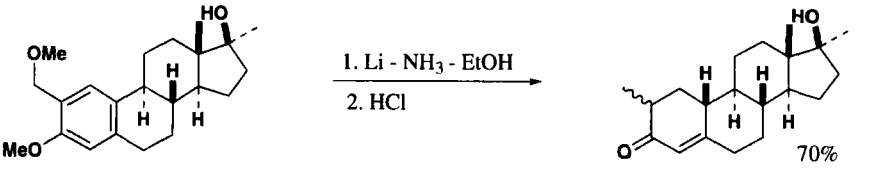
(77)[73]

The Birch reduction of 17α-oxaestranes has been reported by Pettit *et al.*[74]



(78)[74]

A concomitant reduction of a methoxymethyl ether was observed in the course of the Birch reduction of 2-methoxymethyl-17-methylestradiol-3-methyl ether.[75]



(79)[75]

On the other hand, an ether group at position C-17 is unchanged under the Birch conditions even in the case of a trimethylsilyl ether.[76]

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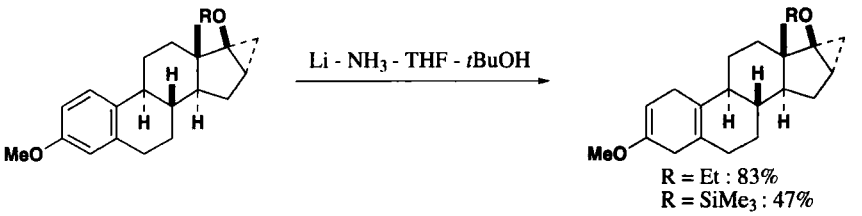
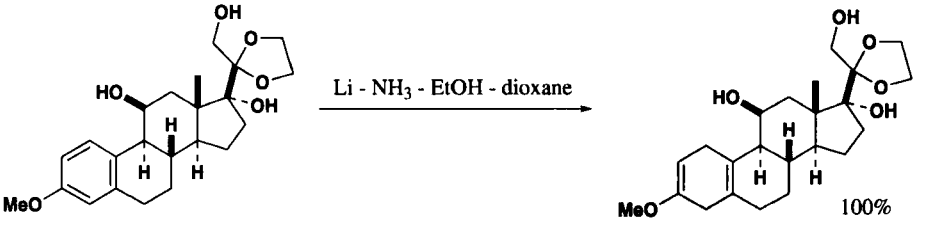
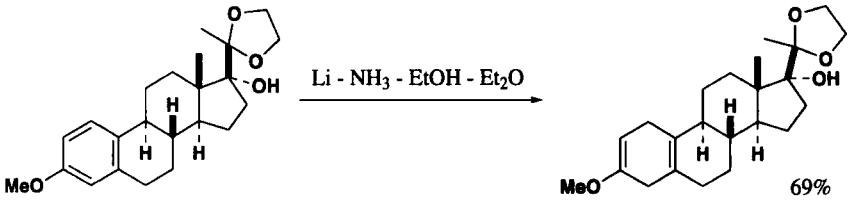


(80)[76]

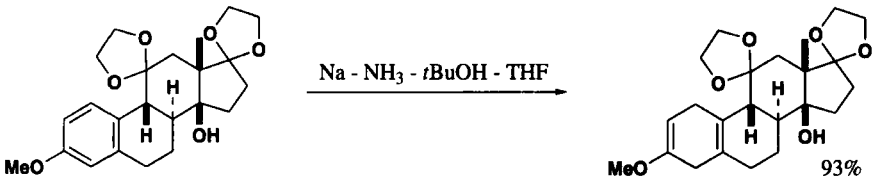
When the Birch reduction is not followed by an acid treatment, ethylene ketal groups present on the molecule remain unchanged.



