STUDIES IN THE SYNTHESIS AND BIOLOGICAL PROPERTIES OF CYCLOPROPANE CONTAINING STEROIDS

by

Chwi Wan Wie

A Thesis Submitted to the

Faculty of Graduate Studies and Research

of the University of Manitoba

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ABSTRACT

The studies outlined in this thesis are directed towards the synthesis of cyclopropane and cyclopropanol containing steroids derivatives in order to determine the effect of the cyclopropane structure on the biological properties of the steroid ring system.

The synthesis of cyclopropane containing steroids has been prompted by the character of the cyclopropane structure which is unique in its physical and chemical properties. The epimeric 2β,4β-cyclo-5α-androstane-3α,17β- and 3β,17β-diol 17-acetate have been synthesized from 2α,4α-dibromo-5α-androstane-3α,17β- and 3β,17β-diol 17-acetate, respectively, by an intramolecular 1,3-elimination of bromide with zinc-copper couple in ethanol. Isomerization of the endo- cyclopropanol to the exo-cyclopropanol is shown to occur either with the couple or zinc acetate. The stereochemistry at C-3 of the epimers is established by the p.m.r. spectra of 2β,4β-cyclo-5α-androstane-3α,17β- and 3β,17β-diol diacetate, and further confirmed by solvolysis of 2β, 4β-cyclo-5α-androstane-3α,17β- and 3β,17β-diol 17-acetate 3-tosylate in sodium acetate/acetic acid.

Application of the above synthetic route to the 17β-hydroxy-5α-estran-3-one series gave 2β,4β-cyclo-5α-estrane-3β,17β-diol 17-acetate, isolated as the corresponding diacetate. The 3α-epimer was not obtained. It was shown in the 5α-androstane series that the proportion of cyclopropane to olefin formed by 1,3- as opposed to 1,2-elimination in the debromination step is dependent upon the stereochemical relationship between the C-2/C-4 bromine and the C-3 hydroxyl substituents of the 2α,4α-dibromoalcohols. To further investigate this reaction, di-

and tri- brominated derivatives of 5α-androstane and 5α-estrane were isolated and their structures determined by spectrometric analysis. The low yield of 2β,4β-cyclo-5α-estrane-3β,17β-diol 17-acetate and the lack of the 3α-epimer was attributed to the formation of 2,4-dibromo-alcohols possessing an axial-equatorial relationship between the bromine and alcohol substituents during the bromination and reduction steps.

2α,3-Cyclopropano-5α-androstane-3β,17β-diol has also been synthesized by addition of the Simmons-Smith reagent to 3(2-chloroethoxy)-5α-androst-2-ene-17β-yl acetate followed by cleavage of the resulting 3β(2-chloroethoxy)-2α,3-cyclopropano-5α-androstane-17β-yl acetate with n-butyl lithium. Addition of the Simmons-Smith reagent to several other steroid enol ethers were also investigated. The results are consistent with the greater reactivity of 5-membered over 6-membered ring olefins and the greater reactivity of enol ether over enol acetate towards the reagent.

The first examples of secondary and tertiary steroid cyclopropanol derivatives have been prepared and some biological tests carried out. The secondary cyclosteroid alcohols were prepared by means of a novel 1,3-elimination. Anabolic/androgenic and skin irritancy tests were carried out for the steroid cyclopropanols and their derivatives by standard assay methods. Among these compounds, 2β,4β-cyclo-5α-androstane-3α,17β-diol 17-acetate showed weak antiandrogenic activity. Irritancy tests to determine the potential for co-carcinogenic activity of the cyclopropanol moiety showed no significant effect.

