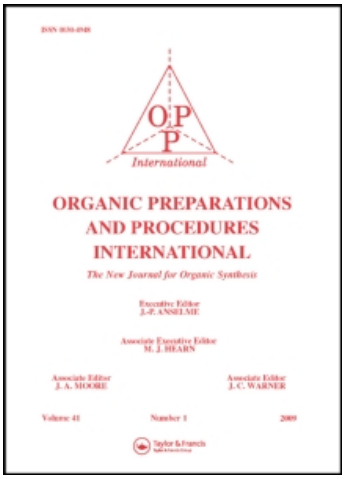

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF MODIFIED STEROIDS IN THE ANDROSTANE AND ANDROSTENE SERIES

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To cite this Article Stéphan, Elie(2006) 'SYNTHESIS OF MODIFIED STEROIDS IN THE ANDROSTANE AND ANDROSTENE SERIES', Organic Preparations and Procedures International, 38: 3, 217 — 305
To link to this Article: DOI: 10.1080/00304940609355990
URL: http://dx.doi.org/10.1080/00304940609355990

ORGANIC PREPARATIONS AND PROCEDURES INT., 38 (2), 217-305 (2006)

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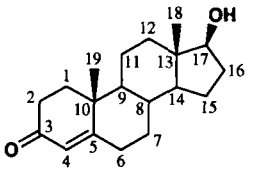
ABBREVIATIONS

Ac, acetyl; AD, androstenedione; ADT, androsterone; epi-ADT, epiandrosterone; AIBN, 2,2'-azobisisobutyronitrile; 9-BBN, 9-borabicyclo[3.3.1]nonane; Bn, benzyl; Bz, benzoyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DAST, diethylaminosulfur trifluoride; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; IBX, 2-iodoxybenzoic acid; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; MCPBA, *m*-chloroperbenzoic acid; NBS, *N*-bromosuccinimide; PCC, pyridinium chlorochromate; T, testosterone; TBAF, tetra-*n*-butylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TFA, trifluoroacetic acid; Tf_2O, triflic anhydride, TMS, trimethylsilyl; THP, tetrahydropyranyl; TsOH, *p*-toluenesulfonic acid

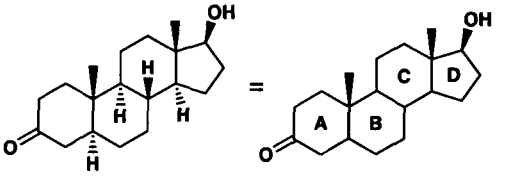
INTRODUCTION

The synthesis of modified steroids is still a field of major interest as attested by several reviews in the recent period. These papers dealed with various particular aspects of steroid's chemistry like transition-metal-catalyzed reactions,[1] synthesis of enantiomeric steroids,[2] glycosylation[3] or 17β-reduction by microorganisms.[4] The present review concerns more generally the synthesis of modified steroids in the androstane and androstene series, the goal being to summarize the most important reports referenced in *Current Contents* during the period 1995-2004. The work published on hetero-steroids (such as *aza*-steroids) will not be treated; we consider also that the chemistry starting from 17-functionalized steroids, with the purpose of preparing branched-chain compounds, in the pregnane or cholestane series for example, is beyond the scope of the review. *Fig. 1* represents typical compounds in the androstane and androstene series. The basic skeleton of these compounds consists of four rings

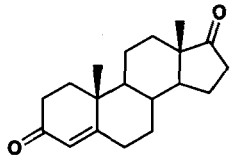
(A to D) with two angular methyl groups at C-10 and C-13 on the β-face. The hydrogens at the stereogenic centers are not represented if their configurations are 5α, 8β, 9α and 14α. This review will examine successively the modifications of the various rings in numbering order.



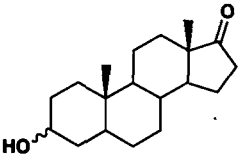
17β-hydroxy-androst-4-ene-3-one or Testosterone (T)



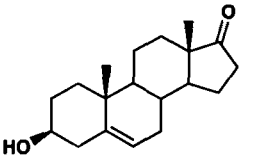
Dihydrotestosterone (DHT)



Androstenedione (AD)



3α-OH : Androsterone (ADT)
3β-OH : epi-ADT



Dehydroepiandrosterone (DHEA)

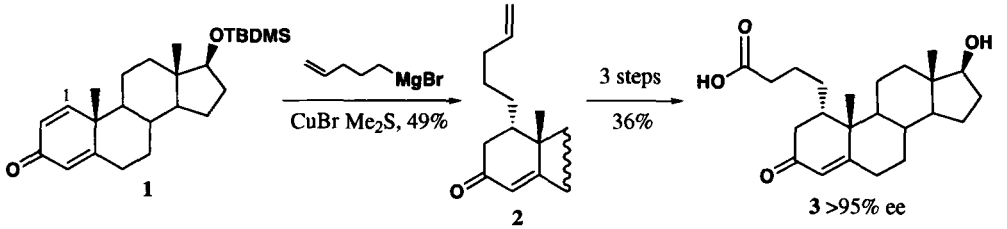
Fig. 1

Testosterone is a well known hormone that is essential for the development of secondary sexual characteristics (voice, hair, body shape ...) and function of the reproductive system in males. Various illnesses result of decreased amounts of testosterone in males or increased levels in females.[5] The substituted androstenediones may be inhibitors of aromatase, an enzyme complex which catalyzes the conversion of androstenedione and testosterone to estrone and estradiol.[6] The interest in synthesizing new modified steroids is directed at modifications of their biological properties. Specific examples are noted within this review.

I. MODIFICATIONS OF RING A

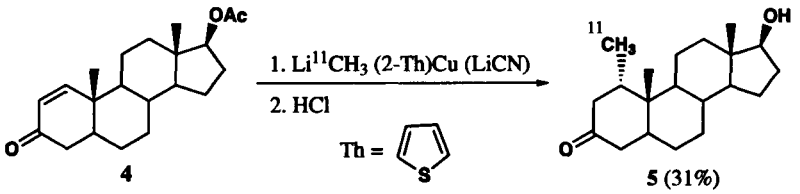
1. 1-Substituted Compounds

1-Substituted steroids were prepared by 1,4-Michael addition of various groups *via* organocuprates or arylaluminum compounds to 1,2-dehydro-3-ketosteroids (or Δ^1-3-ketosteroids). The addition occurred from the sterically less hindered α-face and gave 1α compounds. The synthesis of the 1α-(3'-carboxypropyl)testosterone **3** in 14% overall yield (*Scheme 1*) started from a suitably protected boldenone **1**.[5] Immunogens and tracers were prepared from the acid **3**.



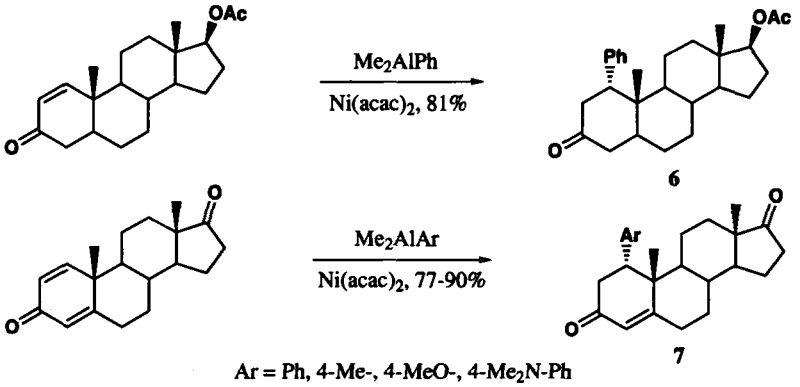
Scheme 1

Conjugate 1,4-addition of labelled cuprates to enone **4** afforded labelled mesterolones **5** (^{11}C and ^{13}C) in low yields (*Scheme 2*).[7] The labelled cuprates were prepared from addition of lithium (2-thienyl)cyanocuprate to a solution of ^{11}C- or ^{13}C-methyllithium. The ^{11}C mesterolone (31% yield) is a potential candidate for Positron Emission Tomography (PET) imaging of the androgen receptor in prostate cancer.



Scheme 2

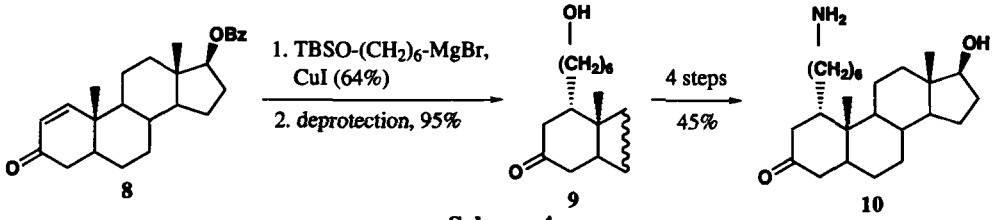
The nickel-catalyzed 1,4-addition of aryldimethylaluminum compounds to 3-oxo-Δ^1- or $\Delta^{1,4}$-steroids gave access to 1α-arylsteroids **6** and **7** in good to high yields (*Scheme 3*), the alanes being prepared by transmetallation of organolithium compounds with dimethylaluminum chloride.[8] The reaction of PhMgBr in the presence of catalytic CuBr yielded only the 1,2-addition products and the yields of the adduct were lower for the reaction with high-order cuprate ArThCuCNLi.



Ar = Ph, 4-Me-, 4-MeO-, 4-Me$_2$N-Ph

Scheme 3

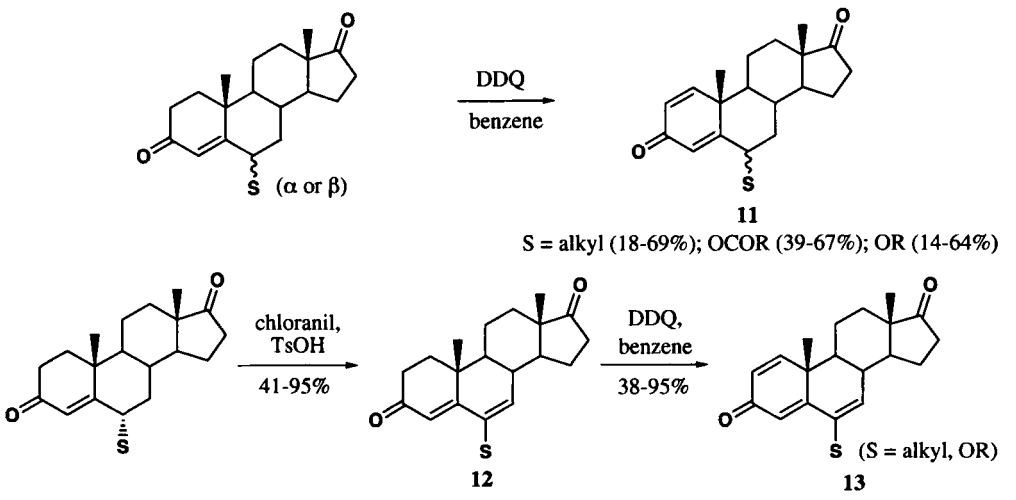
The 1α-aminohexyl-dihydrotestosterone **10** was prepared by 1,4-addition of a cuprate, starting from steroid **8** (*Scheme 4*).[9] Compound **10** showed a high binding affinity to sex hormone – binding globulin.



Scheme 4

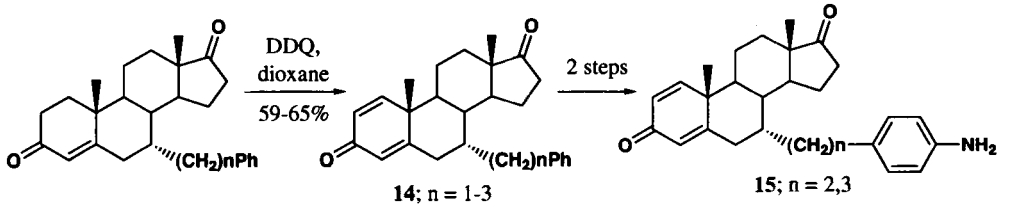
2. 1,2-Dehydrogenation

The dehydrogenation of steroids is frequently performed by oxidation with quinones such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) or chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone). This reaction is not always regioselective and the yields may be low. Several androstadienediones and androstatrienediones, which may be inhibitors of aromatase, were prepared in various yields (*Scheme 5*) by this method such as 6-substituted steroids **11, 12** and **13**.[10-13]



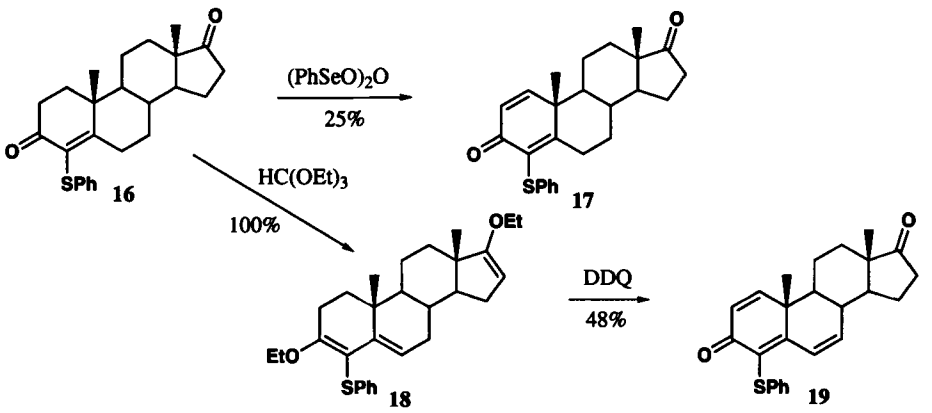
Scheme 5

A series of 7-substituted compounds **14** was prepared in the same way in yields of 59-65%.[14] The aryl rings of the steroids **14** were then nitrated, this reaction resulting in a mixture of *ortho* and *para* isomer with an overall yield of 70-85%, and some *para* compounds were reduced to their corresponding amines **15** in 68-82% yields (*Scheme 6*).



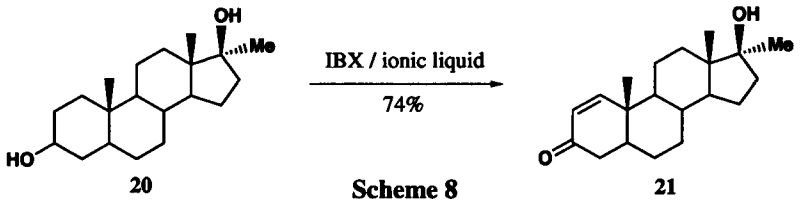
Scheme 6

The dehydrogenation of the steroid **16** was more complex.[15] The oxidation with DDQ gave mixtures and low yields. Barton's procedure[16] (benzeneseleninic anhydride) was therefore used to obtain **17** in 25% yield. The synthesis of androstriene-dione **19** utilized the intermediate enol ether **18**. Treatment of this compound with two equiv. of DDQ resulted in the formation of **19** in moderate yield (*Scheme 7*).



Scheme 7

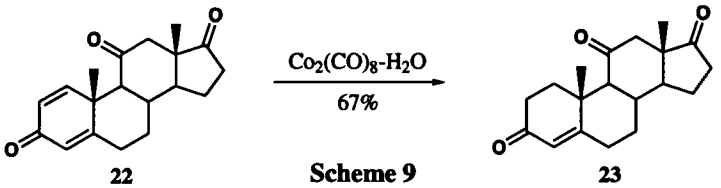
A one-pot synthesis of enone **21** was recently reported *via* 2-iodoxybenzoic acid (IBX)-mediated oxidation of androstane diol **20** either in dimethylsulfoxide (DMSO) at 65°C[17] or in an ionic liquid at room temperature[18] (*Scheme 8*). This environmentally friendly procedure gave 8-10% of the regioisomer 17α-methyl testosterone as by product.



20 **Scheme 8** **21**

3. Selective 1,2-Reduction

A selective reduction of unsaturated carbonyl compounds, using $Co_2(CO)_8$–H_2O has been used to reduce the 1,2-dehydroadrenosterone **22** into steroid **23**.[19] The reducing species are presumed to possess the properties similar to that of $CoH(CO)_4$ and were not reactive towards sterically encumbered enones such as pulegone or carvone. The regioselective 1,2-reduction of **22** point out a greater steric congestion at the 4,5-position (*Scheme 9*).



22 **Scheme 9** **23**

4. 2-Substituted Compounds

2-Substituted steroids were prepared from either 3-keto-4,5-dehydro-steroids or 2-methylene compounds (*Fig. 2*).

The reaction of protected testosterone **24a** with limited amounts of CH_3I and *tert*-BuOK at –60°C gave a mixture of 2α- and 2β-methyl steroids, with minimal formation of the dimethylated product.[20] The 2α- and 2β-androstenediones (ADs) **25** and **26** were respectively obtained from this mixture after deprotection and subsequent Jones oxidation. These methylated ADs were also prepared in low yields *via* hydrogenation (with H_2-tris(triphenylphosphine)rhodium chloride) of the 2-methylene steroid **27** after removal of the 17-silyl group and

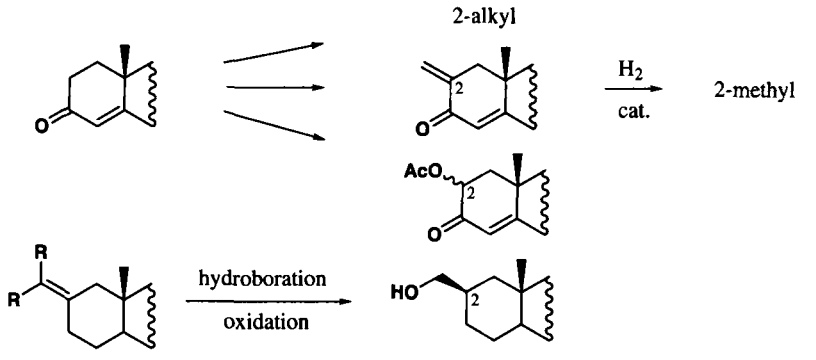
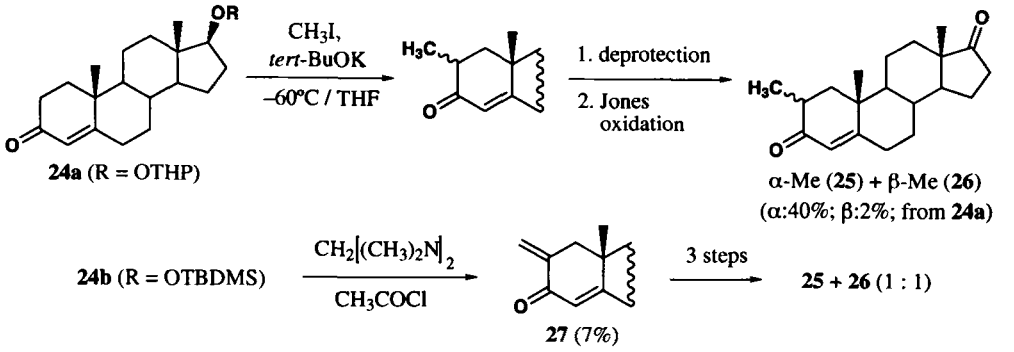


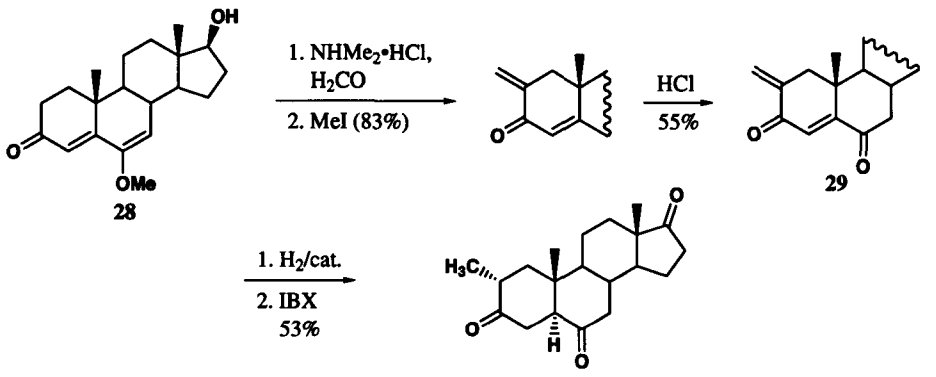
Fig. 2

oxidation (*Scheme 10*). A mixture of 2,2-dimethyl and 2α-methyl-6β,19-epoxy ADs was obtained in moderate yields by methylation of the epoxy analog of **24a**. Treatment of steroid **25** with *N*-bromosuccinimide (NBS) gave 2-methyl-1,4-diene (31%) as well as small amount (6%) of 6α-bromo-2-methyl-1,4-diene while the 6β-bromide was formed in high yield from 2,2-dimethyl AD.[21]



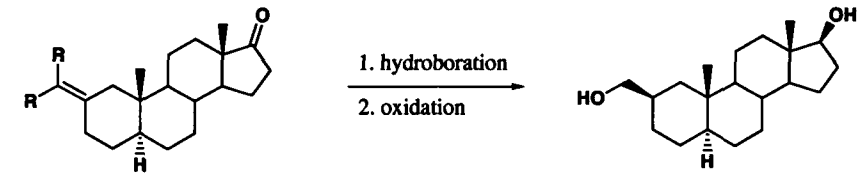
Scheme 10

The synthesis of 2α-methylandrostane-3,6,17-trione **30** was also achieved *via* hydrogenation of a 2-methylene steroid **29**. Steroid **29** was reduced by catalytic hydrogenation (H_2/PtO_2) to give a mixture of keto/hydroxy derivatives that was finally oxidized by IBX to the desired steroid **30** in 53% yield from **29** (*Scheme 11*).[22]



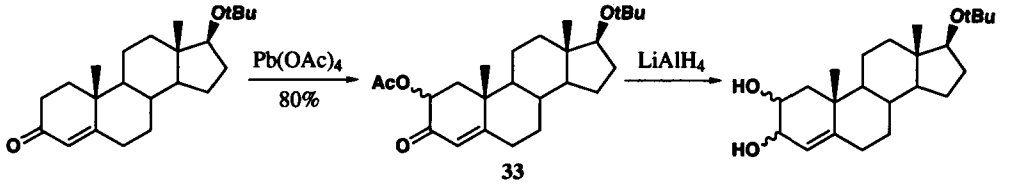
Scheme 11

The 2β-hydroxymethyl steroid **32** was obtained in moderate yield by hydroboration of either 2-methylene- (**31a**) or 2-dihalomethylene-(**31b**) androstanones (*Scheme 12*).[23,24] Steroids **31a,b** were prepared from androstane-2,17-dione and the facial selectivity in the hydroboration was attributed to steric factors.