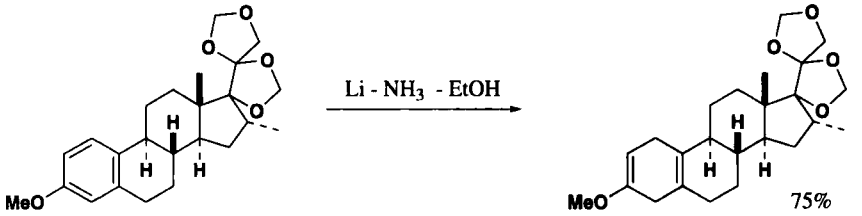
(81)[46]



(82)[77]

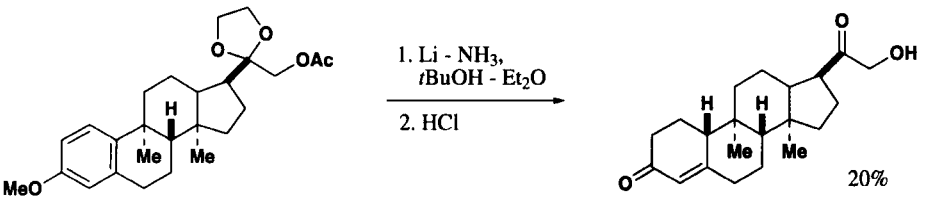


(83)[78]



(84)[79]

Obviously, when an acid hydrolysis is carried out after the Birch reduction, the corresponding ketone is isolated.



(85)[32]

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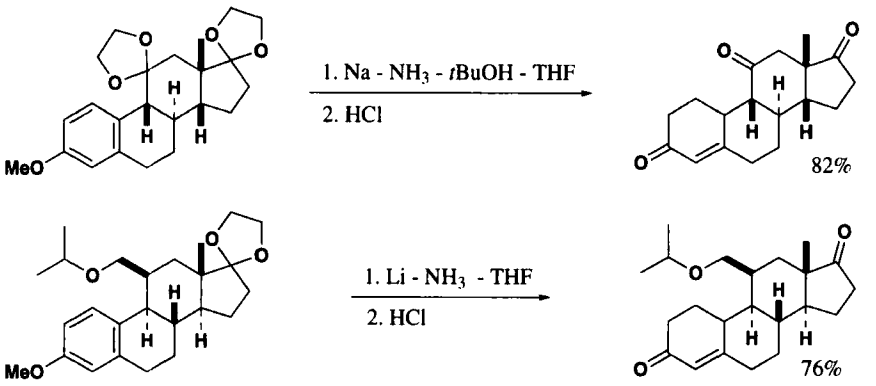
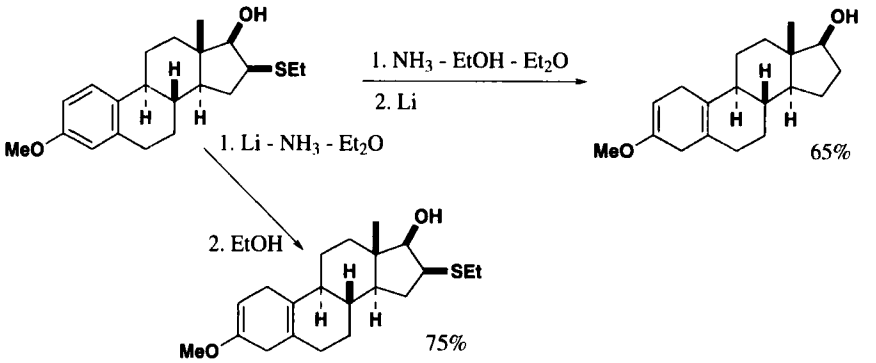