The mass spectra of the epimeric 3-substituted hydroxy- and ethoxy-derivatives of 5,6α-cyclopropano-5α-cholestane have been measured. In

addition to the well-known electron-induced decomposition of substituted cholestane, particular fragment ions appear in all the spectra at m/e 247, 301, and 302; a strong signal at m/e 329 appears in the spectra of the 3β-alcohol and isomeric 3-ethers, whereas in the spectrum of the 3α-alcohol, this ion is much less abundant. The 3α-ether also has a prominent signal at m/e 384 not present in the other spectra. Deuterium labelled compounds were synthesized and mechanisms leading to these fragment ions are suggested and rationalized on the basis of mass spectral data of the unlabelled and deuterium-labelled derivatives. The formation of these characteristic fragment ions have been related to the presence of the cyclopropane ring in the 5,6α-cyclopropano-5α-cholestane derivatives.

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ABBREVIATIONS

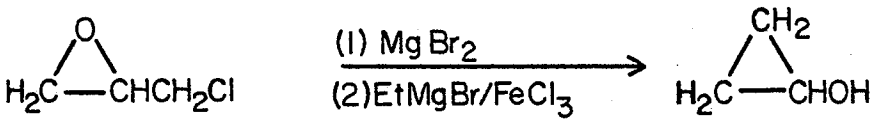
Ac	Acetyl
Bu	Butyl
Et	Ethyl
Me	Methyl
Pr	Propyl
Suc	Succinoyl
THP	Tetrahydropyranyl
TMS	Trimethylsilyl
Ts	p-Toluenesulfonyl
s	Singlet
d	Doublet
t	Triplet
q	Quartet
o	Octet
m	Multiplet