31a (R = H); **31b** (R = Cl or Br) **Scheme 12** **32** (45-64%)

An epimeric 1:1 mixture of 2-acetoxy derivative **33** was obtained in good yield by lead tetraacetate treatment of a protected testosterone.[25] This mixture was then reduced quantitatively to the corresponding diol, obtained as a diastereoisomeric mixture (*Scheme 13*).

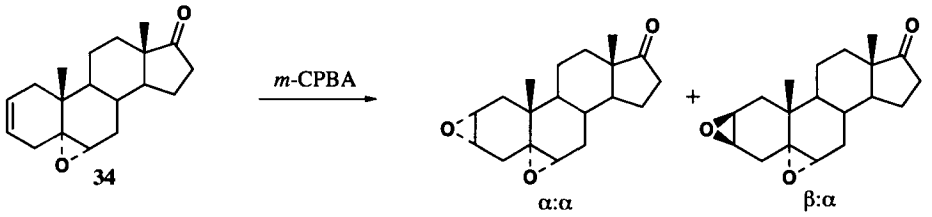


33

Scheme 13

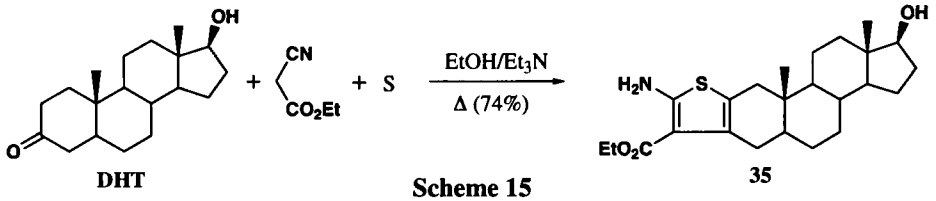
5. 2,3-Functionalization

A transannular directing effect of one androstane epoxide on the stereochemistry of a second epoxidation was reported.[26] Epoxidation of steroid **34** gave a 3/1 mixture of α:α/β:α-diepoxide (yields not given), whereas the epoxidation of androst-2-ene-17-one gave attack on the α-face only (*Scheme 14*).



Scheme 14

A heterofused steroid **35** was obtained in 74% yield by reaction of DHT with ethyl cyanoacetate and elemental sulfur (*Scheme 15*).[27]

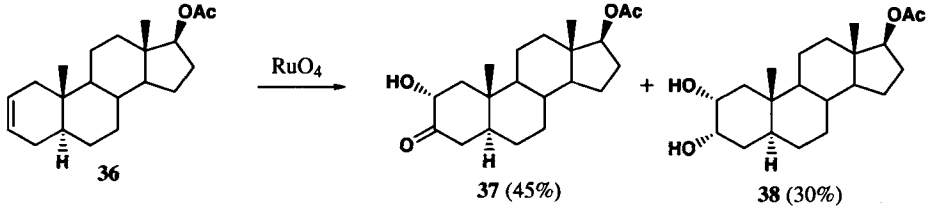


DHT

Scheme 15

35

The oxidation of androstene **36** with RuO_4 (in acetone/water) gave a mixture of 2α-hydroxy-3-ketosteroid **37** and 2α,3α-dihydroxy-compound **38**.[28] A RuO_4 oxidation mechanism, very likely similar to the permanganate oxidation of alkenes was proposed (*Scheme 16*).



36

37 (45%)

38 (30%)

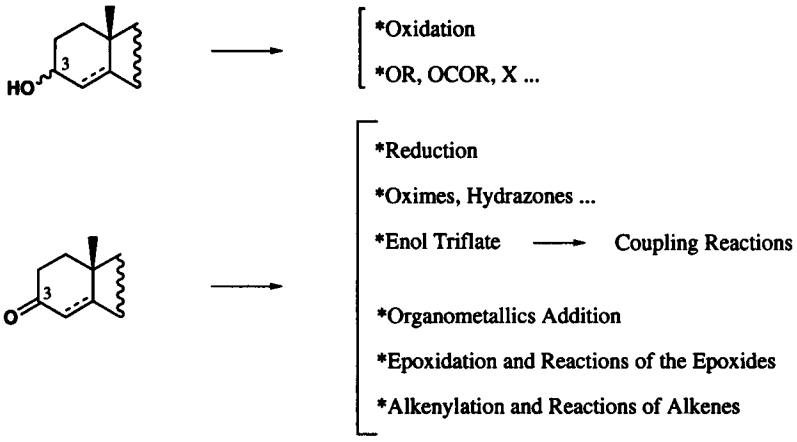
Scheme 16

6. 3-Modified Steroids

The 3-modified steroids were generally prepared from 3-hydroxy- or 3-keto-compounds. The synthesis of the new steroids was therefore based on classical modifications of the starting functions as shown in *Fig. 3*.

a) Redox Reactions

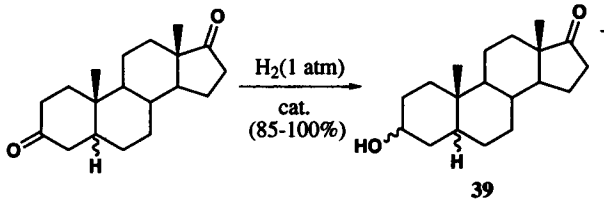
The oxidation of an androstane-diol into a 3-keto-steroid with simultaneous 1,2-dehydrogenation has been previously cited (see *Scheme 8*). The oxidation at C-3 without dehydrogenation was performed with 1.2 equiv of IBX.[17,18] The regioselective hydrogenation of androstane-3,17-dione into 3-hydroxy-androstane-17-one **39** was reported (85-100% yields) using Me_2PPh-stabilized copper(I) hydride[29] or Cu/SiO_2[30] as catalysts. The major product



Access to 3-Modified Steroids

Fig. 3

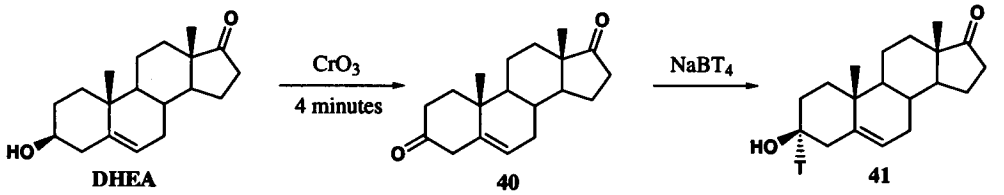
resulted from preferential axial hydride addition for the 5α-epimer in contrast to the preferential formation of the 3α-hydroxysteroid for the 5β-epimer (*Scheme 17*).



epimer	catalyst	3β-OH/3α-OH
5α	$[(Me_2PPh)\ CuH]_6$	6/1
5α	Cu/SiO_2	3/1
5β	$[(Me_2PPh)\ CuH]_6$	1/2.5

Scheme 17

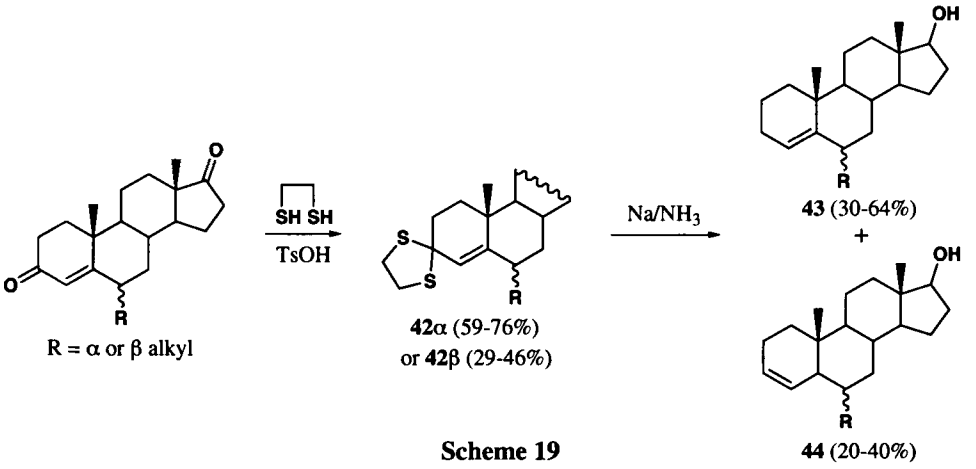
A synthesis of (3α-T)-dehydroepiandrosterone(DHEA) **41** was described,[31] based on the selective reduction of a 3-keto-5-ene intermediate **40** with tritiated sodium borohydride. The concomitant formation of testosterone was a result of some reduction at the 17-carbonyl, accompanied by an isomerisation of the 5,6 double bond to the 4,5-position (*Scheme 18*).



Scheme 18

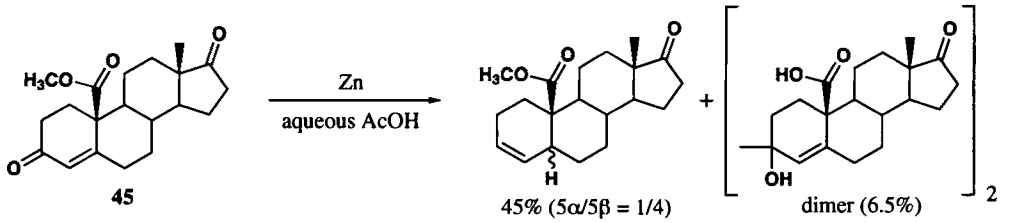
The reduction of the steroid 4-ene-3-one into 3- or 4-ene has been reported by three different methods. The desulfurization of dithioacetals with Na-liquid NH_3 was used to prepare 6-alkylandrostanes (*Scheme 19*).[32] Treatment of 6α- or 6β-alkylated AD with ethane-

1,2-dithiol gave the dithioacetals **42** in moderate yields. The relatively low yields of the 6β-alkyl steroids **42β** was due to partial epimerization of the axial alkyl group to the thermodynamically more stable 6α-isomer. Desulfurization of the thioacetals yielded 4-ene 17β-ols **43** in 30-64% yields. Production of their 3-ene isomer **44** (20-40% yields) was observed in the reaction with the **42α** steroids. Oxidation of the 17-ols **43** and **44** with Jones reagent yielded the corresponding 17-ones in 80-95% yields.



Scheme 19

The reduction of the steroid **45** with zinc in acetic acid gave a mixture of the isomeric 5α- and 5β-enes (45% global yield), together with a dimeric steroid (*Scheme 20*).[33]

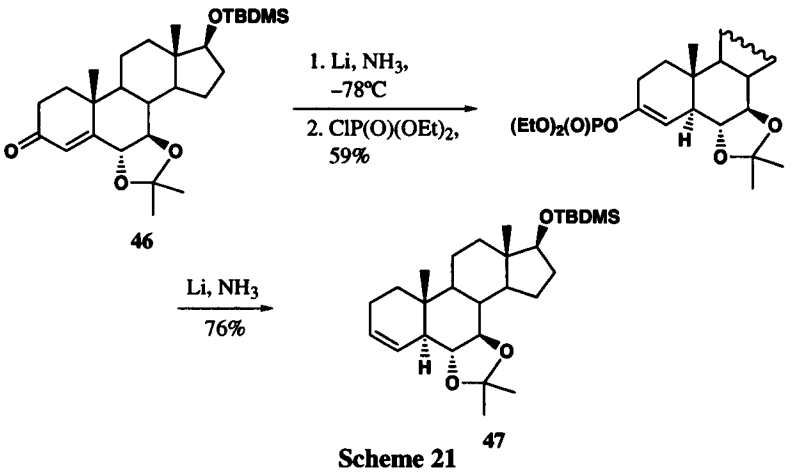


Scheme 20

Another methodology was used within the synthesis of a polyhydroxysteroid.[34] The reduction of **46** with lithium in NH_3-THF followed by trapping of the resultant enolate anion with diethyl chlorophosphate provided an alkenyl phosphate that was subjected to reduction with lithium in ammonia to afford the androstene **47** (*Scheme 21*).

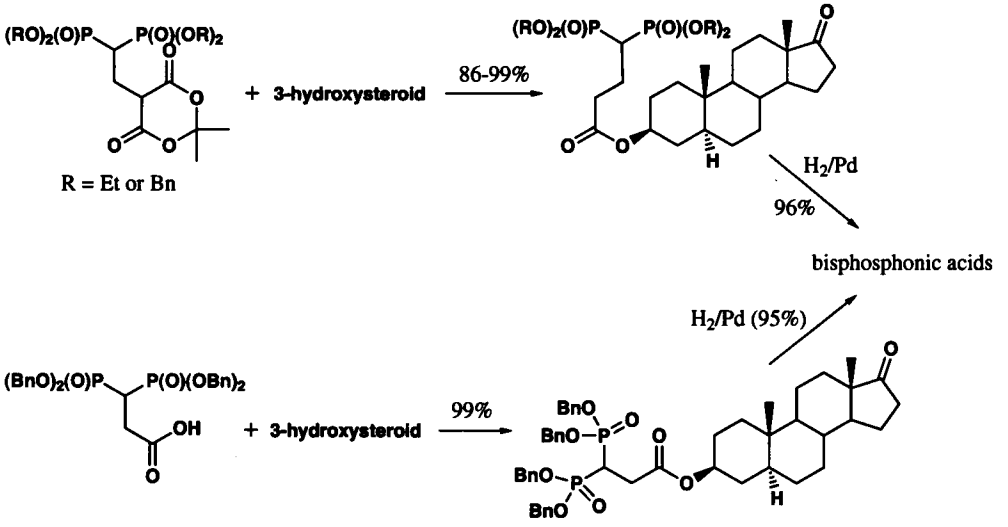
b) 3-Modified Compounds from 3-Hydroxysteroids

3-Hydroxysteroids have been transformed into esters, ethers, halo derivatives, etc. The glycosylation of steroids has been reviewed recently[3] and the methods used for the reactions of the relatively unreactive hydroxyl group at C-3 are well documented in this paper.



Scheme 21

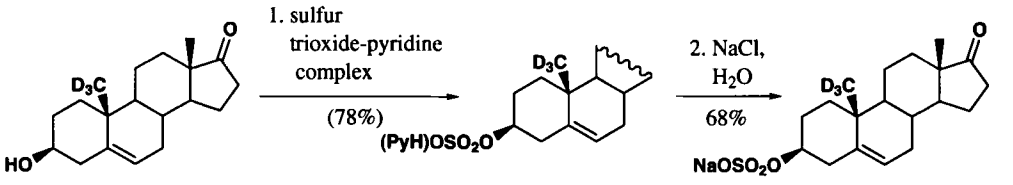
Steroidal amidoesters have been prepared by esterification of C-3 hydroxylic group with 4-N,N-*bis*(2-chloroethyl)aminobenzoic anhydride to evaluate their cytotoxic effect.[35] The sulfamoylation at the 3β-OH of dehydroepiandrosterone (DHEA) or of an androstene-3,17-diol gave sulfamates in good yields.[36] *bis*(Phosphonic acid)-steroid conjugates, which are potential bone resorption inhibitors, were synthesized in high yields by esterification or trans-esterification of 3-hydroxysteroids such as epi-ADT (*Scheme 22*).[37]



Scheme 22

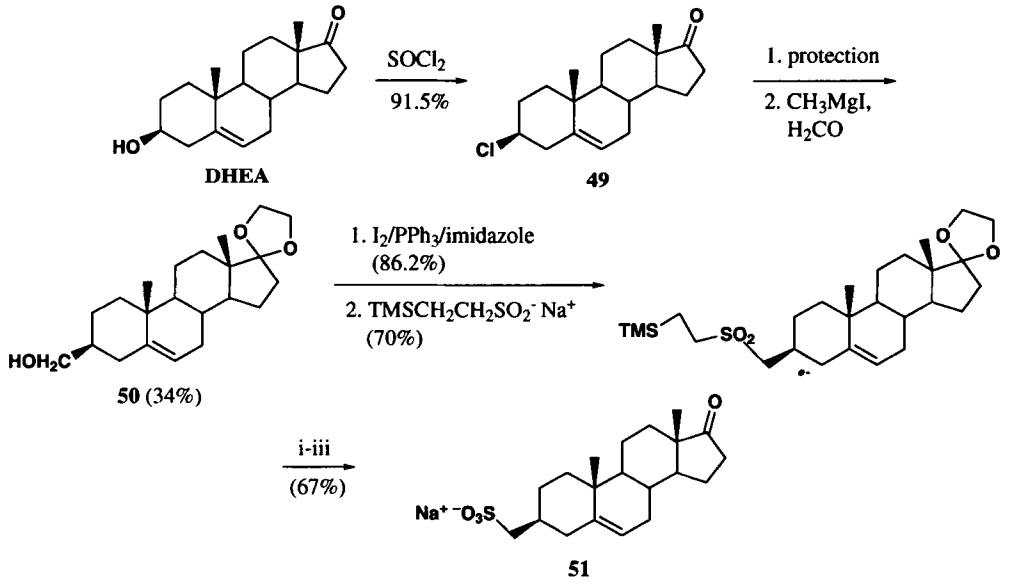
An UDP-glucoronosyltransferase (UGT; UDP, uridine-5'-diphosphate) trisubstrate analogue containing a methylene acetal-linked androsterone unit was prepared from a 3α-hydroxy-androstane-17-one *via* the methylthiomethyl derivative.[38] A sulfate of (19-D_3)-DHEA

48 was prepared in good yield by the reaction of the former steroid with sulfur(VI) oxide-pyridine complex followed by transformation of the resulting pyridinium salt into sodium salt (*Scheme 23*).[39]



DHEA 19-D_3 **Scheme 23** **48**

Sodium androst-5-ene-17-one-3β-methylene sulfonate **51** was synthesized in 6 steps from DHEA.[40] Treament of DHEA with excess $SOCl_2$ yielded chloride **49** in high yield. Transformation of the chloride to the Grignard reagent and reaction with paraformaldehyde afforded the alcohol **50** in 34% yield from **49**. This alcohol was then successively transformed in good yields into iodide, sulfone and methylene sulfonate **51** (*Scheme 24*).