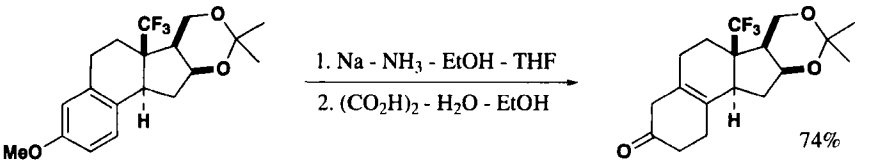
5. Reduction of Thiosteroids

A function such as an alkyl sulfide is normally reduced under the Birch reduction conditions. Thus, Takeda *et al.* reported the Birch reduction of 16β-ethylthioestradiol 3-methyl ether into 1,4-dihydroestradiol 3-methyl ether.[81] However, when the reaction was quenched by adding ethanol within eight minutes after the addition of the ethereal solution of steroid, 16β-ethylthio-derivative was obtained in a good yield. Thus, the reduction of the anisole ring proceeds slightly more rapidly than the reductive cleavage of the C-S bond.



6. Reduction of Halogenated Steroids

Whereas fluorinated steroids[36,37,82] remain unaffected by the Birch conditions, the loss of the chloride atom occurs by hydrogenolysis.[83]



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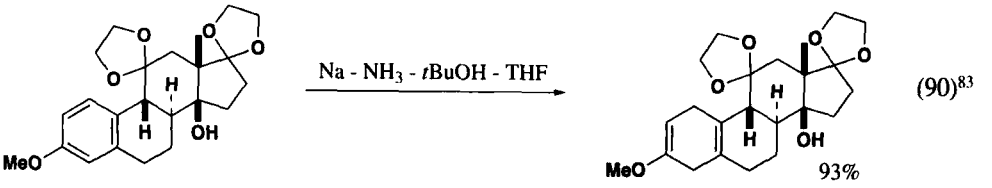
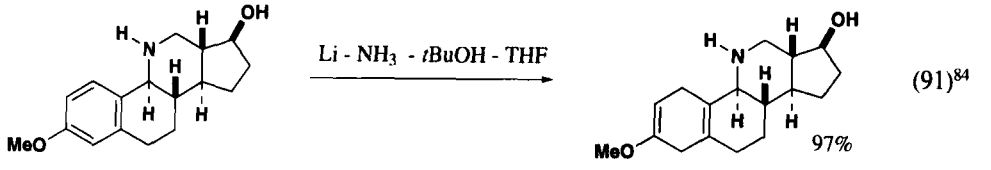


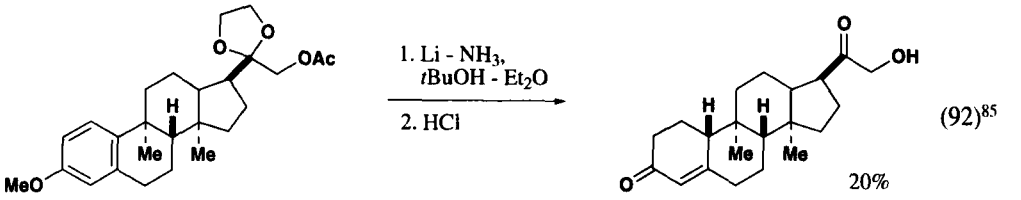
(90)[83]

7. Reduction of Hetero-Steroids

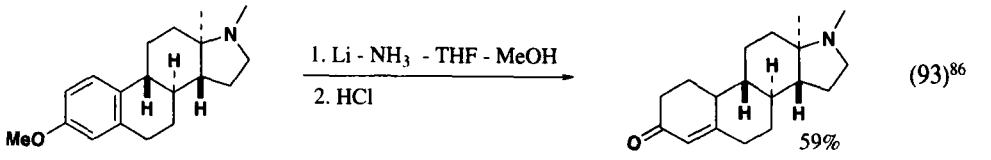
Several examples of Birch reductions involving hetero-steroids are collected below.