Anab.	Anabolic
Andro.	Androgenic

I. SYNTHESIS AND BIOLOGICAL PROPERTIES OF CYCLOPROPANOL CONTAINING STEROIDS

A. Introduction

The synthesis of cyclopropanol was first discovered accidentally by Magrene and Cottle [1] in 1942 from the reaction of epi-chlorohydrin (1) with magnesium bromide followed by treatment with ethylmagnesium bromide and ferric chloride. Cyclopropanol (2) was obtained in a maximum purity of 87% (Scheme 1). This was the first cyclopropanol isolated.

Scheme 1



1 2

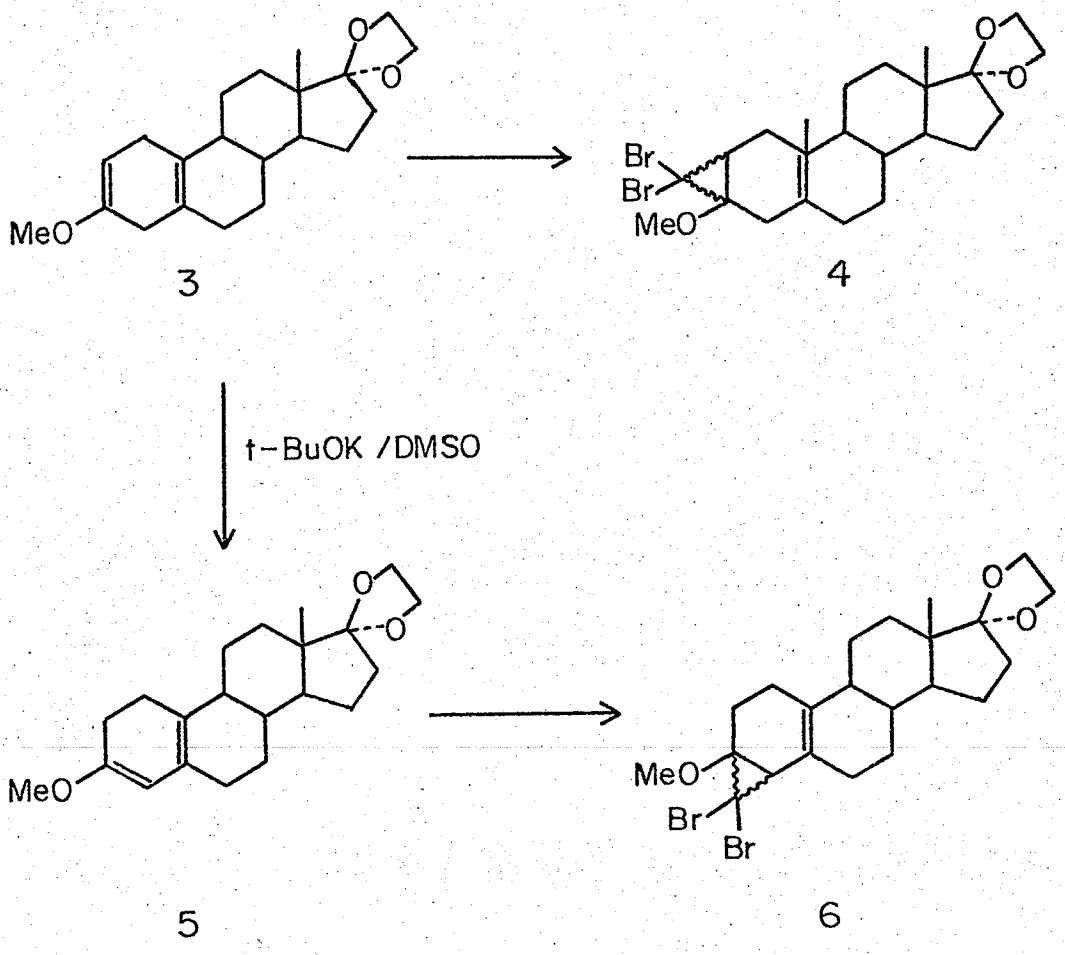
Since then little interest has been taken in this simple molecule and, until the last decade, the chemistry of cyclopropanols has not been extensively investigated. Cyclopropanol chemistry has been reviewed independently by DePuy [2] and Schöllkopf [3] in 1968 and more recently, a review written by Gibson and DePuy [4] has provided a summary of the methods of preparation of simple cyclopropanols. Although a wide variety of methods have been developed to synthesize cyclopropanols and their derivatives, few of them are readily applicable to the synthesis of steroid cyclopropanols. The following methods have been applied to the formation of steroid cyclopropanols and derivatives.