DHEA **49**

50 (34%)

51

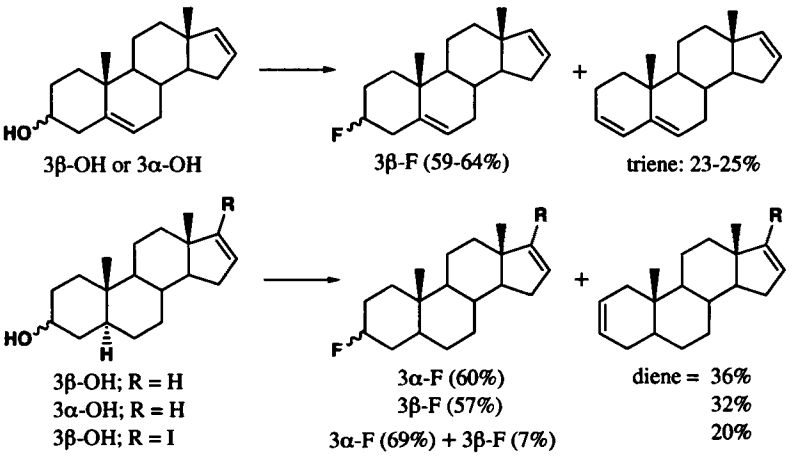
i) CsF/DMF; ii) HCl; iii) NaCl

Scheme 24

The preparation of 3-fluorosteroids was achieved by reaction of 3β- or 3α-hydroxysteroids with *n*-perfluorobutanesulfonyl fluoride in the presence of 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) at 0-5°C.[41] Inversion of configuration was evident in the major product, except for the 5,6-dehydro-3β-sterol for which retention predominated. This reaction depends upon the temperature, elimination being favored at 25°C (*Scheme 25*).

The regioselective acetylation and deacetylation of steroids compounds has been studied by several authors. The deacetylation of the four isomers of **52** was performed on alka-

line alumina, by using a microvawe oven.[42] After deacetylation of the primary acetoxy group, the rate of deacetylation depends of the configuration at C-16 and C-17. The 3-acetoxy group react faster only for *trans* 16,17-isomers since the 17-acetoxy group is sterically hindered by the 18-methyl group. When the functional groups at C-16 and C-17 are in the *cis* orientation, cyclic orthoesters are formed, transformed further on alumina to yield 3-acetates.



Scheme 25

The lipase-catalysed deacetylation of **53** was also reported.[43,44] The 16-acetoxy group was removed regioselectively by used of the lipase from *Candida antarctica* whereas the 3-acetoxy group was removed using *Candida cylindracea or Candida rugosa* (*Fig. 4*).

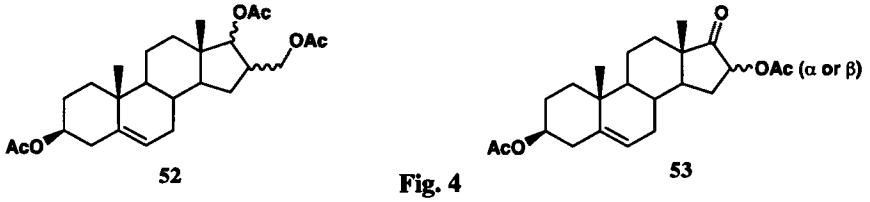
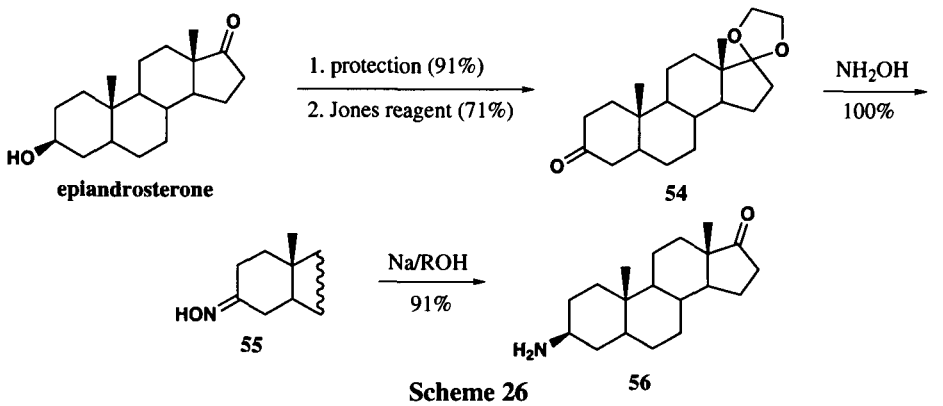


Fig. 4

c) 3-Nitrogen Derivatives

A 3β-aminosteroid **56** was obtained in four steps from epiandrosterone *via* oxime.[45] Oxime **55** was reduced with sodium in 2-propanol to produce the 3β-amine **56** in good yield (*Scheme 26*).

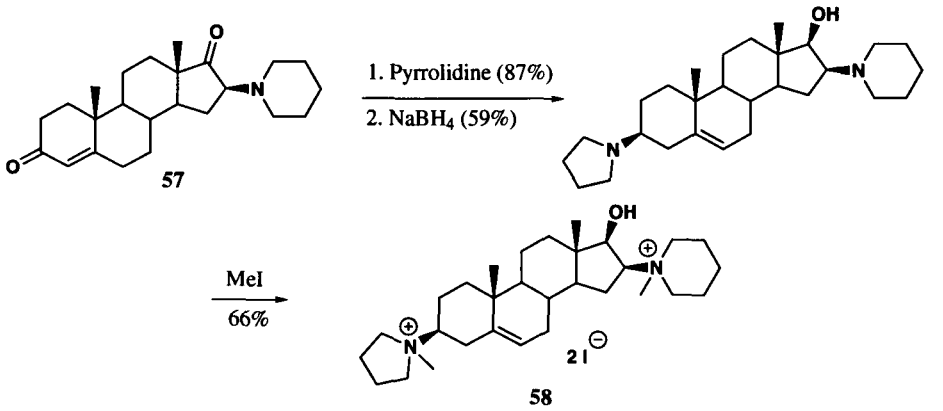
Various steroidal 3-oxime ether derivatives have also been synthesized starting from testosterone acetate or 17α-substituted testosterones.[46] The 3-ketosteroids were first subjected to oximation and the oximes were then alkylated by various alkylaminoethyl halides. The E configuration was reported for all derivatives.



epiandrosterone 54 55 56

Scheme 26

A bisquaternary ammonium steroid **58** was prepared in good yield from the 3-oxo-4-ene-16-piperidino steroid **57**. The enone was converted into enamine that was reduced to a 3β-pyrrolidino derivative followed by quaternization with methyl iodide to give **58** (*Scheme 27*).[47]

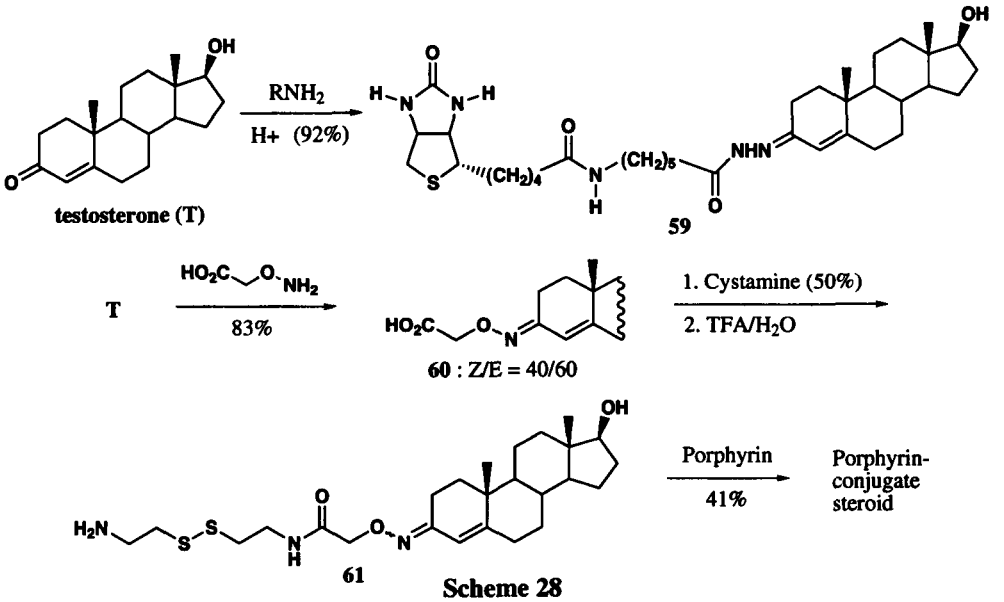


57 58

Scheme 27

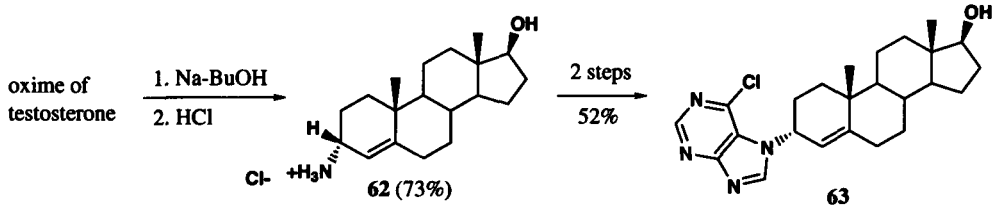
A hydrazone formation has been used to prepare a 3-biotinylated testosterone **59**, with the goal of obtaining a mimic ligand binding (*Scheme 28*). The NMR data do not distinguish between *syn*- or *anti*-configuration.[48] A porphyrin-steroid conjugate was synthesized from testosterone in order to get a semi-synthetic catalytic antibody (*Scheme 28*).[49] Testosterone was reacted with carboxymethoxylamine to give a mixture of Z- and E-isomers of 3-oximino **60** in 83% yield. This acid **60** was then coupled with a N-protected cystamine followed by deprotection to afford the 3-substituted steroid **61**. Finally, **61** reacted with a diacid porphyrin to give the target compound.

A 3-biotinylated 4-androstene-3,17-dione tracer was also prepared from 3-carboxymethyloxime AD by acylation of the biotinyl moiety.[50] A mixture of the two amino



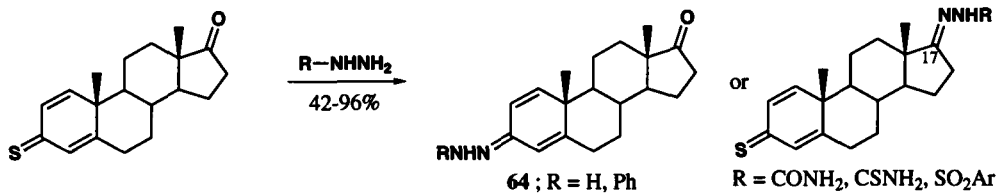
Scheme 28

epimers of C-3 was obtained by reduction of the oxime of testosterone, from which the 3α-aminosteroid **62** was crystallized in good yield.[51] Nucleobase-coupled steroids were then prepared from this amino compound (*e. g.* **63**, *Scheme 29*).



Scheme 29

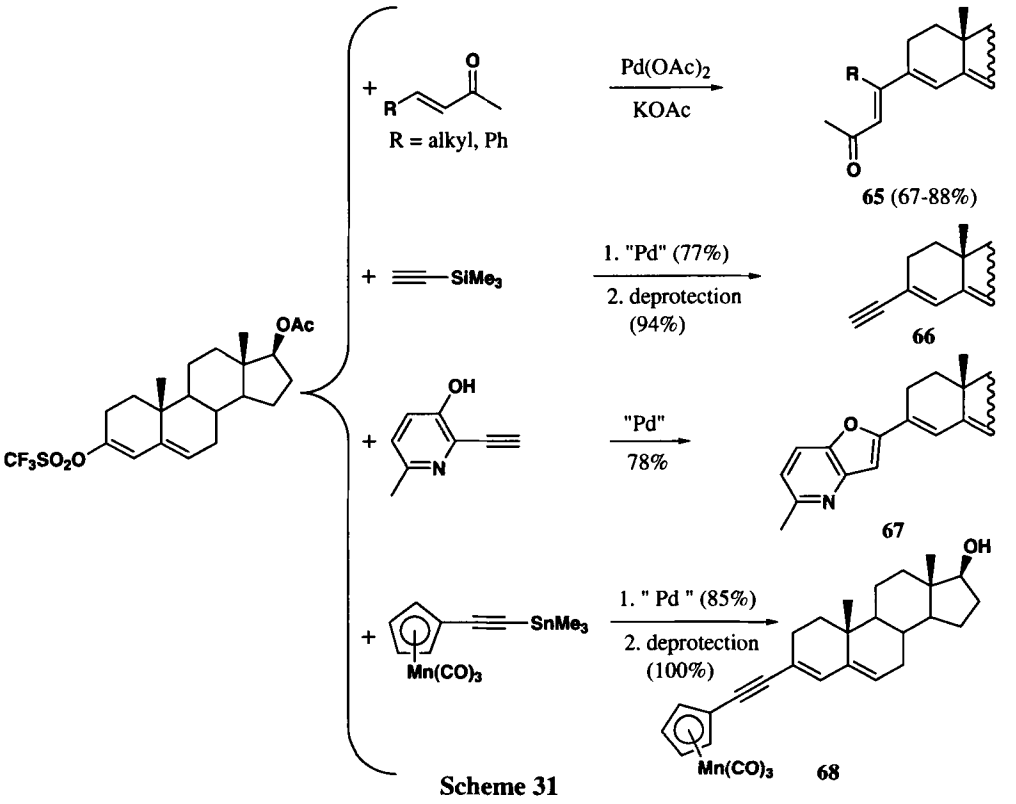
A regiospecific synthesis of androsta-1,4-diene-3,17-dione 3-hydrazones **64** (59-93% yields) from 3-thionocompounds was described.[52] Due to the high reactivity of the thiono group, nucleophilic attack at position 3 was favored over position 17. More drastic conditions yielded the 3,17-*bis*(hydrazones). However, other N-nucleophiles are more reactive toward position 17 (*Scheme 30*).



Scheme 30

d) Palladium-Catalyzed Reactions

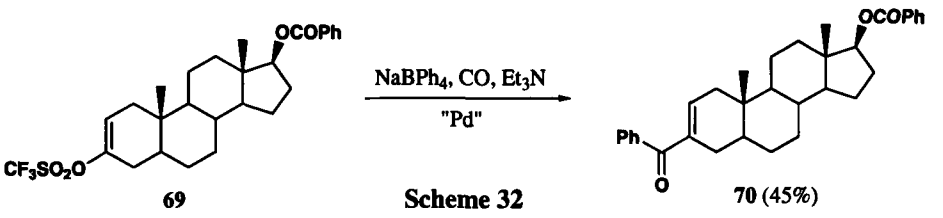
The palladium-catalyzed coupling has been used to attach fluorescent or enzymatic labels to the 17β-acetoxy-DHT *via* the derived enol triflate under standard conditions.[53] The enol triflate of 17β-acetoxytestosterone reacted with α,β-unsaturated carbonyl compounds in presence of $Pd(OAc)_2$ and an excess of KOAc (Heck reaction). The coupling was highly regioselective, the products **65** being formed in 67-88% yields *via* preferential attack at the β carbon of the olefin (*Scheme 31*).[54] The steroidal alkyne **66** was synthesized in high yield by



Scheme 31

desilylation of the coupling product of the same enol triflate with trimethylsilylacetylene (*Scheme 31*).[55] 2-Ethynyl-3-pyridinols gave 2-substituted furopyridines (*e. g.* **67**) by treatment with vinyl triflates through a coupling/cyclization process in presence of palladium catalysts.[56] The Stille coupling was used to introduce a metallocarbonyl marker in steroid starting from the same triflate.[57] The enol triflate reacted with a trimethyltin ethynylcyclopentadienyl-manganesetricarbonyl compound to afford an organometallic derivative of testosterone **68** after deprotection (*Scheme 31*).

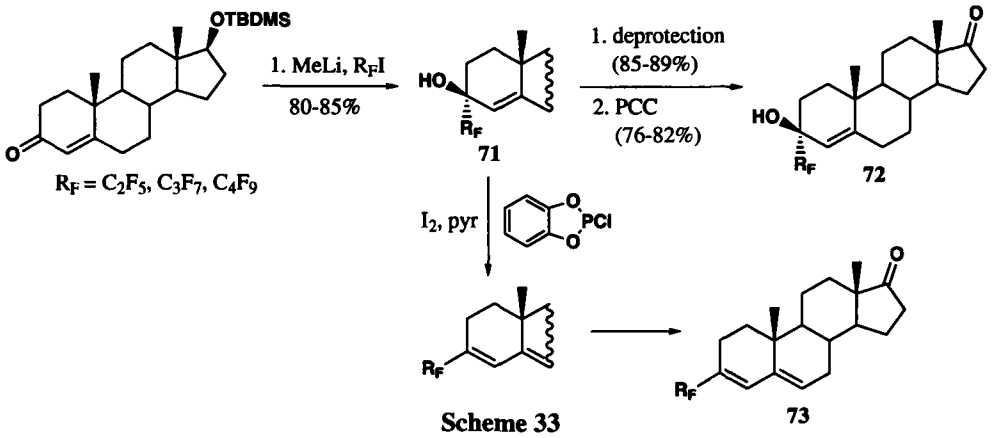
A palladium-catalyzed carbonylation reaction was reported to afford steroidal phenyl ketones.[58] The enol triflate **69** was converted to ketone **70** in moderate yield (*Scheme 32*).



69 **Scheme 32** **70** (45%)

e) Organometallic Additions to 3-Ketosteroids

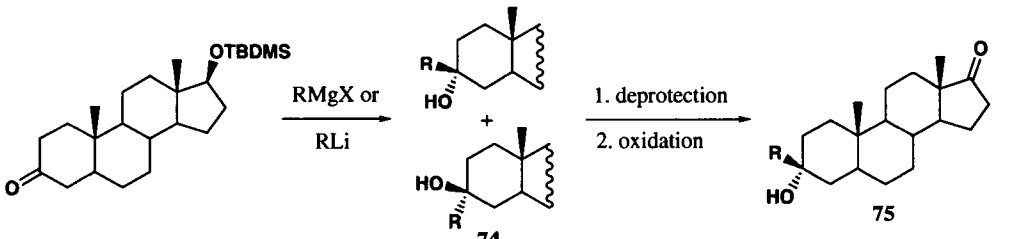
The perfluorinated organometallic reagents (R_FLi) were added to 17β-O-TBDMS testosterone to afford stereospecifically a first series of 3β-hydroxy-steroids **71** (80-85% yields), which were then deprotected and oxidized in good yields at the 17 position into steroids **72** (*Scheme 33*). Steroids **71** were also dehydrated, by a new method using 1,2-phenylene phosphorochloridite and iodine with pyridine in CH_2Cl_2, to produce the 3,5 dienes **73** in 77-86% yields. The double bond of compounds **71** was isomerized followed by deprotection and oxidation to afford 5-ene isomers of **72** in good yields.[59]



Scheme 33

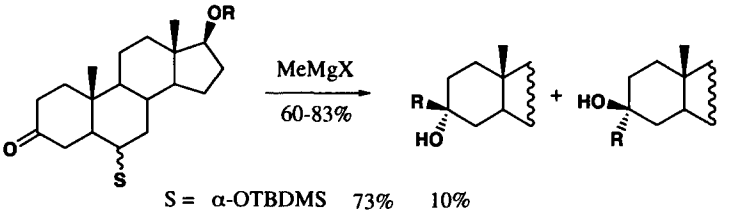
The addition of organometallic reagents to a protected DHT (37-88% yields) was used to prepare a series of androsterone derivatives **74**. Generally, a mixture of the two stereoisomers at position 3 were obtained, the proportion varying according to the nature of the alkyl group: attack of Grignard reagents with a saturated alkyl group proceeded preferentially through the equatorial attack while vinyl-, allyl-, phenyl- and benzylmagnesium bromide occurred preferentially through the axial attack. 3β-R Steroids **74**, separated by flash chromatography, were then converted into androsterones **75** (*Scheme 34*).[60,61]

The stereochemistry of Grignard reagents attack at C-3 is influenced by the presence of substituents at C-6 (*Scheme 35*).[62] The proportion of equatorial attack was increased by the presence of a bulky substituent on the α-side (6α-OTBDMS) while reduced in the presence of a flattened carbonyl group.