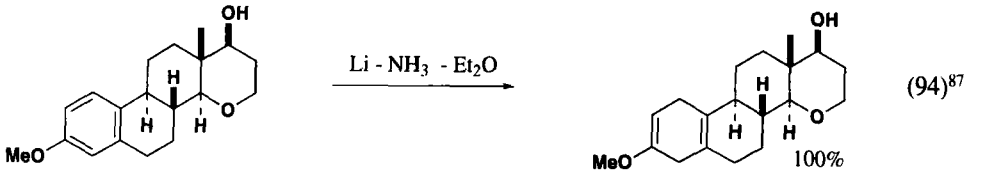
(91)[84]



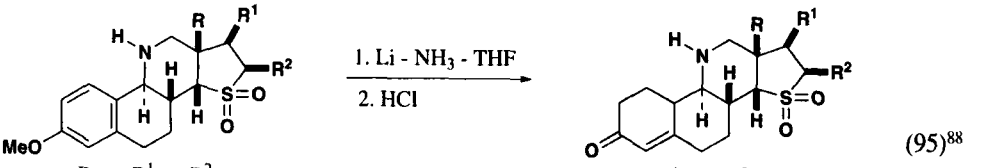
(92)[85]



(93)[86]



(94)[87]



R	R^1	R^2
H	OAc	H
H	H	OAc
Me	OAc	H

R	R^1	R^2	(%)
H	OH	H	73%
H	H	OH	62%
Me	OH	H	58%

(95)[88]

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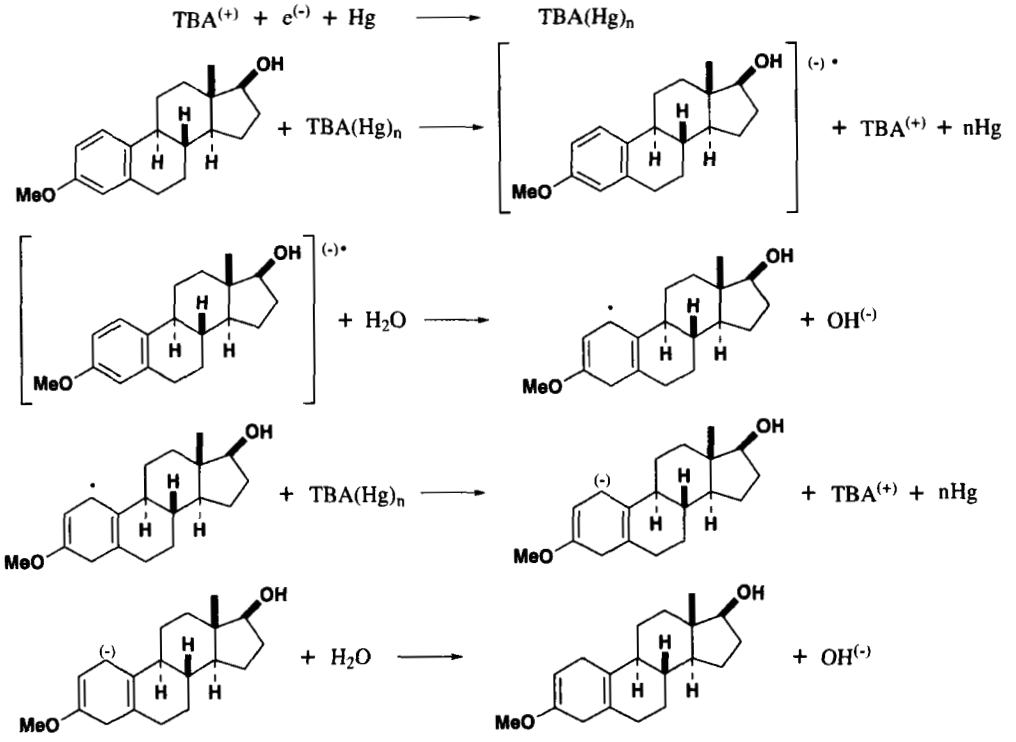
IV. CATHODIC BIRCH REDUCTIONS