(a) Addition of dihalocarbene/carbene to enol ethers or acetates

Reaction of dihalocarbenes with the double bond carrying the methoxyl group in the 2,3- or 2,5-dihydroanisole derivatives has been

reported by Birch and Graves [5]. Birch, Graves, and Siddall [6] have successfully added dibromocarbene generated from bromoform and potassium tertiary butoxide to the enol ethers of 1,2- and 1,4-dihydroestrone 17-ethylene ketal (3 and 5). This reaction gave mainly the adducts 4 and 6, respectively, with a minor proportion of an adduct involving both double bonds (Scheme 2).

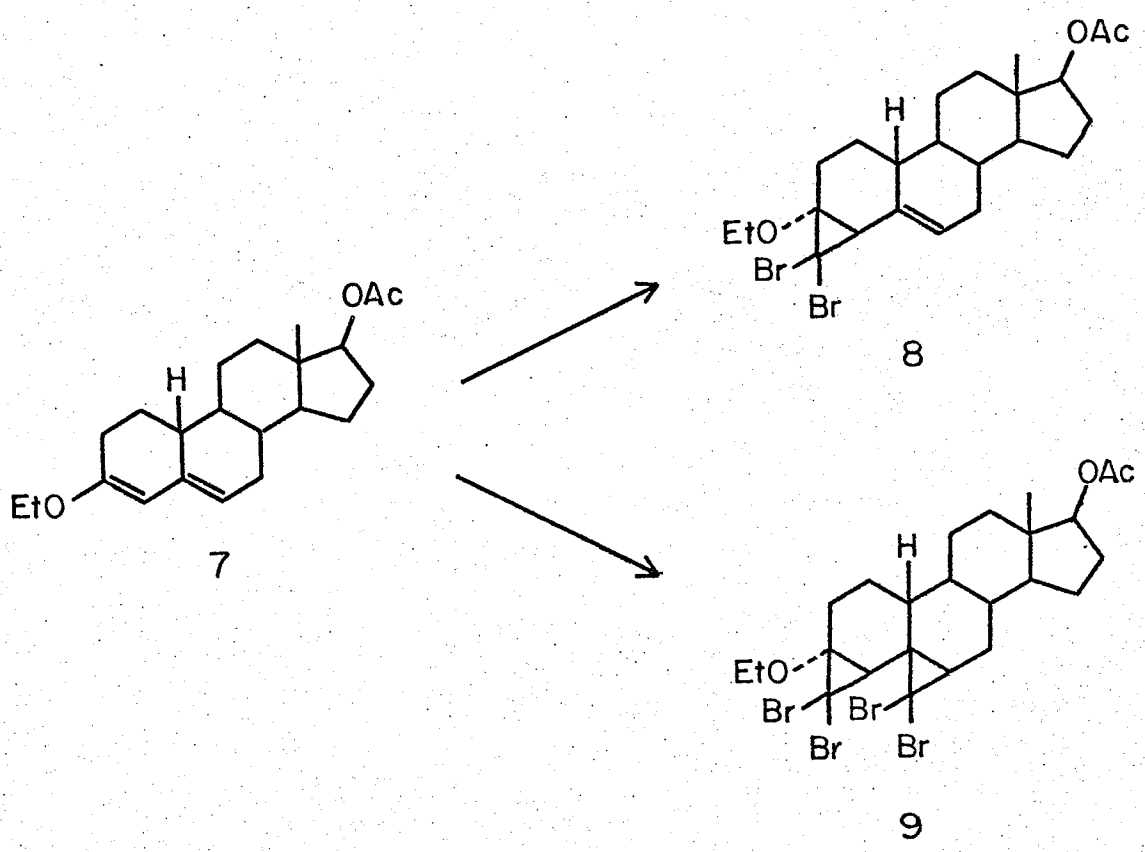
Scheme 2



3 4 5 6

Similarly, Font [7] has reported the reaction of dibromocarbene with 3-ethoxy-estra-3,5-diene-17β-yl acetate (7) to give the mono- and dicyclopropylethyl ether (8 and 9) (Scheme 3).

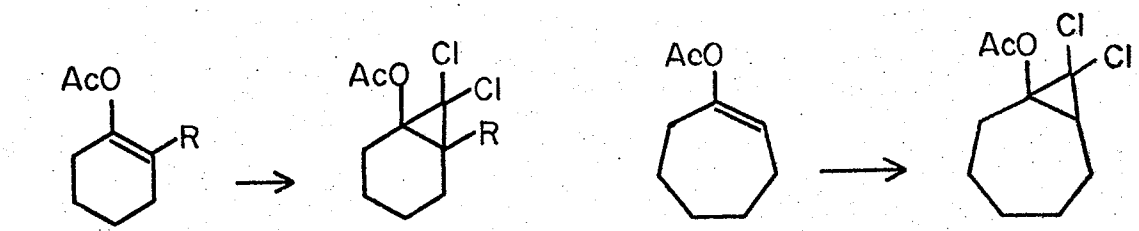
Scheme 3



Stork, Nussim, and August [8] have shown that the enol acetates of cyclohexanone (10a), cycloheptanone (12), and 2-methylcyclohexanone (10b) can be converted to the corresponding dichlorocarbene adducts 11a, 13, and 11b in good yields by heating with phenyl(bromodichloromethyl)mercury in benzene (Scheme 4). Under the same conditions, the 3-acetoxy-5α-cholest-2-ene (14) and the isomeric 3-ene (16) gave the dichlorocarbene adducts 15 and 17 in 83 and 72% yields, respectively (Scheme 5). These substances have not been converted into the corres-

ponding halogen free cyclopropanols.