OH ax / OH eq = 40/60 to 87/13
R = alkyl, vinyl, phenyl, allyl, benzyle
yields = 37 to 88%

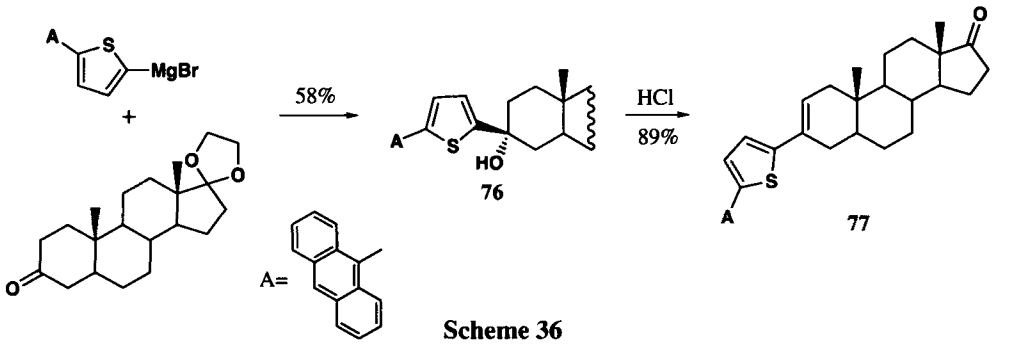
Scheme 34



S =	α-OTBDMS	73%	10%
S =	=O	32%	45%
S =	H	65	35 (relative %, ref. 60)

Scheme 35

The 3α-hydroxysteroid **76** was prepared in moderate yield by addition of an excess of Grignard reagent to a 17-protected androstane-3,17-dione. The regioselective elimination of water occurred with simultaneous removal of the acetal group to afford steroid **77** (*Scheme 36*).[63] The reaction of Grignard reagent with ketosteroid under acidic work-up led directly to **77**.

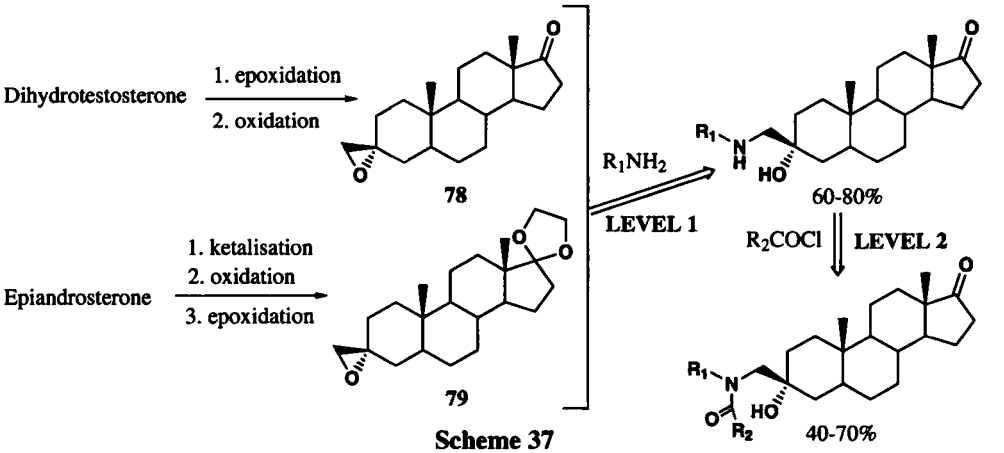


Scheme 36

f) 3-Spiro-oxiranes for Combinatorial Chemistry

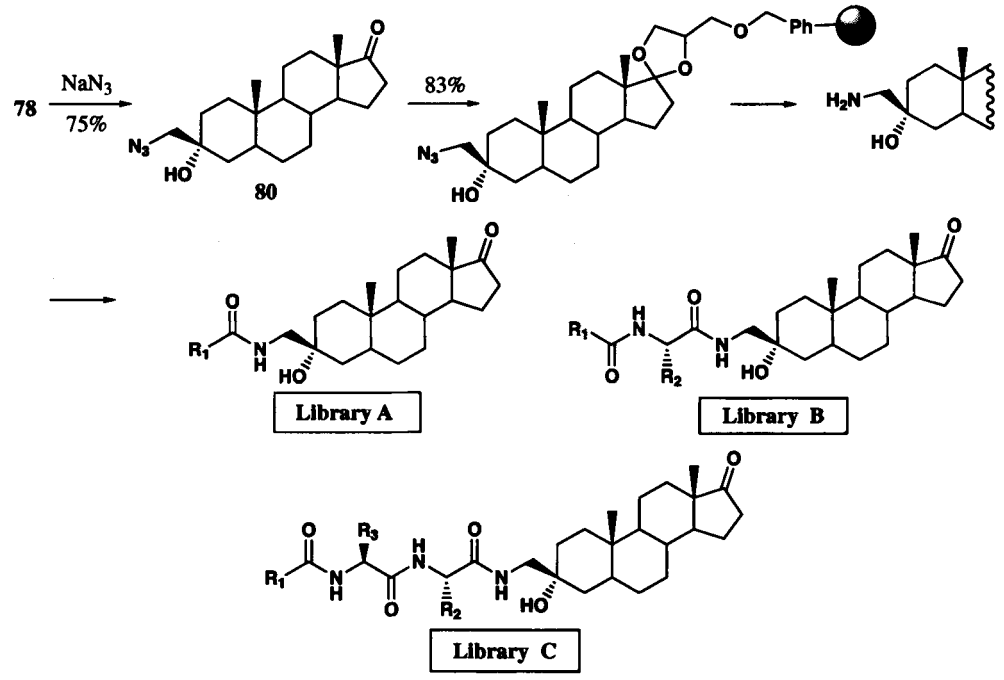
A two-level library of 3β-amido-3α-hydroxy-5α-androstane-17-ones compounds was synthesized using the solution-phase parallel synthesis[64,65] from the oxiranes **78** and **79**. Compound **78** was obtained in 70% yield from stereoselective reaction of DHT with dimethylsulfoxonium methylide followed by oxidation of 17-OH. The synthesis of **79** started with epiandrosterone: the carbonyl group was first protected, the 3-OH was then oxidized into a keto group that

was epoxidized (*Scheme 37*). The two types of reaction consisted respectively of opening regioselectively the oxirane by a series of amines (level 1, in 60-80% yields) and of adding an aliphatic acyl chloride (level 2, in 40-70% yields) to each set of amines, to give the corresponding amides. A library of 3-carbamate derivatives was also prepared from aminoalcohols.



Scheme 37

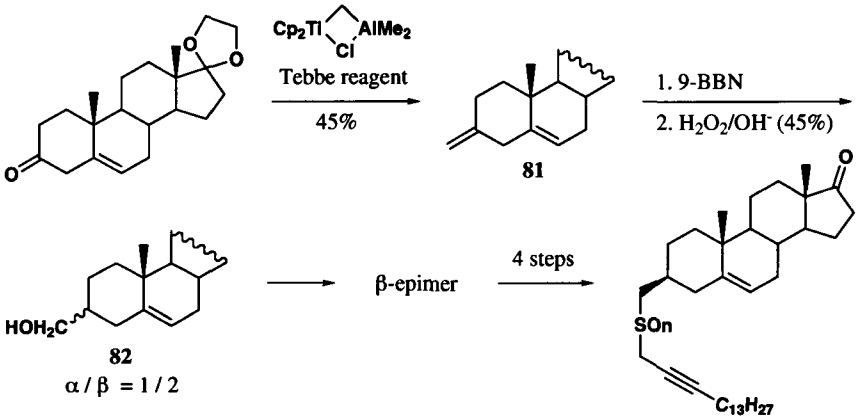
A solid-phase synthesis of 3β-peptido-compounds was also developed.[66,67] The solid-phase synthesis of libraries started by reducing the azide function to the amine. Amino acids were then used as building blocks to generate the libraries A-C in 23-58% overall yields (*Scheme 38*).



Scheme 38

g) 3-Modified Steroids via Alkenylation

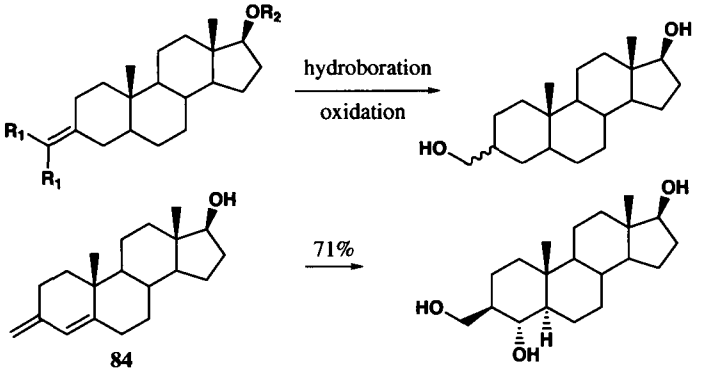
3β-(2-Alkynylsulfonylmethyl) steroids were obtained from a 3-methylene compound **81**.[68] This diene **81** was obtained by the reaction of the corresponding 3-keto-steroid with a titanium-aluminum methylidene complex (Tebbe reagent), the basic Wittig reagent giving predominantly the conjugate diene. The hydroboration of **81** with the bulky 9-BBN gave a 1:2 ratio of α to β 3-hydroxymethyl steroids **82** (*Scheme 39*). The β epimer was separated by



Scheme 39

liquid chromatography and converted into acetylenic sulfones **83** *via* classical reactions (thioacetate, thiol, disulfide, sulfone). The same process was used to synthesized 3β-(2-alkynylsulfonyl) steroids from 3β-mercapto compounds.

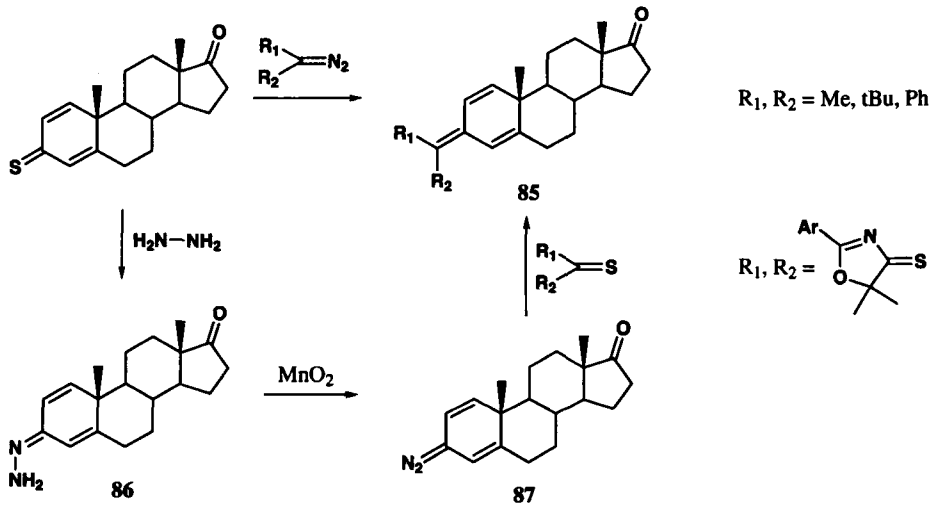
The synthesis of 2-hydroxymethyl compounds from the 2-alkenyl steroids has been described in Section 4. The same reactions were used for hydroboration of 3-alkenyl compounds.[23,24] Mixtures of 3α- and 3β-isomers were obtained whereas the reaction was stereospecific at the position 2. The hydroboration of steroidal 3,4–diene **84** was also performed.[69] The stereochemistry of the 1,3-diol was rationalized in terms of an intermediated four-membered cyclocarboborane (*Scheme 40*).



	3α	3β
$R_1 = R_2 = H$	66%	23%
$R_1 = Br; R_2 = Ac$	60	32
$R_1 = Cl; R_2 = Ac$	58	23

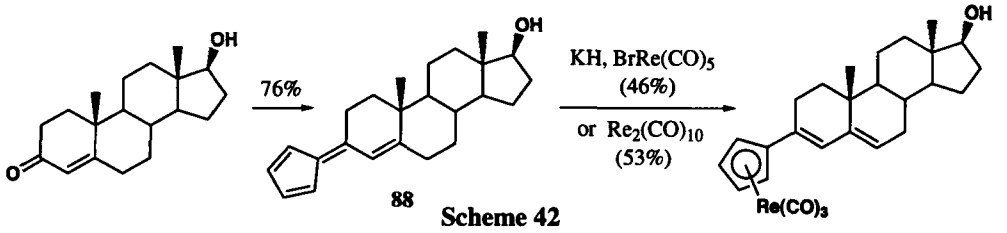
Scheme 40

The Barton-Kellogg olefination was used to synthesized new steroids.[70,71] In the direct pathway, a 3-thionosteroid was treated with a diazoalkane to give olefins **85** in yields of up to 70%. Since the synthesis of the diazoalkanes for compounds containing an oxazoline sub-structure was unsuccessful, an indirect pathway was used (*Scheme 41*). The steroid hydrazone **86** was oxidized into diazo steroid **87**. The reaction of **87** with thiocarbonyl compounds gave the olefins **85** in 25-88% yields. The oxazinylidene products are luminescent dyes.



Scheme 41

Cyclopentadienyltricarbonylrhenium substituted steroids have been prepared from fulvene **88**,[72,73] the fulvene being synthesized in 76% yield by the method of Little and Stone.[74] The $CpRe(CO)_3$ substituted steroids were then prepared in two ways (46-53% yields). The fulvene reacted under basic conditions with $Br\text{-}Re(CO)_5$ and under neutral conditions with $Re_2(CO)_{10}$ (*Scheme 42*).



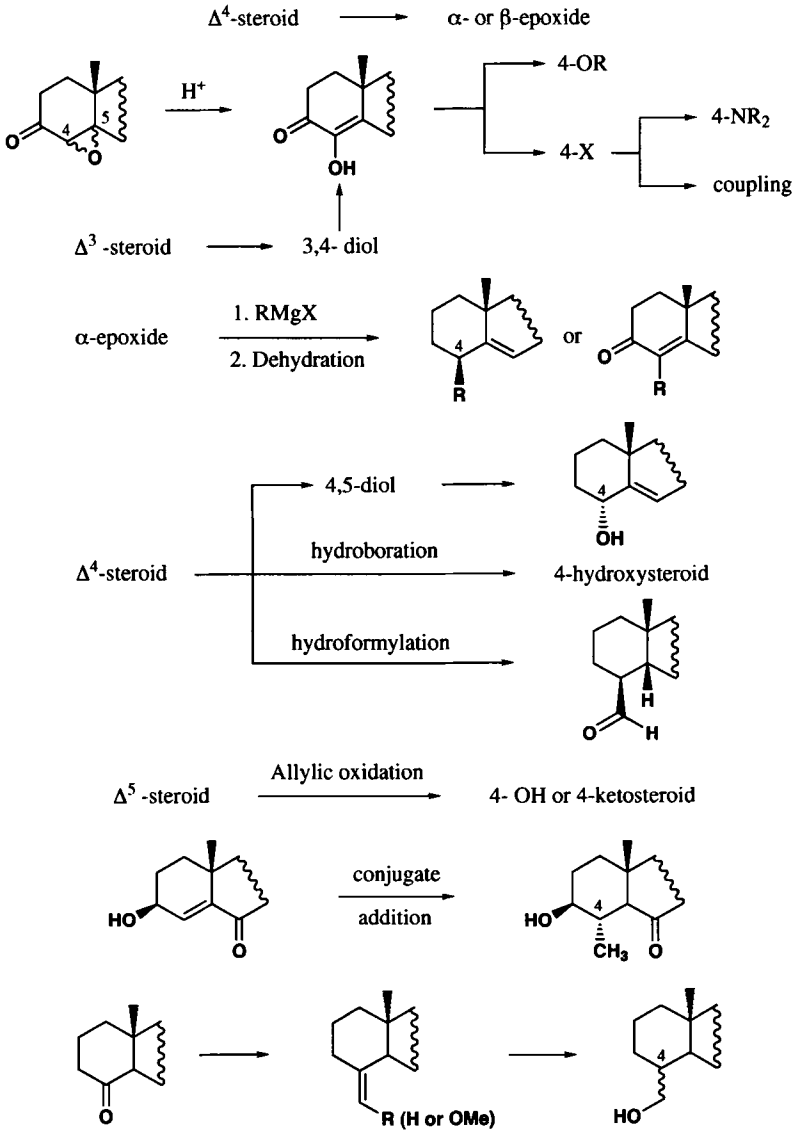
Scheme 42

7. 3,17-Modified Steroids

Various chromophoric compounds containing a rigid steroid spacer were prepared for studying the intramolecular energy transfer.[75-78] The synthesis of these 3,17-disubstituted androstenes involved classical reactions.

8. 4- and 4,5-Modified Steroids

The 4- and 4,5-modified steroids were prepared by various strategies, the most common being summarized in *Fig. 5*.



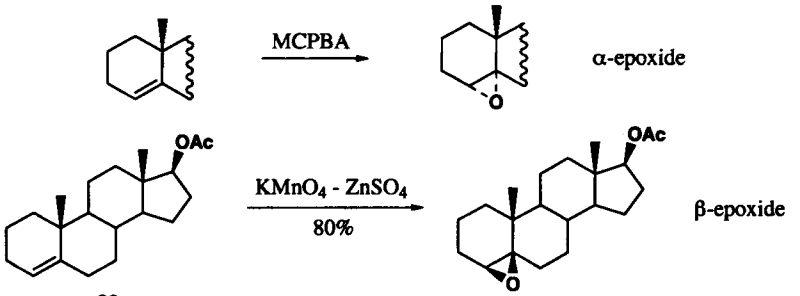
Access to 4- and 4,5-Modified Steroids

Fig. 5

a) Epoxidation of Δ4-Steroids

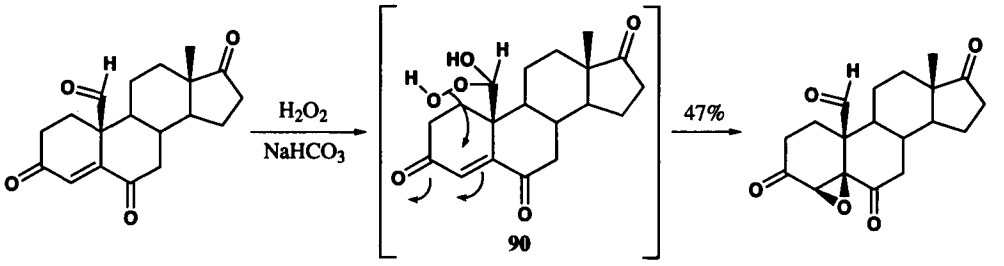
The epoxidation of Δ4-steroids with peracids affords predominantly the α-epoxides except in the case when a β-hydroxy or an analogous group is in the allylic position. In such cases, *syn* stereo-directing effects have been reported, leading mainly to β-epoxidation.[79-81] A 1.4/1

mixture of α/β isomers was however reported for the reaction of 19-(*tert*-butyldimethylsilyloxy)-androst-4-en-17-one with *m*-chloroperbenzoic acid[82] and the epoxidation of some androsta-4,6-dienes with MCPBA has been shown to give 4β,5β; 6α,7α-diepoxides.[83] These results showed the directing effects of various substitutions on the selectivity of this reaction. Efforts have been pursued in the synthesis of steroidal β-epoxides. For example, a mixture of $KMnO_4$-$CuSO_4$ has been found to be a highly β-selective and high-yield epoxidation reagent for Δ^4, Δ^5 and Δ^7 unsaturated steroids in cholestane and pregnane series.[79] The β-epoxidation of 17β-acetoxy-androst-4-ene **89** has been also performed with biphasic systems derived from $KMnO_4$ – metal sulfate, the best yield (80%) being obtained with zinc sulfate (*Scheme 43*).[80]



Scheme 43

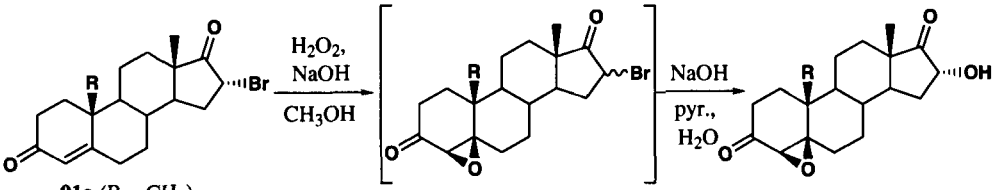
The epoxidation of 4-ene **89** with hydrogen peroxide catalyzed by porphyrin complexes allowed some control of the preferential formation of α- or β-epoxides (β/α = 0.5 to 3) but simultaneous allylic oxidation gave by products.[81] A selective epoxidation of olefins by perfluoro-*cis*-2,3-dialkyloxaziridines was applied to various steroids.[84] The epoxidation of androst-4-ene-3,17-dione afforded the α-epoxide with 50% *de*. Various 19-oxygenated 4β,5β-epoxides were also synthesized in moderate yields.[85-87] The 19-oxo-steroids reacted with hydrogen peroxide in presence of a weak base to give the β-epoxy derivative (43-47% yield). An initial reversible formation of a 19,19-hydroxy hydroperoxide **90** was assumed, followed by intramolecular epoxidation (*e. g. Scheme 44*).