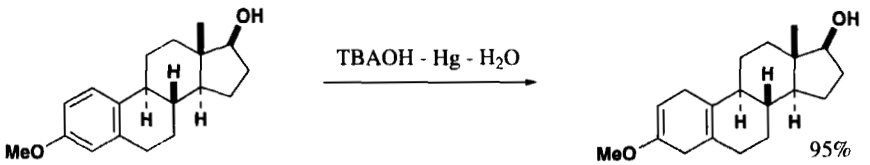
Although the yields of 1,4-dihydroaromatics with the Birch method are often high, the experimental procedure is somewhat tedious, the solutions are strongly basic, and solubility of the reactant in the medium sometimes presents a difficulty. An electrochemical alternative to the Birch reduction (firs reported by Kaiser and co-workers[89] in the case of simple aromatic compounds) using tetraalkylammonium electrolytes, a mercury pool cathode and aqueous solutions has been achieved by Kariv-Miller and his co-workers.[90] The reaction is an indirect electron transfer, since the electrolytic process forms an amalgam, which is consumed in the reduction of the aromatic ring (*Scheme 4*).



Scheme 4

The four last steps of the proposed mechanism are analogues to the Birch reduction, and in effect, an electrogenerated amalgam (first step) takes the place of alkali metal.

The first positive results under these conditions were achieved with β-estradiol 3-methyl ether which was reduced in 95% yield,[90a] similar high yields were obtained under lithium or sodium-ammonia reduction conditions.[12]



(96)[90a]

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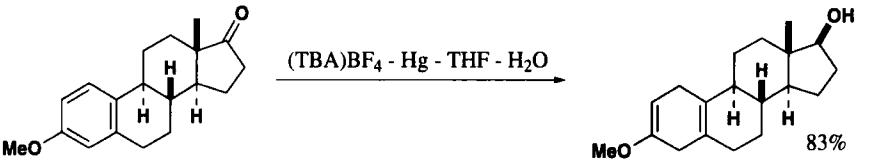
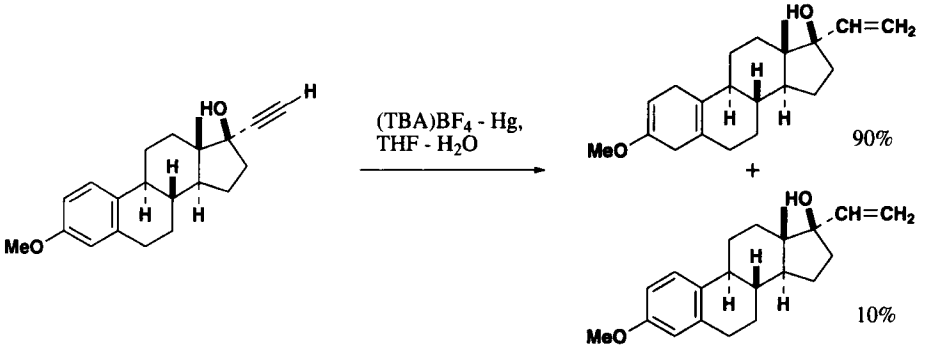
Estrone 3-methyl ether presented an interesting substrate for the electroreduction,[89b] since due to its low solubility, it could not be satisfactorily reduced by the Birch method.[91]



(97)[91]

Under the same conditions, 17α-ethynyl estradiol led to the compound bearing a double bond at position 17α as the major product.[90b]



(98)[90b]

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V. CONCLUSION

This report is an update of the scope and limitations of the Birch reduction of steroids with a view to demonstrating it's selectivity and the possibility for various functional groups to be present or not on the steroid skeleton. This catalogue of examples provides a compelling illustration of the great utility of the Birch reduction developed by Birch six decades ago. This reaction is still one of the most powerful and highly used synthetic procedures. Its success led to the 19-norprogestagens including the first oral contraceptives. It was initially the only process available to prepare them and without it, their development would certainly have been greatly delayed.

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