Scheme 4



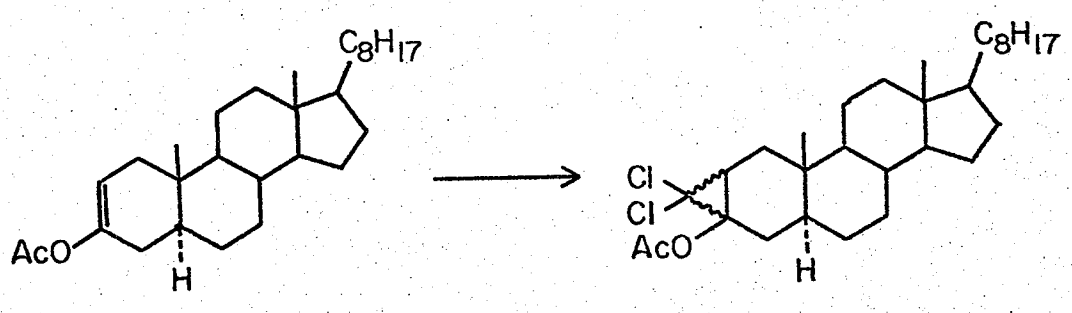
10a, R = H
b, R = CH_3

11a, R = H
b, R = CH_3

12

13

Scheme 5



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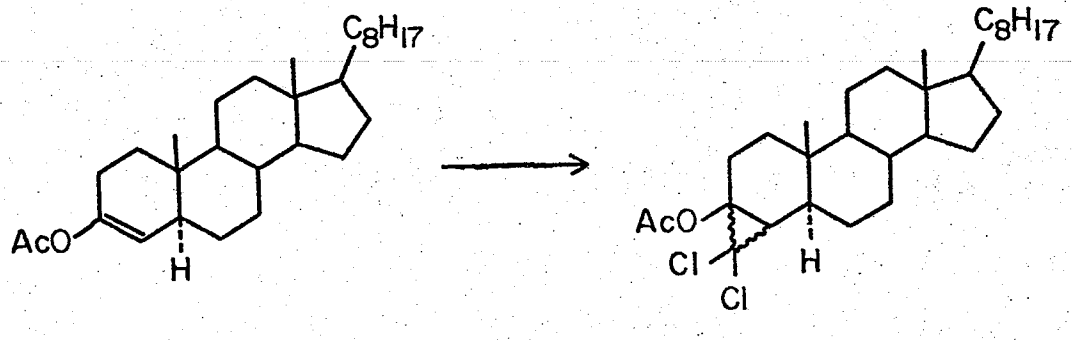

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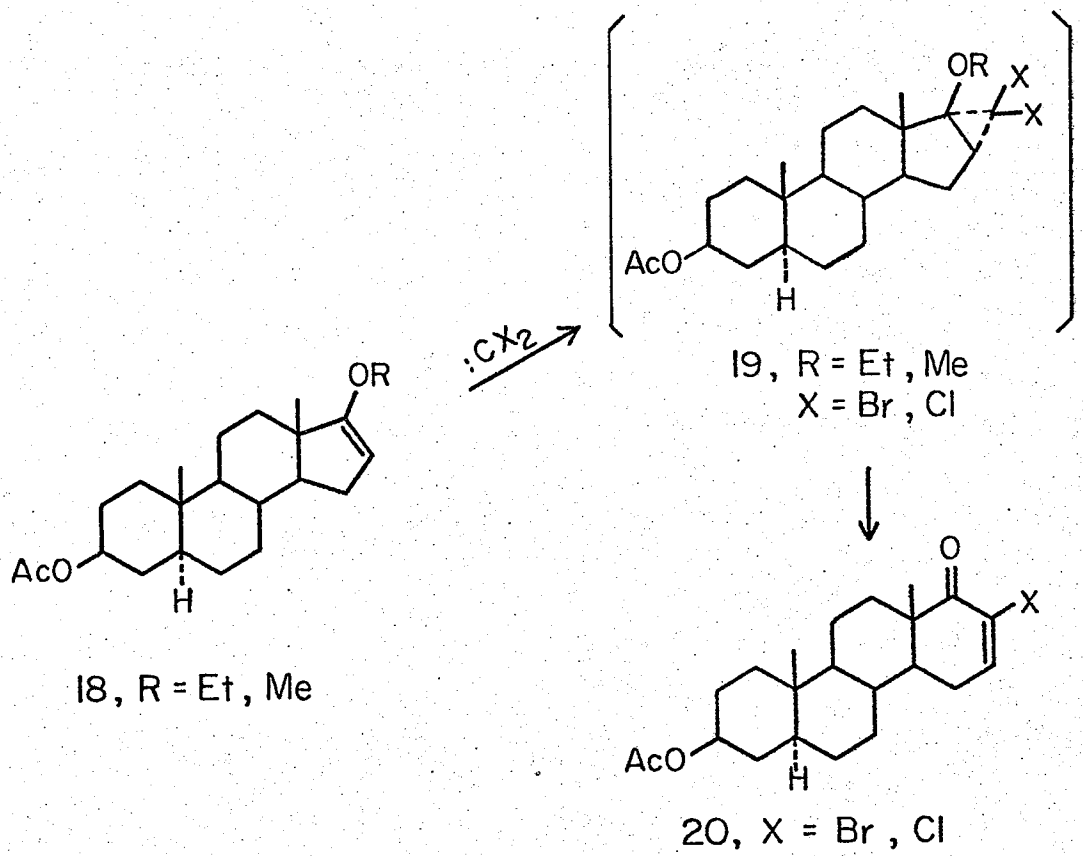
17