Scheme 44

The alkaline epoxidation of 4-en-3-one steroids usually gives the β-epoxide as the major product. For example, the epoxidation of steroids **91a,b** with H_2O_2 in the presence of NaOH produced β-epoxides with epimerization at C-16. The 16α-hydroxy derivatives **92a,b**

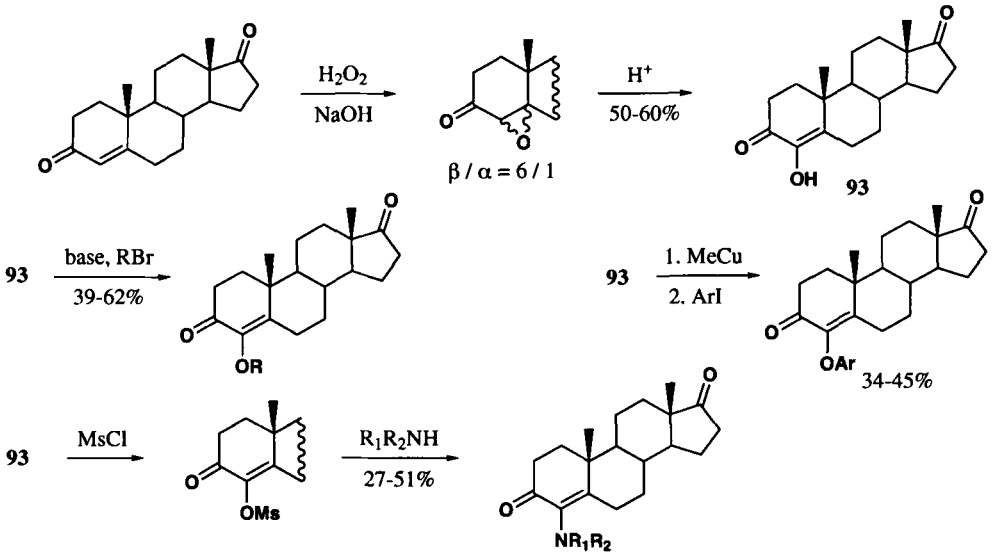
were synthesized in moderate to good yields by alkaline hydrolysis of either the epimeric epoxides (R = CH_3) or the 16α-epimer (R = CH_2OH). The 16α-bromoepoxide (31% yield) must then be separated from its epimer (*Scheme 45*).[87]



Scheme 45

b) Synthesis of 4-Substituted Androst-4-ene-3-ones

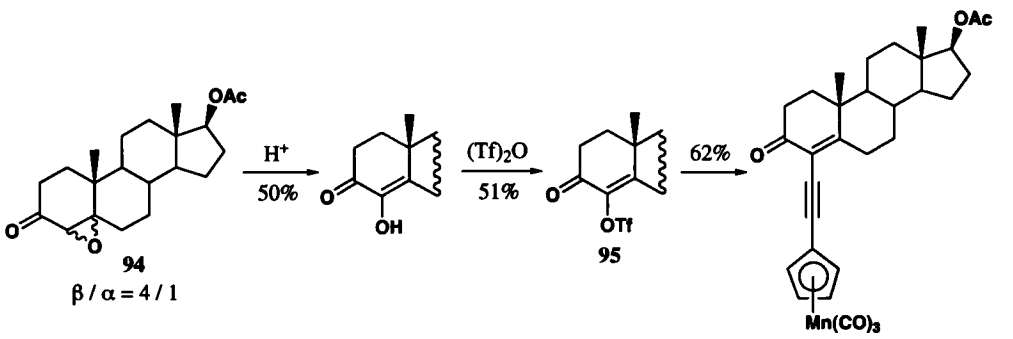
The 4-hydroxyandrostene dione (4-HOA) and other 4-substituted androstene diones (AD) are aromatase inhibitors.[88] 4-HOA **93** is classically prepared by acidic treament of the mixture of β and α epoxides resulting of the epoxidation of AD with H_2O_2 under basic conditions. 4-Amino-, 4-alkoxy- and 4-aryloxy-AD were synthesized from 4-HOA.[88] Treatment of **93** with *t*-BuOK and alkyl bromides afforded the 4-alkoxy series (39-62% yields), the 4-aryloxy analogs being synthesized in moderate yields (34-45%) by preparing 4-copper alkoxide followed by treatment with aryl iodides. The synthesis of the 4-amino-AD (27-51%) was achieved through the mesylate of 4-HOA (*Scheme 46*).



Scheme 46

The enol triflate **95** was also prepared, in moderate yield, from a mixture of epimeric epoxides **94** through the 4-OH compound. This enol triflate was then coupled with a tin

acetylide (see *Scheme 31*) to afford the $CpMn(CO)_3$ substituted steroid **96** in 62% yield (*Scheme 47*).[57]



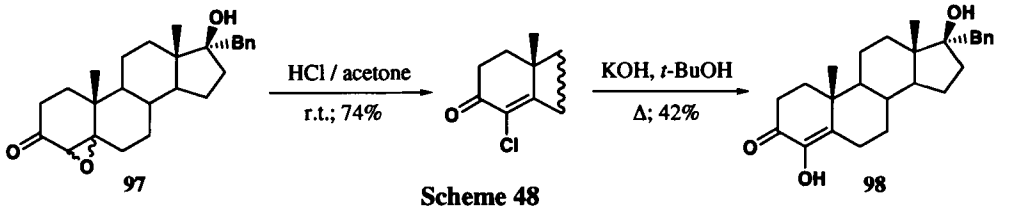
94
β / α = 4 / 1

95

96

Scheme 47

The epoxides may also be transformed into 4-halosteroids. Steroid **94** gave the vinyl bromide by treatment with NaBr in the presence of an acidic resin[57] and the 4-Cl derivative was obtained by a mild acidic treatment of the epoxides **97** (*Scheme 48*). The 4-OH steroid **98** was then obtained by direct substitution of vinylic chloride. Epoxide **97** was also opened in basic conditions (NaOH in refluxing MeOH) yielding the 4-OMe derivative (57% yield).[89]



97

98

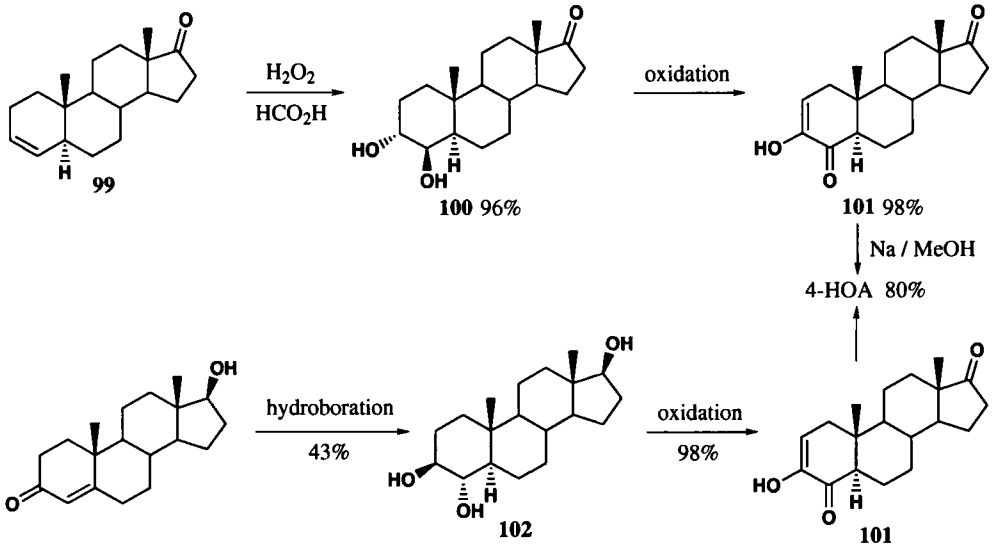
Scheme 48

Two novel approaches to the synthesis of 4-HOA were also achieved. The first synthesis[90] started with 5α-androst-3-ene-17-one **99**, prepared by zinc reduction of AD. The treament of **99** with performic acid (generated *in situ*) led to the *trans*-diaxial diol **100**, that was probably formed *via* the epoxide. The 4-HOA was then formed in two steps: oxidation to **101** followed by isomerization (*Scheme 49*). Another short synthesis of 4-HOA started from commercially available testosterone.[91] The hydroboration/oxidation of testosterone gave the 3,4-diol **102** that was oxidized into **101**, the precursor of 4-HOA (*Scheme 49*).

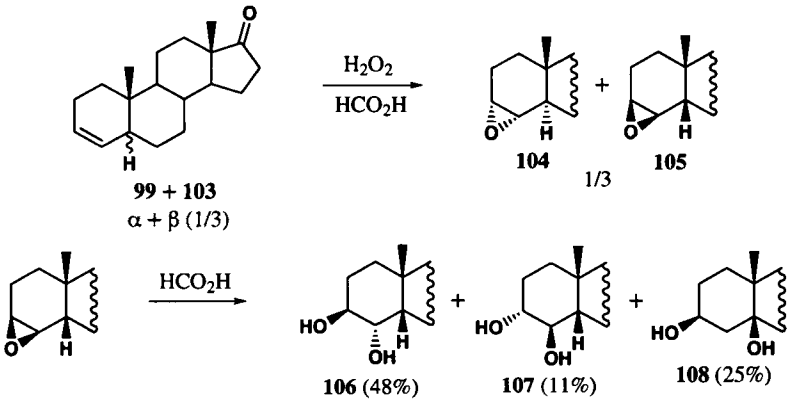
c) Vicinal Diols from Δ^3 and Δ^4-Steroids

A mixture of **99** (*Scheme 49*) and its 5β-epimer **103** (2.3/1)was obtained by zinc reduction of AD. Crystallization of the mixture gave pure **99** in 60% yield and the mother liquor was a 1/3 mixture of **99/103**. Epoxidation of this mixture gave a 1/3 mixture of the epoxides **104** and **105**, the β-epoxide **105** being isolated by crystallization (yield not given). A mixture of diols **106-108** was then obtained by reaction of **105** with formic acid at room temperature. The formation of the abnormal products **107** and **108** was investigated through deuterium labelling studies. The diol **107** was formed through a *trans*-diequatorial epoxide ring opening and the 1,3-diol **108**

arose through an intramolecular rearrangement (*Scheme 50*).[92] All the *vic*-diols were precursors for the synthesis of 4-HOA.

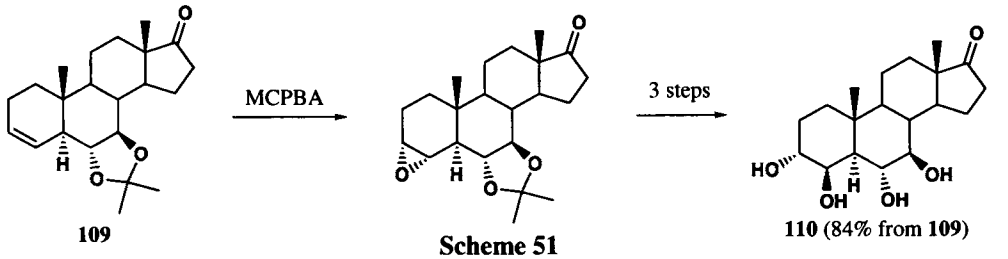


Scheme 49



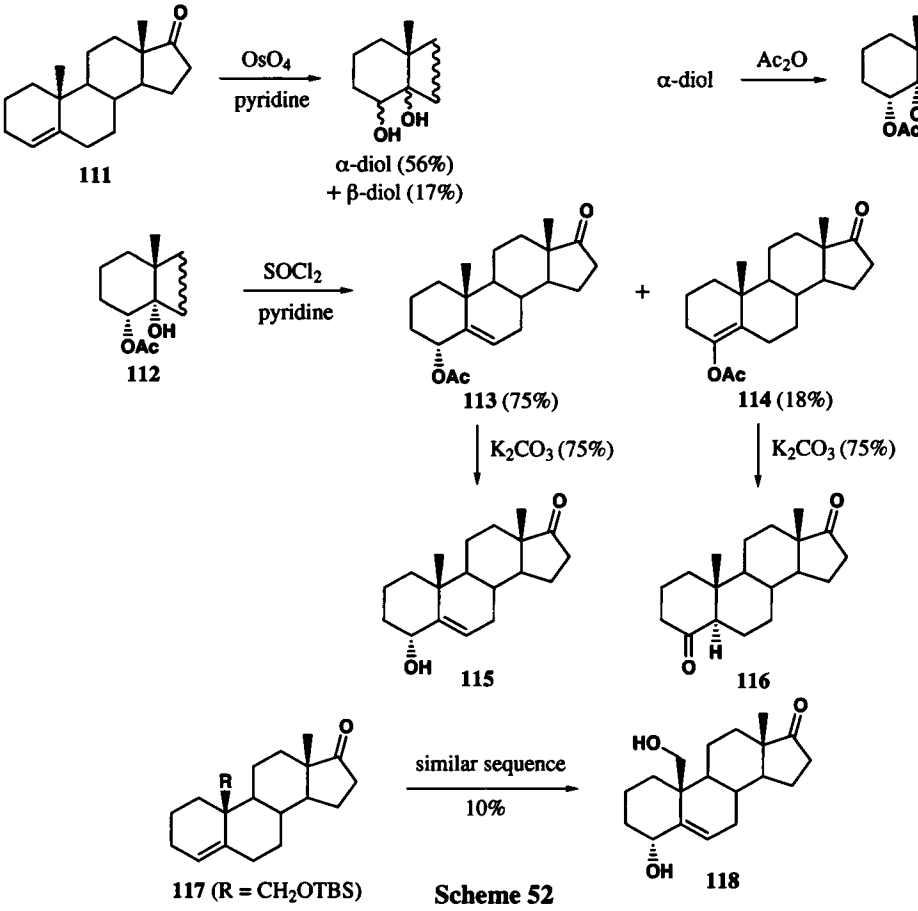
Scheme 50

The stereoselective epoxidation of steroid **109** gave an α-epoxide that was then converted into a polyhydroxysteroid **110** by opening of the epoxide with AcOH followed by base hydrolysis (*Scheme 51*).[34]



Scheme 51

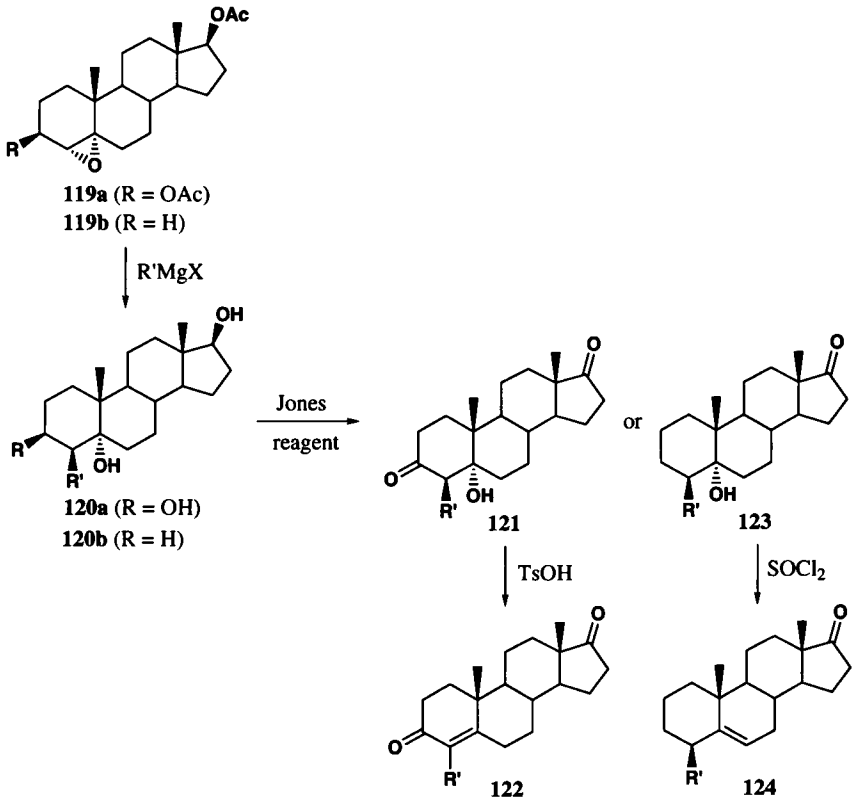
cis-Diols were prepared by osmylation of Δ^4-steroids (*Scheme 52*).[93] A 3/1 mixture of α/β diols was observed in the reaction of **111** with OsO_4. Acetylation of the α–diol followed by dehydration with $SOCl_2$ afforded a mixture of 5-ene-4-acetate **113** (75%) and 4-enol acetate **114** (18%); products **115** and **116** were then obtained in good yields by alkaline hydrolysis. The same sequence has been used to prepare the dihydroxy-steroid **118** in 10% yield from **117**. The α- and β-diols were obtained in equal amounts and in moderate yields for the dihydroxylation of steroid **117**. Various 4-acyloxy steroids were prepared from the α-diol, using acyl anhydrides other than Ac_2O for the acylation at the 4-OH.[94]



d) Reaction of Epoxides with Grignard Reagents

Grignard reaction of the epoxy compounds gave access to 4-substituted steroids (*Scheme 53*).[88,94] Reaction of the epoxide **119a** with alkyl and aryl Grignard reagents gave triols **120a** (51-92%) which were oxidized to give the 4β-substituted diones **121** in 49 to 90% yields. Treatment of the 5α-ols with TsOH in refluxing ethanol gave a series of androstene-diones **122** in 34-95% yields.[88] The reaction of epoxide **119b** with alkyl and benzyl Grignard

reagents gave the 4β-substituted diols **120b** in low yields (13-34%). These compounds were then treated with Jones reagent to afford 17-keto-steroids **123** in 43-96% yields. The reaction of these compounds with $SOCl_2$ produced the 4β-substituted 5-ene steroids **124** (72-99%).[94]

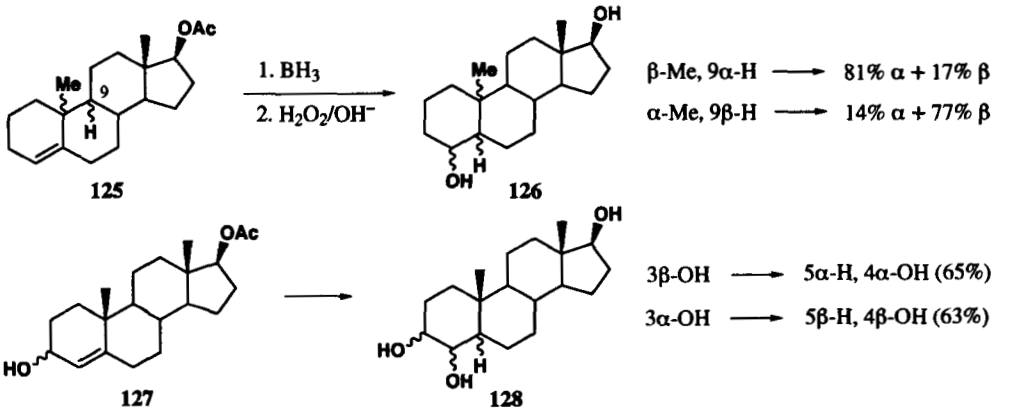


Scheme 53

e) Synthesis via Hydroboration Reactions

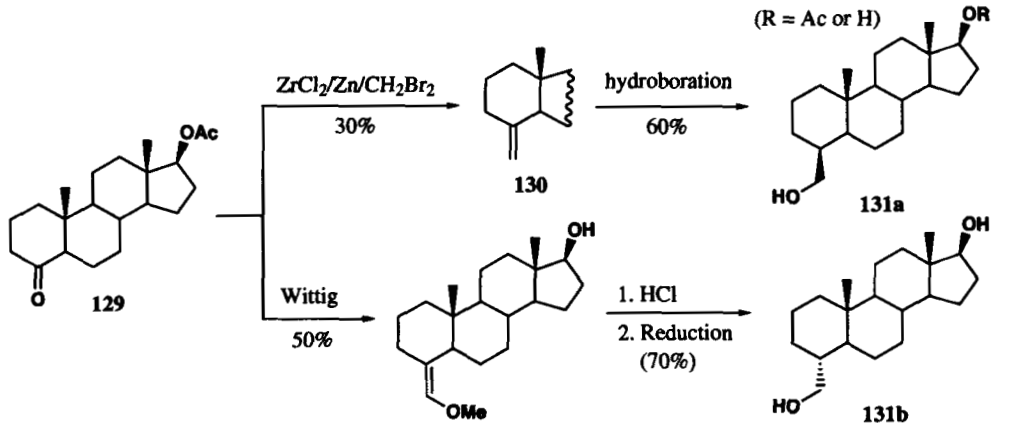
4-Modified steroids may be also prepared by hydroboration of appropriate unsaturated compounds. The hydroboration/oxidation of steroids **125** gave diols **126** in high yields.[95] These diols were obtained as a mixture of 4α-hydroxy-5α-H (α compound) and 4β-hydroxy-5β-H (β compound) steroids, the stereochemistry being determined by that of the C-10 methyl group: the hydroboration occured mainly at opposite side of this group (*Scheme 54*). The same reaction with compounds **127** afforded either α- or β-hydration compounds **128** in good yields. The allylic OH group at C-3 directed the hydroboration to the *anti* face.

Epimeric 4α- and 4β-hydromethyl steroids were prepared from the 4-ketosteroid **129**.[96] The ketosteroid was converted into 4-methylene compound **130**, in moderate yield, using zirconium dichloride, zinc and dibromomethane. The hydroboration of alkene **130** gave access to the 4β-hydroxymethyl steroid **131a**, as a mixture of 17-OH and 17-OAc compounds.



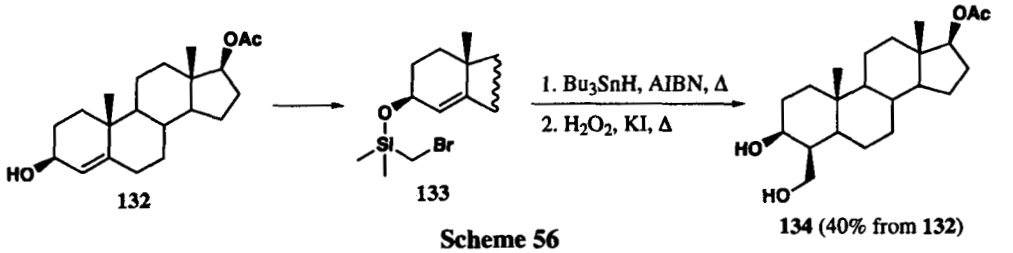
Scheme 54

The 4α-epimer **131b** was obtained in better yield *via* a Wittig reaction on the ketosteroid **129** followed by hydrolysis with HCl and reduction of the resulting aldehyde (*Scheme 55*).



Scheme 55

The 3-hydroxy-4-hydroxymethyl compound **134** was prepared in moderate yield from steroid **132**, using a procedure developed by Stork;[96,97] **132** was converted into its silyloxy derivative **133** which was cyclized with tributylstannane and AIBN. The crude product was then oxidized to give **134** (*Scheme 56*).

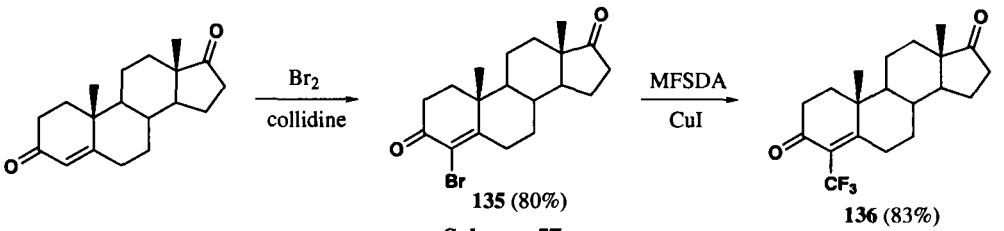


Scheme 56

The hydroboration of 3,5- and 4,6-steroidal dienes was also performed, 4,6-diols being mainly obtained as mixture of diastereoisomers.[69]

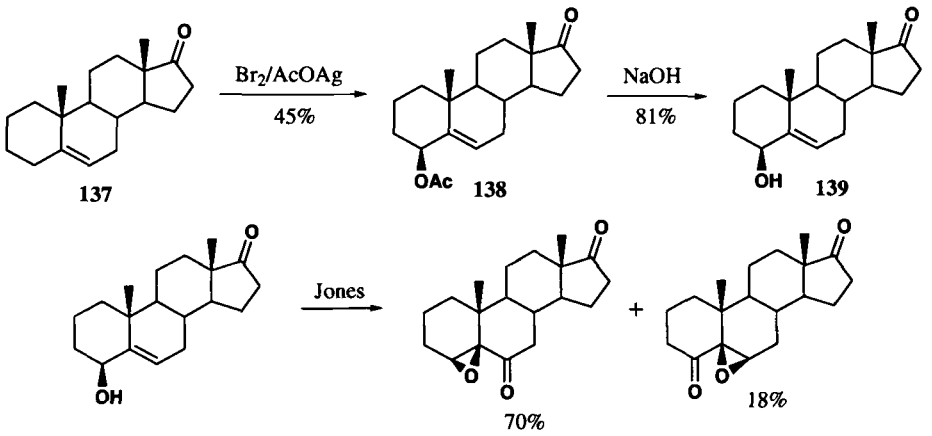
f) Miscellaneous

The 4-trifluoromethylsteroid **136** was synthesized in high yield from AD by a two-step procedure.[98] The bromination of AD afforded 4-bromo compound **135** and the target compound **136** was then obtained by reaction of **135** with a trifluoromethylating reagent MFSDA (methyl fluorosulfonyldifluoroacetate). This steroid exhibited high 5α-reductase inhibitory activity (*Scheme 57*).



Scheme 57

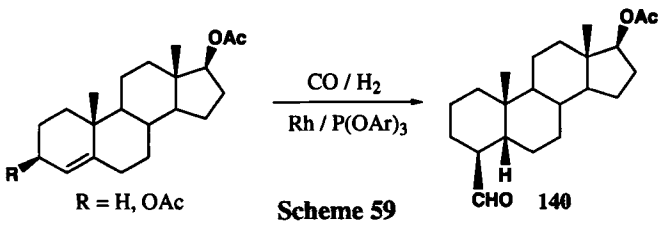
The allylic acetoxylation of 5-ene steroid **137** with bromine and silver acetate gave a mixture of products, the major one being the 4β-acetoxy derivative **138** (6-substituted steroids were formed as minor products). The 4-hydroxy-steroid **139** gave a mixture of 4,5- and 5,6-epoxides with Jones' reagent, whereas the oxidation with CrO_3-pyridine gave a mixture of conjugated 4- and 6-ketosteroids (*Scheme 58*).[99]



Scheme 58

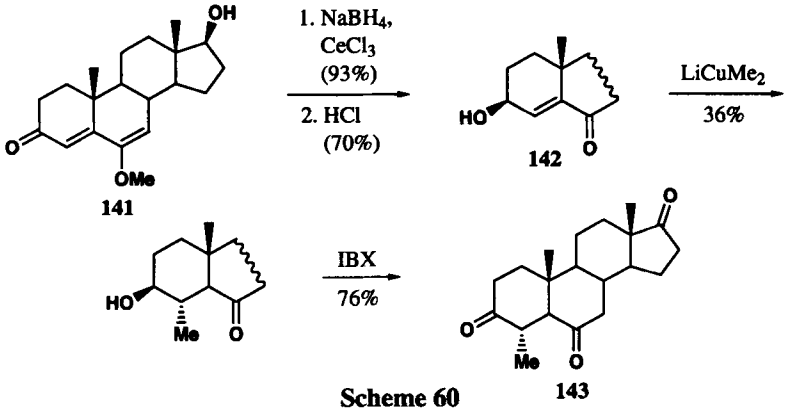
The 5-en-4,7-diones were by-products (14% yields) in the allylic oxidation of 5-ene steroids with pyridinium dichromate.[100] The diastereoselective hydroformylation of Δ^4-steroids was achieved with rhodium-phosphite catalysts, the best yield of 4-formyl steroid **140** being 68%.[101] This reaction is the first example of catalytic carbonylation at the β face (*Scheme 59*).

A 4α-methyl trioxosteroid **143** has been synthesized by a key $LiCuMe_2$ addition to the α,β-unsaturated compound **142**.[22] The steroid **142** was prepared in high yields from ketosteroid



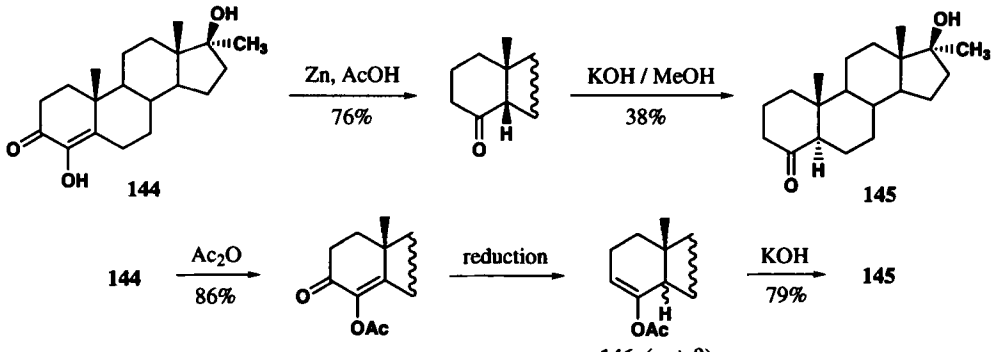
Scheme 59

141, by reduction at C-3 (93% yield) followed by hydrolysis of the enol ether function (70%). A low yield (36%) was observed for the key conjugate addition of the cuprate. The target compound **143** was then obtained by IBX oxidation of the diol (*Scheme 60*).



Scheme 60

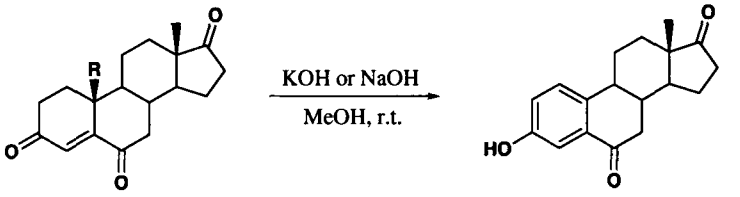
Finally, the 4-ketosteroid **145** was prepared in two ways from diosphenol **144** (*Scheme 61*).[102] In the first sequence, diosphenol was reduced to a 4-keto-5β-H steroid followed by a low yield epimerization at C-5 into **145**. The second sequence involved the reduction of acetylated diosphenol into a mixture of epimeric enol acetates **146** (α/β = 1/0.85). The yield for this step was not given but a poor yield (6.5%) of the α-epimer, obtained by crystallization, was reported. Alkaline hydrolysis of the enol acetate mixture, accompanied by epimerization at C-5 gave **145**.



Scheme 61 **146** (α + β)

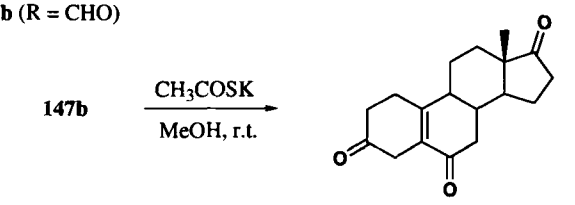
9. Aromatization of Androgens

The aromatization of various androgens with human placental aromatase afforded estrogens.[103,104] The rate of aromatization was higher for 19-hydroxy- and 19-oxo-compounds compared to a 19-CH_3 substrate,[103] and decreased for 6-alkoxy-substituted androgens.[104] 19-Oxygenated androst-4-ene-3,6,17-triones **147a,b** were converted in good to high yields into 6-oxoestrone **148** by treatment with a strong base (*Scheme 62*).[105] The treatment of **147b** with weak bases afforded the 19-nor derivative **149** as the major product (56-67%).



147a (R = CH_2OH)
147b (R = CHO)

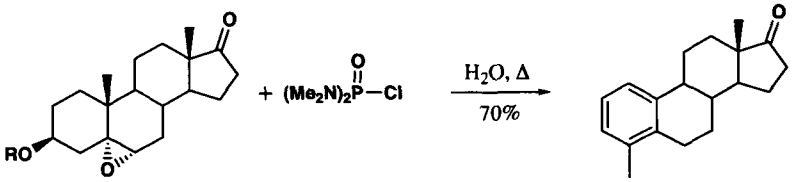
148 (65-93%)



149 (67%)

Scheme 62

The epoxy-sterols **150** were converted in good yield into aromatic steroids (*Scheme 63*).[106] The reaction of tetramethyldiamidophosphoric acid chloride with these steroids was assumed to proceed *via* dienol-benzene rearrangements.



150 (R = H, $MeSO_2$)

Scheme 63

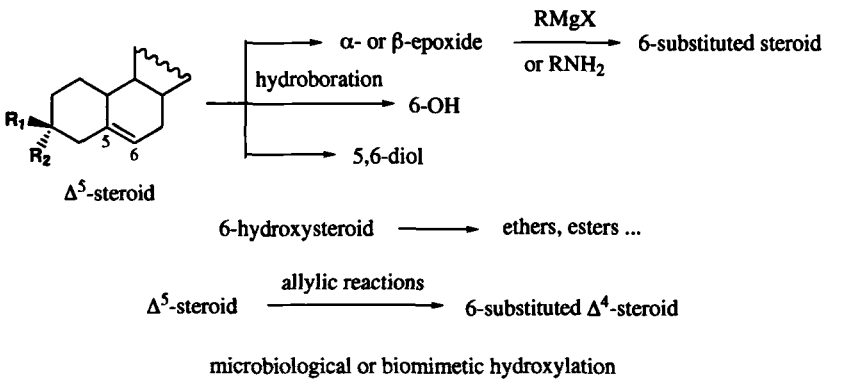
II. MODIFICATIONS OF RING B

1. 5,6 and 6-Substituted Compounds

The main strategies that were developed for preparation of 6-modified steroids are summarized in the *Fig. 6*. Δ^5-steroid is a generic term for 5,6-dehydro-compounds.

a) Epoxidation of Δ^5-Steroids

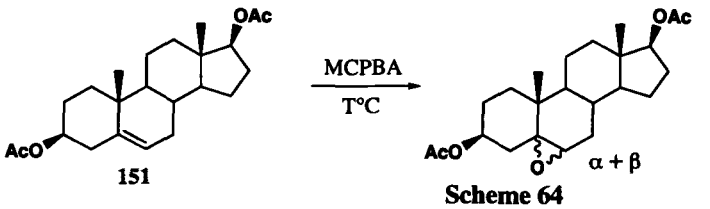
The epoxidation of Δ^5-steroids by peracids is known to produce a mixture of α- and β-epoxides, the stereochemical outcome being influenced by the nature of the substituents,



Access to 5,6- and 6-Substituted Steroids

Fig. 6

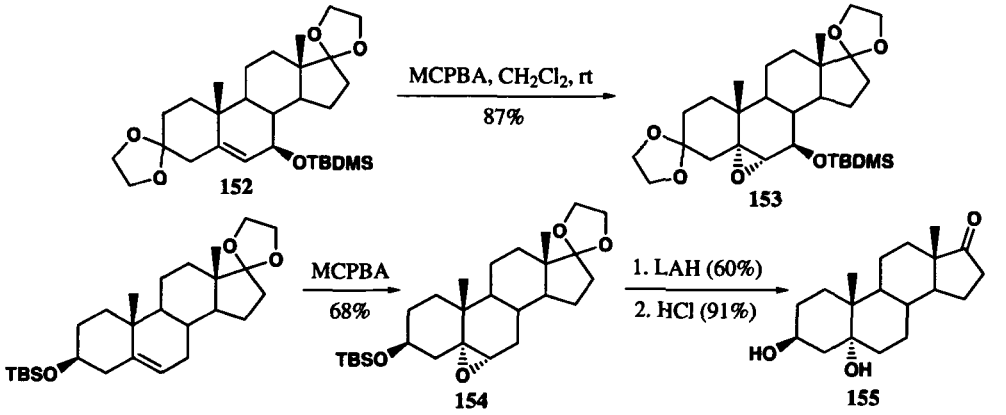
particularly at C-3 and C-10. The effect of temperature has been also studied for the reaction of diacetate **151** with MCPBA.[107] The exclusive formation of α-epoxide could be observed at –20°C and the α/β ratio decreased with the temperature (*Scheme 64*).



T°C	α / β
–20	99 / 1
0-5	88 / 12
15-25	77 / 23
>30	60 / 40

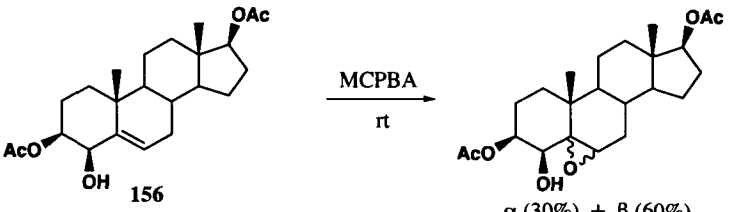
Scheme 64

Some stereospecific epoxidations with MCPBA have been reported. The 5-ene-7β-protected steroid **152** was transformed into α-epoxide **153** upon epoxidation with MCPBA in dichloromethane at room temperature[34] and the α-epoxide **154** was prepared from corresponding ketal, by epoxidation with MCPBA in chloroform at 0°C (*Scheme 65*). Reductive cleavage of **154** followed by deprotection, gave sterol **155** in good yield.[108]



Scheme 65

A directing effect of a 4β-hydroxy group has also been reported (*Scheme 66*).[109] The epoxidation of the compound **156** with MCPBA at room temperature gave a 2:1 mixture of β- and α-epoxides.