Enol ethers of 5α-androstan-17-one (18) add dichloro- and dibromocarbene, but the initially formed dihalocyclopropane derivatives (19) are too unstable for isolation, being rapidly rearranged to give the corresponding 17-halogeno-D-homoandrost-16-en-17a-one (20), as shown by Johns and Salamon [9] (Scheme 6).

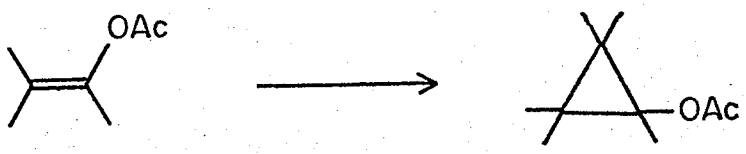
Scheme 6



(b) Methylene addition to enol acetates or ethers

Simmons and Smith [10] who developed the methylenation of olefins with a mixture of zinc-copper couple and diiodomethane have synthesized cyclopropyl acetate (21) by addition of methylene to various vinyl acetates (22) (Scheme 7), but the yields were poor.

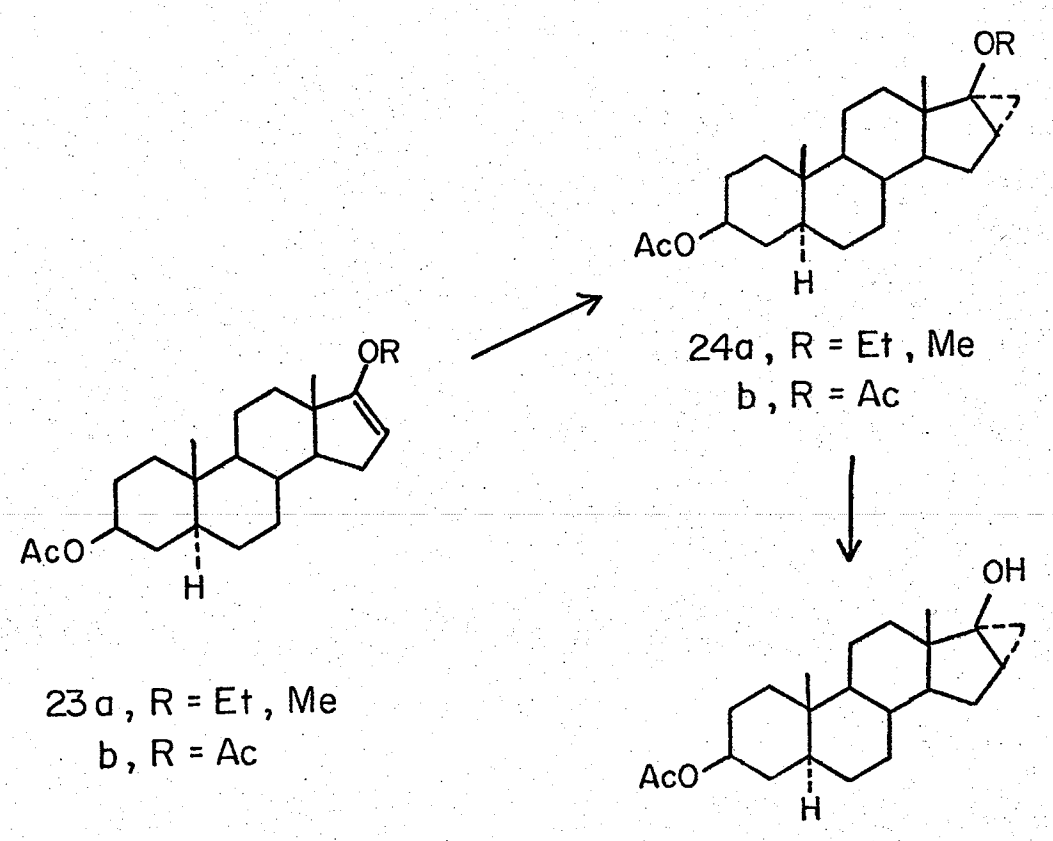
Scheme 7



21 22

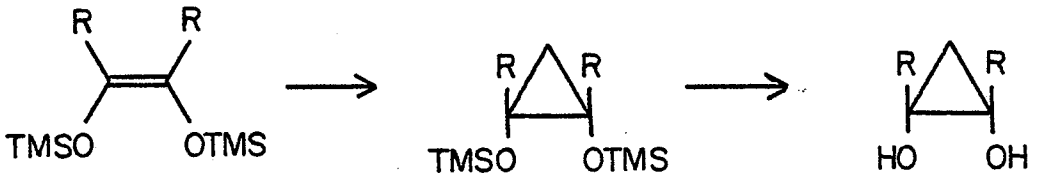
Addition of carbene, using diethylzinc and diiodomethane, to the enol ether (23a) and enol acetate (23b) derivatives of several 17-oxo steroids have been reported by Johns and Salamon [9]. The cyclopropyl acetate (24b) afforded the cyclopropanol (25) with lithium aluminum hydride (Scheme 8).