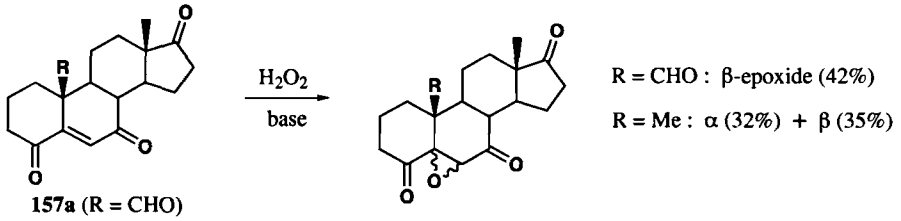


156

α (30%) + β (60%)

Scheme 66

The β-epoxide was also the sole or the major product for the reaction of steroids **157a** and **157b** with hydrogen peroxide in basic medium.[110] The tetraone **157a** was reacted with H_2O_2 in the presence of a weak base ($NaHCO_3$) in methanol, to afford the β-epoxide in 42% yield, whereas a strong base, NaOH, may be used for the reaction of **157b** with H_2O_2. A slight excess of the β-epoxide was observed in the latter case (*Scheme 67*). The formation of a hydroperoxide intermediate, followed by intramolecular attack on the β-face, was assumed in the former case, as for the epoxidation of the 19-oxygenate Δ^4-compounds (cf. *Scheme 44*). The reaction of androst-5-ene-4,17,19-trione with H_2O_2 in the presence of $NaHCO_3$ gave the β-epoxide in poor yield (25%).[86]



157a (R = CHO)
157b (R = Me)

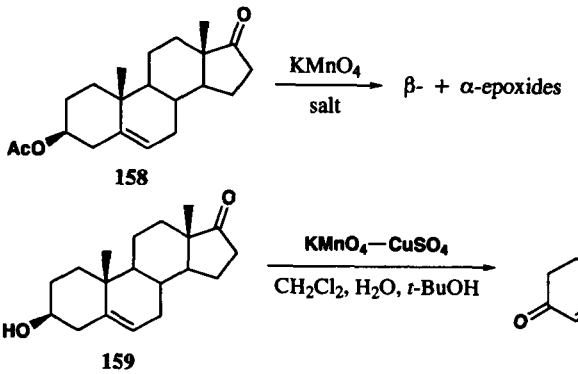
R = CHO : β-epoxide (42%)

R = Me : α (32%) + β (35%)

Scheme 67

The efforts in the synthesis of steroidal β-epoxides from Δ^4-compounds have been previously reported. The same type of reactions was used for the selective β-epoxidation of Δ^5-steroids. The epoxidation of androst-5-ene-17-one with $KMnO_4$-$ZnSO_4$ afforded 76% yield of β-epoxide.[80] The reaction was also achieved with other salts such as metal sulfates or nitrates,[111] copper sulfate,[112] and sodium perborate.[113] *Scheme 68* presents a comparison for the epoxidation of 3β-acetoxy-androst-5-ene-17-one **158** with various salts. The epoxidation with $KMnO_4$-$Fe_2(SO_4)_3$ appears to be a high yield and low cost method.[111] The epoxide was not isolated for the reaction of 3β-hydroxy-steroid **159** with $KMnO_4$-$CuSO_4$, which afforded the 6β-hydroxy-AD **160** in 45% yield (*Scheme 68*).[112]

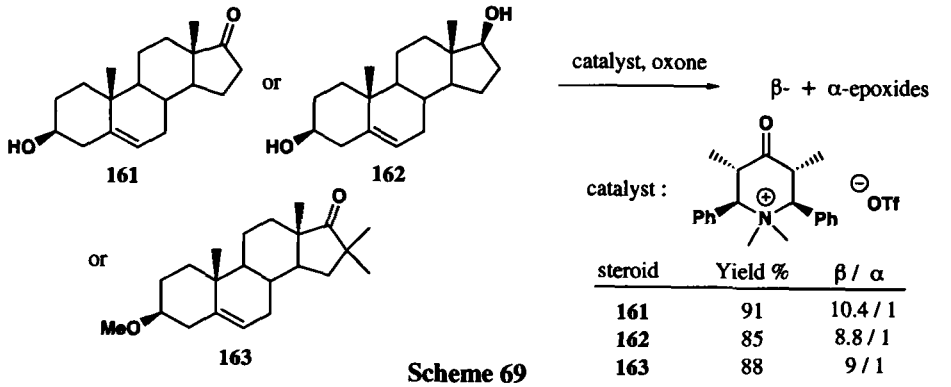
A β-stereoselective catalytic epoxidation of **158** has been effected by a ruthenium(II) bioxazoline complex under aerobic conditions, in the presence of isobutyraldehyde at room



salt	β/α	yield %
$Fe_2(SO_4)_3 \cdot nH_2O$	98/2	93
$Fe(NO_3)_3 \cdot 9H_2O$	94/6	92
$NaBO_3$	4/1	33

Scheme 68

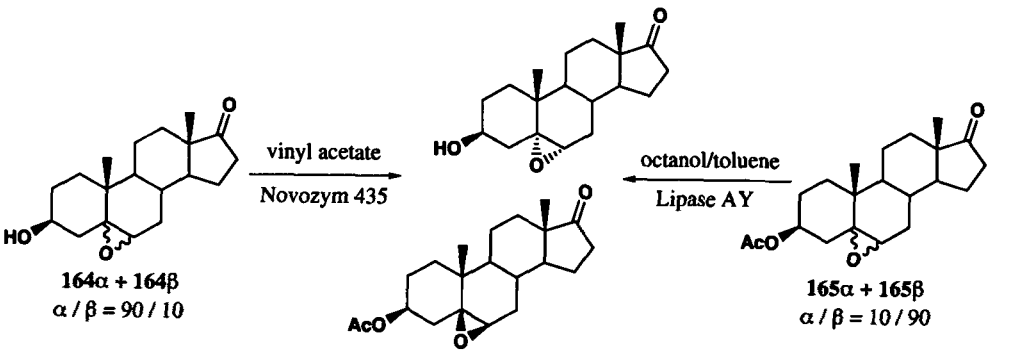
temperature, in 90% yield and with a β/α ratio of 96/4.[114] Another catalytic method used hindered ketones as the catalysts and oxone as the oxidant.[115] Some typical results are given on the *Scheme 69*.



steroid	Yield %	β / α
161	91	10.4 / 1
162	85	8.8 / 1
163	88	9 / 1

Scheme 69

Stereoisomerically pure 3β-hydroxy-5,6-epoxysteroids were obtained by combining selective chemical methods for α- and β-epoxidation with enzymatic stereoselective esterification or deacetylation, as described on the *Scheme 70*.[116] The stereoselective transesterification of

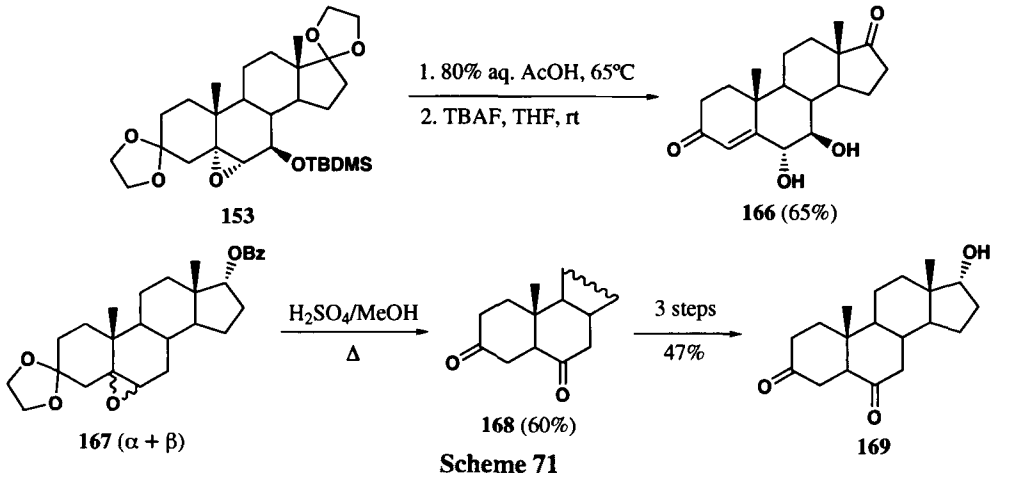


Scheme 70

the β-epoxide **164β** was used to remove the minor β-isomer in an α-enriched mixture (67-72% yield in **164α**), whereas the stereoselective deacetylation of the α-epoxide **165α** was performed in order to remove the α-isomer in a β-enriched mixture. This reaction was followed by a mild deacetylation method for hydrolysis of the 3-acetate to afford **164β**.

b) Reactions of 5,6-Epoxy-Steroids

The epoxides have been transformed into other steroids by classical reactions. Hydrolysis of the epoxide **153** (see *Scheme 65*) with aqueous acetic acid at 65°C, followed by deprotection of the 7-OH group, afforded the dione diol **166** in good yield (*Scheme 71*).[34] The diketo compound **168** was synthesized in 60% yield by acidic treatment of a 1/1 mixture of epoxides **167** and gave access to 17α-hydroxysteroid **169** in moderate yield (*Scheme 71*).[22]

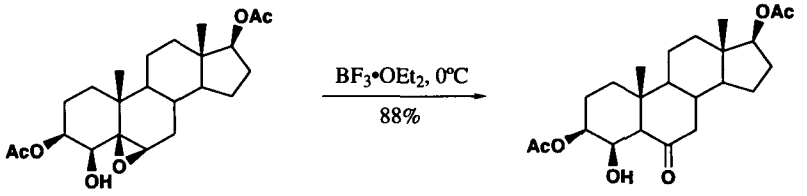


153 **166** (65%)

167 (α + β) **168** (60%) **169**

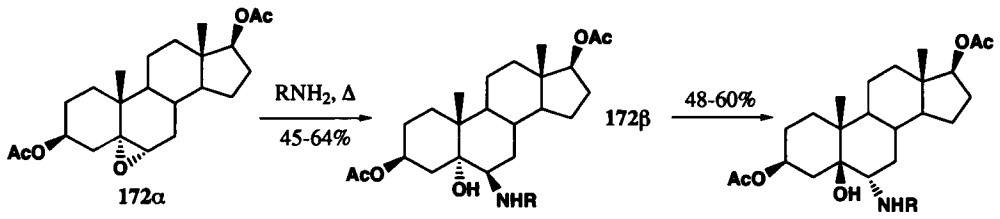
Scheme 71

The reductive cleavage of an epoxide has been previously cited (*Scheme 65*). The β-epoxide **170** smoothly rearranged to a 6-ketosteroid **171** with boron trifluoride etherate in ether in 88% yield (*Scheme 72*). The failure of the α-epoxide to rearrange was explained in term of a difficult 6β-hydrogen shift.[109]



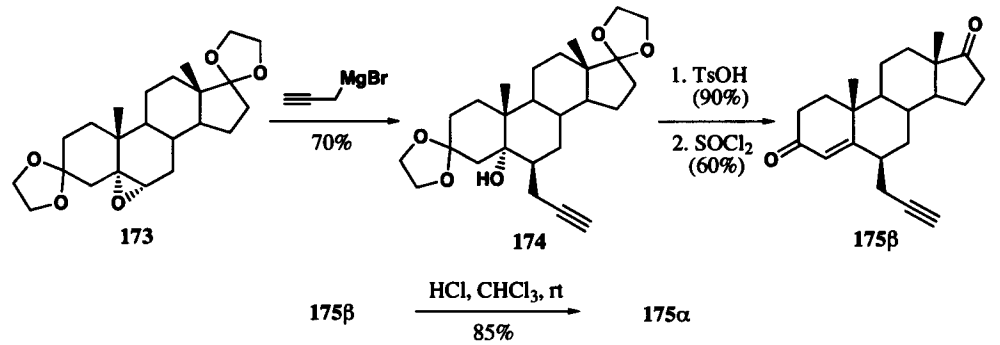
170 **Scheme 72** **171**

The treatment of epoxides **172α** and **172β** with various alkyl and arylamines led to the formation of corresponding 6β- or 6α-substituted amino derivatives in 45 to 64% yields (*Scheme 73*).[107]



Scheme 73

Grignard reaction of the epoxy compounds gave also access to 6-substituted steroids. The synthesis of 6-propargyl AD **175** started with α-epoxide **173**. The treatment of **173** with propargylmagnesium bromide gave compound **174** in 70% yield. The deprotection of the hydroxy ketal was achieved with TsOH (90% yield), followed by dehydration with thionyl chloride to afford the target 6β-substituted AD in 60% yield.[117] The 6β-epimer was then converted into 6α-compound, in high yield (85%), under acidic conditions (*Scheme 74*).

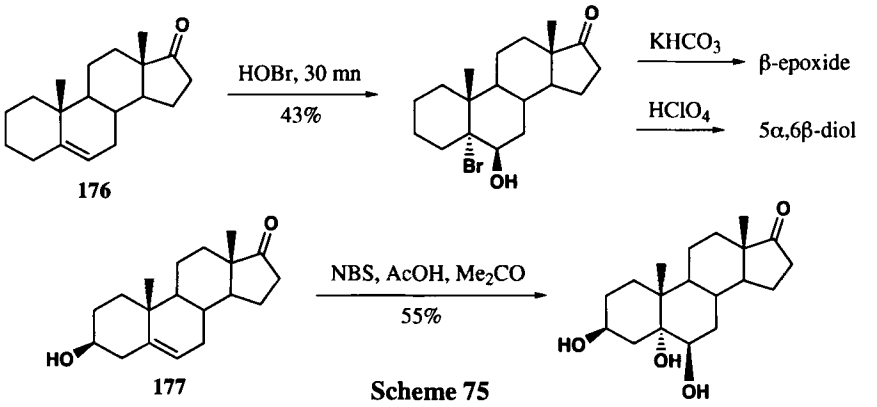


Scheme 74

Series of 6α- and 6β-alkyl AD[118,119] were also synthesized in the same manner, starting from **173**. The Grignard reaction of the epoxide with the organomagnesium compounds, like the deprotection step (with $HClO_4$ in THF), occurred in high yields. Moderate yields (50-73%) were however reported for the dehydration step with $SOCl_2$. The isomerization of the 6β-epimers into the 6α-equatorials compounds was achieved with HCl in methanol and afforded mixtures of epimers (α/β ratio of about 5/1).

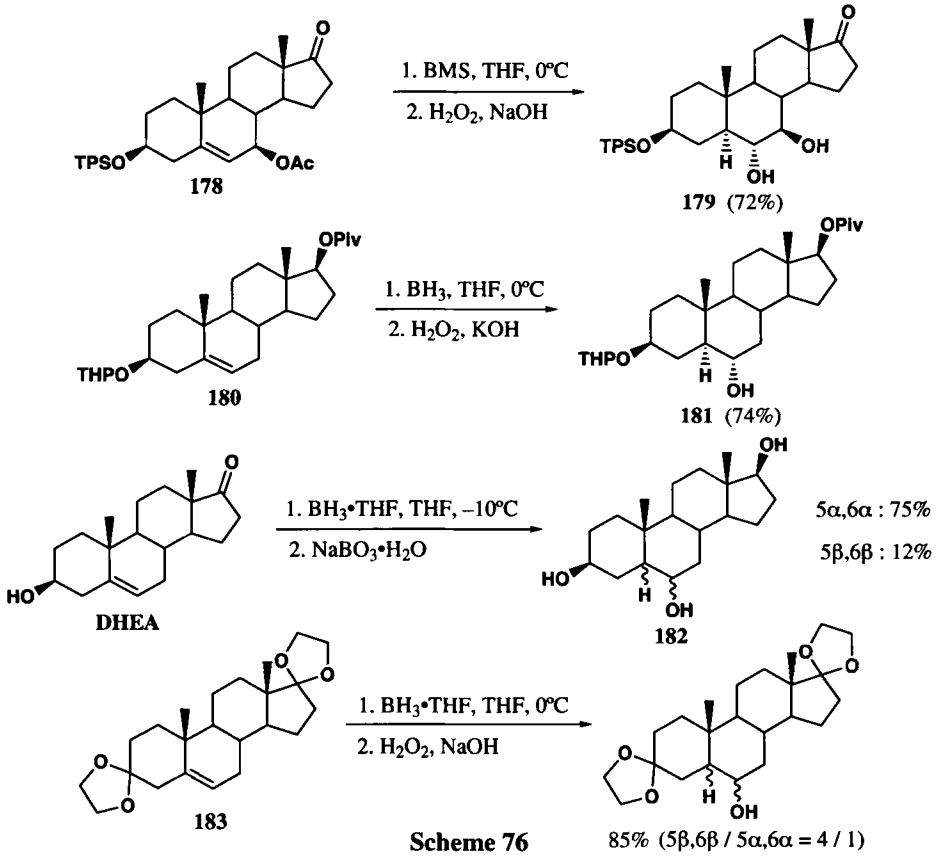
c) Addition to Δ^5-Steroids

The reaction of steroid **176** with hypobromous acid gave the addition product in a short reaction time. The yield decreased upon prolonged reaction times and by-products, such as α- and β-epoxides, were formed. Treatment of the bromohydrin with $KHCO_3$ in methanol at room temperature gave the β-epoxide. On the other hand, reaction of the bromhydrin with $HClO_4$ in aqueous dioxane produced the 5α,6β-diol *via* hydrolysis of the epoxide (yield not given).[120] A 5α,6β-diol was also obtained, in 55% yield, for the reaction of dehydroepiandrosterone **177** with NBS and AcOH in acetone (*Scheme 75*).[108]



Scheme 75

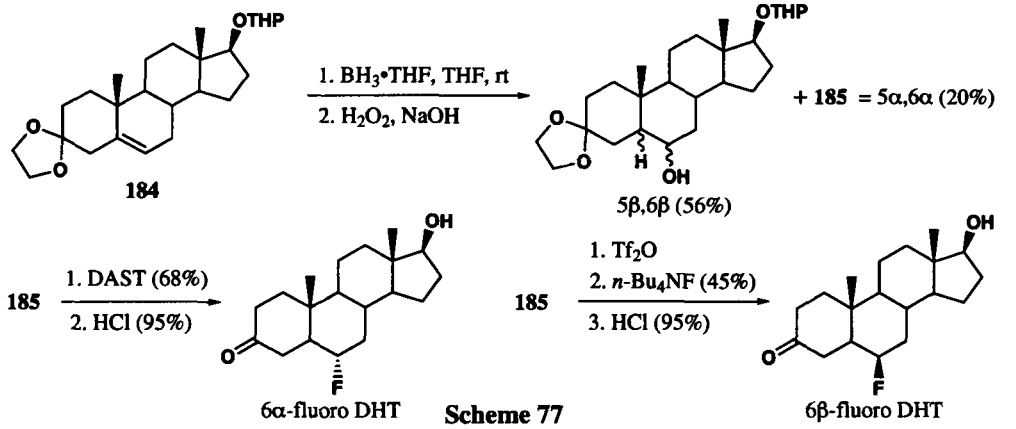
The hydroboration/oxidation of various Δ^5-steroids has been performed. A highly stereoselective addition of borane-dimethyl sulfide complex (BMS) at the α face of steroid **178** afforded the diol **179** in 72% yield[121] and 6α-hydroxysteroid **181** was prepared in 74% yield by hydroboration reaction of the double bond 5,6 of compound **180**.[62] A mixture of α- and β-addition compounds were obtained (75% and 12% yields) from DHEA, a triol **182** being obtained due to concomitant reduction of the 17-keto group (*Scheme 76*).[22] The α-epimer of steroid **182**



Scheme 76

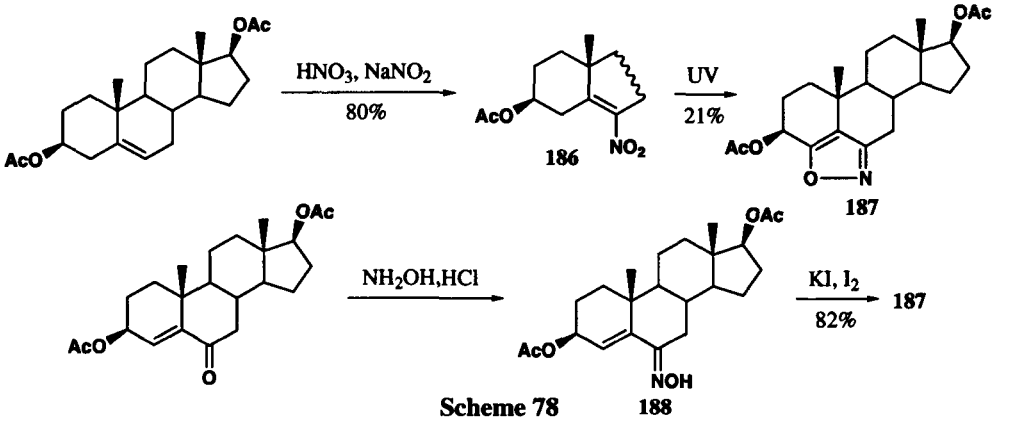
was then oxidized into trione (74%), 3,17-dione (85%) or 3-ketosteroid (30%) with appropriate oxidizing reagents. The β-epimer of **182** was also prepared in high yield from the 6α-hydroxy-3,17-dione. This dione was ketalized, then oxidized at C-6, the 6-keto compound being reduced into a 6β-hydroxy-steroid that gave the target compound after deketalization.[22] A predominant *cis* addition from the β face was observed in other cases, like for the addition of BH_3•THF to the steroid **183**, which afforded a 4/1 mixture of β/α addition in 85% yield (*Scheme 76*).[122]