Scheme 8



This reaction has been applied by Audibrand, LeGoaller, and Arnaud [11] to several trimethylsilylalkenyl ethers (26) to prepare the cyclopropyl ethers (27), which were then converted to the corresponding alcohols (28) with methyllithium (Scheme 9).

Scheme 9



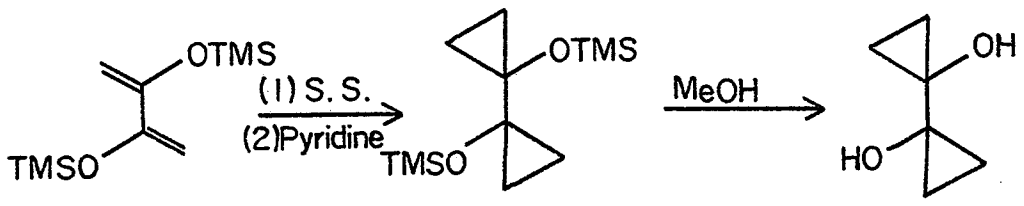
26 27 28

R = Alkyl

This method has later been used by LeGoaller and Pierre [12], Rubottom and Lopez [13], and Murai, Aya, and Sonoda [14] for the synthesis of different types of silyl cyclopropyl ethers and cyclopropanols.

Denis and Conia [15] have introduced a modified Simmons-Smith reaction in which a zinc-silver couple was used instead of the usual zinc-copper couple. They prepared a 1,1'-bicyclopropanol (30) from the bis(trimethyl-siloxy)-2,3-butadiene (29) (Scheme 10).

Scheme 10



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