The steroid **184** gave also a predominant *cis* addition from the β face (*Scheme 77*). A OH group at C-3 directed the hydroboration of Δ^4-steroids to the *anti* face (see *Scheme 54*). It appears clear that the substituents at C-3 and C-7 also have directing effects on the hydroboration of Δ^5-steroids. The minor 6α-OH steroid **185** (20% yield) was then fluorinated by DAST, followed by hydrolysis of the protective groups, to afford the the 6α-fluoro DHT. The trifluoromethanesulfonylation followed by displacement with fluoride ion (TBAF) gave access to the 6β-fluoro DHT (*Scheme 77*).[123]



Scheme 77

The synthesis of new steroidal isoxazoles started from 3,17-diacetoxy-androst-5-ene, which was converted to a 6-nitro compound **186** in good yield.[124] **186** was then rearranged photochemically to give the isoxazole **187** in low yield (21%). Better yields were observed when the isoxazole was prepared by cyclization of the oxime **188** (*Scheme 78*). The oxime was

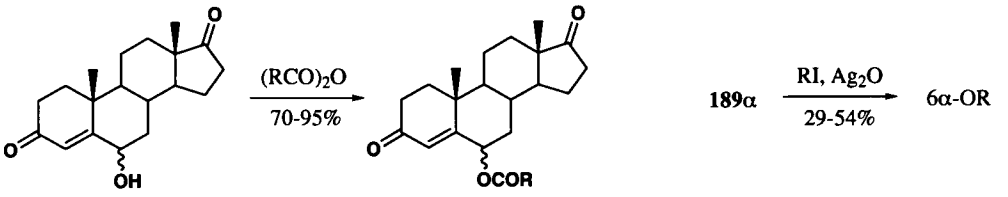


Scheme 78

synthesized from the corresponding 6-ketosteroid (yield not given). The diacetate **187** was then converted into 3,17-dihydroxy- or 3,17-diketo compounds *via* classical methods. Selective hydrolysis of **187** at C-3, followed by oxidation of the OH group and hydrolysis at C-17, afforded a 17β-hydroxy-3-keto steroidal isoxazole in good yield.

d) Ethers and Esters from 6-Hydroxysteroids

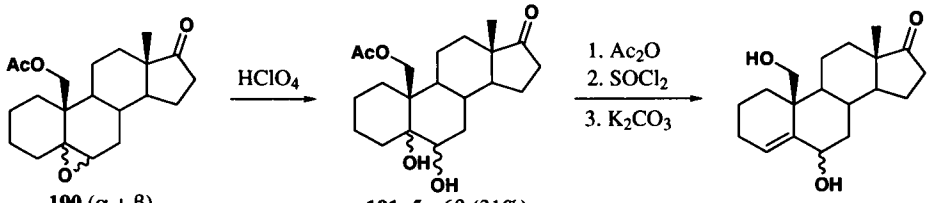
The esterification of the 6α- and 6β-hydroxy steroids **189** with various acid anhydrides afforded the corresponding esters in good to high yields. Treatment of the 6α-ols with an alkyl iodide or benzyl chloride in the presence of Ag_2O gave the 6α-ethers in low to moderate yields (*Scheme 79*). 6β-Alkyl ethers were also obtained in low yields by reaction of androstenedione with *o*-iodosylbenzoic acid and KOH in various alcohols.[12]



189

Scheme 79

Epimeric 5,6-diols **191** and **192** were obtained from hydrolysis of the mixture of β- and α-epoxides **190**.[120] These *trans*-diols were acetylated separately and the resulting acetates were then dehydrated with $SOCl_2$ followed by hydrolysis to afford 4-ene-6α,19-diol in 55% yield from **192** and its 6β-epimer in 39% yield from **191** (*Scheme 80*).[93]



190 (α + β)

191: 5α,6β (31%)
192: 5β,6α (45%)

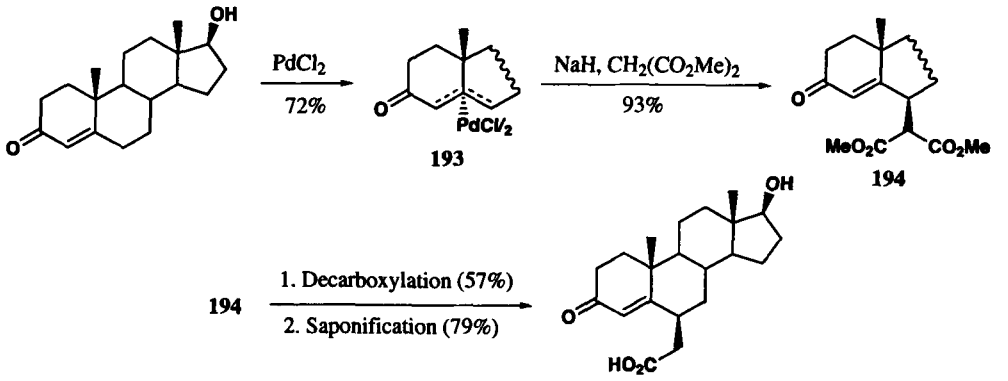
Scheme 80

e) Allylic Reactions of Δ⁵-Androstenes

The allylic acetoxylation of androst-5-ene-17-one with bromine and silver acetate gave 6α- and 6β-acetoxy compounds as by-products.[99] The reaction of Δ^5-steroids with mercury(II) trifluoroacetate generally gave a mixture of products, the 6β-hydroxy-Δ^4-deriva-

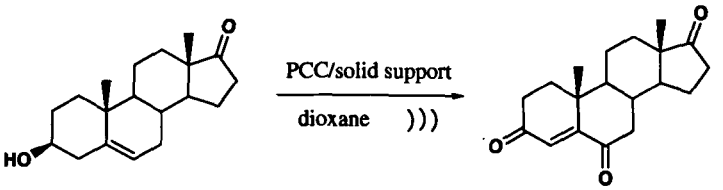
tives being the major product in few cases.[125] The reaction of 3β-acetoxyandrost-5-ene-17-one with palladium(II) trifluoroacetate gave a dimeric 5,6,7-π-allyl steroid palladium complex in high yield (97%). The structure of this complex was established by X-ray crystallography.[126]

The π-allyl testosterone palladium complex **193** allowed the synthesis of the 6β-substituted diester **194** which afforded the acid **195** in good yield after decarboxylation and hydrolysis (*Scheme 81*). The acid **195** was then coupled with a deazaflavinyl alcohol to prepare a new fluorescent probe for cytochrome P 450 3A4.[127]



Scheme 81

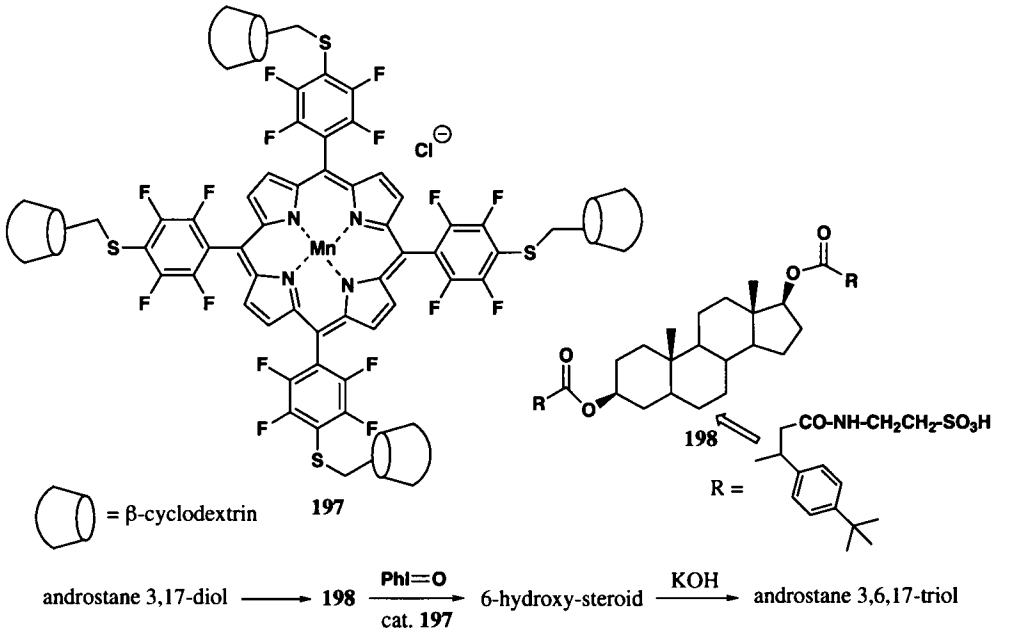
Androst-4-ene-3,6,17-trione **196** was prepared in high yield from DHEA using PCC on montmorillonite K 10 under ultrasonic irradiation (*Scheme 82*).[91]



Scheme 82 **196** (90%)

f) Hydroxylations at C-6

Mimics of cytochrome P-450 (*e. g.* **197**, *Scheme 83*) were used as catalysts for the specific hydroxylation of steroids. 3,17-Androstanediol was converted to the diester **198**, bearing *tert*-butyl groups for binding into the cyclodextrins and sulfonate groups for water solubility. The metalloporphyrin catalyzed the hydroxylation of the steroid at C-6 and with α-configuration, using iodosobenzene as oxidant. The 6α-hydroxy diester was then converted into androstane triol by hydrolysis with aqueous KOH. High yields (up to 100%) were obtained.[128-132] The 3,6,17-steroidal triester was selectively hydroxylated at C-9α by the same process.



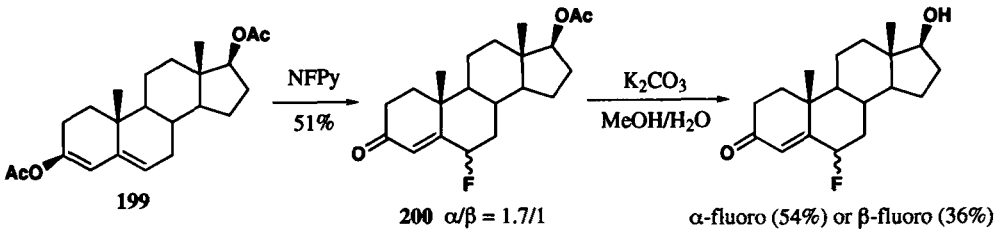
Scheme 83

The biological hydroxylation of various steroids has been described and does not appear to be very selective.[133-135] The oxidation of AD by *Bacillus* Strains gave various hydroxylated compounds, the most abundant being the 6β-hydroxy AD.[133] The microbiological hydroxylation of 3,17-dihydroxyandrostanes by *Cephalosporium aphidicola* occurred at C-6β but also at C-7 or C-11, depending of the configuration of the starting androstanediols.[134] Bovine hepatocyte cultures were used to synthesize 6β-hydroxymethyltestosterone from 17α-methyltestosterone in about 10% yield.[135]

g) Miscellaneous

An electrophilic fluorinating agent, 1-fluoropyridinium pyridine heptafluorodiborate (NFPy) was used to introduce a fluorine atom at C-6 (*Scheme 84*).[123] The steroid **199** was prepared by acetylation of testosterone in 86% yield. The reaction of **199** with NFPy gave a 1.7/1 mixture of α- and β-isomers **200** in 51% yield. The hydrolysis of these steroids was accompanied by elimination of HF and the yields of target 6-fluoro-testosterones were moderate (54% for the α-isomer) or low (36% for the β-compound).

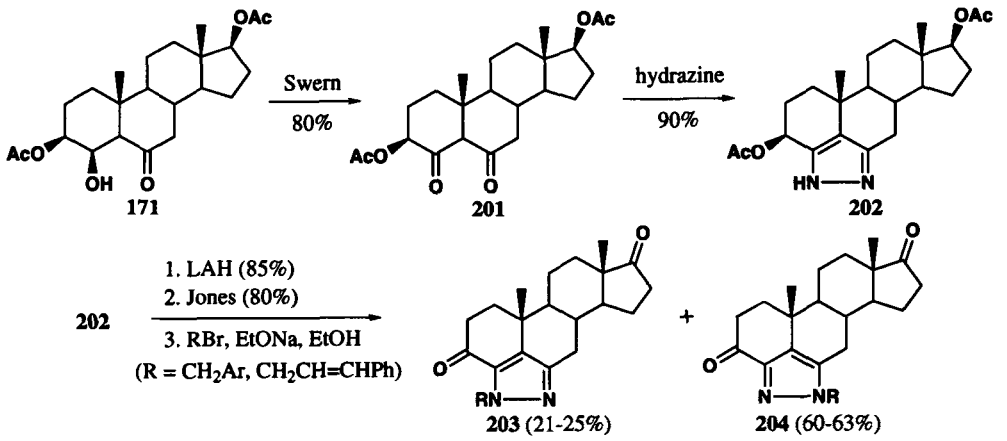
The steroid **171** (see *Scheme 72*) provided access to series of steroidal pyrazoles **203** and **204** through the 4,6-diketo compound **201**.[109] The condensation of **201** with hydrazine resulted in pyrazole **202** in high yield. The reductive deprotection of **202** afforded 3,17-diol



199 200 α/β = 1.7/1 α-fluoro (54%) or β-fluoro (36%)

Scheme 84

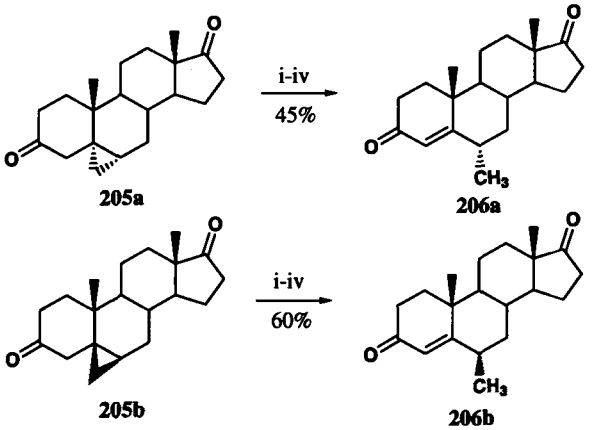
which was oxidized into 3,17-dione, followed by N-alkylation. The alkylation occured preferentially on C-6 (*Scheme 85*). These pyrazoles showed a good inhibitory activity against aromatase.



171 201 202 203 (21-25%) 204 (60-63%)

Scheme 85

A synthesis of 7α- and 7β-methyl AD was performed from the cyclopropano steroids **205a,b**.[136] Treatment of these latter compounds with mercuric trifluoroacetate, followed by reductive work-up with LAH and final oxidation of the resulting alcohols with Jones' reagent gave **206a** and **206b** in 45% and 60% yields, respectively (*Scheme 86*).



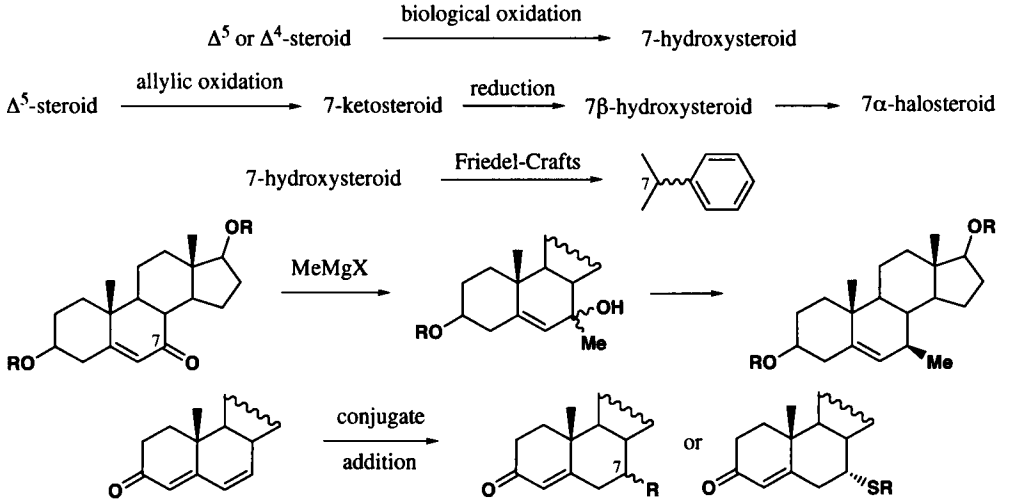
205a **206a** **205b** **206b**

i) $Hg(O_2CCF_3)_2$; i) NaCl; iii) LAH; iv) CrO_3-H^+

Scheme 86

2. 7-Modified Steroids

The main methods which were used for synthesis of 7-modified steroids are summarized in *Fig. 7*.



Access to 7-Modified Steroids

Fig. 7

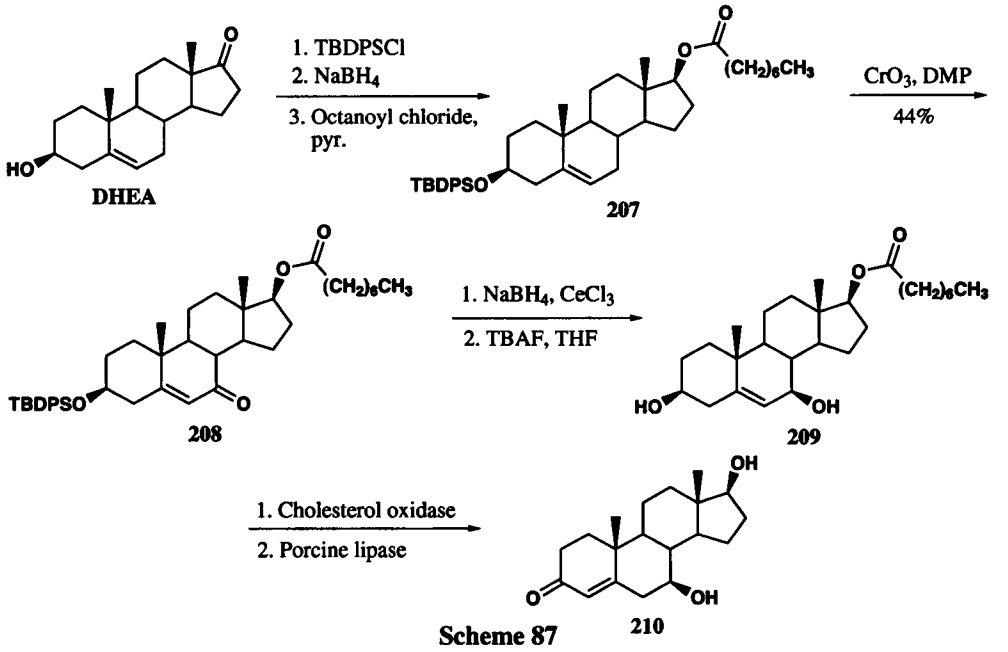
a) Biological Hydroxylations

7-Hydroxylation of dehydroepiandrosterone (DHEA) either in numerous tissues of mouse and rat or by *Fusarium moniliforme* has been reported.[137-139] Incubation of 3β-hydroxyandrost-5-en-17-one with *cephalosporium aphidicola* gave the C-7α (25% yield) and C-7β (31% yield) alcohols as major metabolites.[140] The hydroxylation of 5-ene steroids with oxygen functions at C-3 and C-17 by *Fusarium culmorum* occurred selectively at 7α-axial position. A high yield (96%) was reported for the oxidation of DHEA.[141] The oxidation of testosterone by fermentation with the fungus *Botrytis cinerea* yielded 7β,17β-dihydroxyandrostan-3-one in a good yield (73%), the selective hydroxylation at 7β being accompanied by the reduction of the 4,5-double bond.[142] The microbial hydroxylation of various steroids by fungal strains has also been reported. Androstenedione was metabolized into various hydroxy compounds and testosterone produced the 14α-hydroxytestosterone as the major compound (35%).[143]

b) Synthesis and Reactions of 7β-Hydroxysteroids

A stereoselective synthesis of 7β-hydroxytestosterone **210** was achieved in eight steps from DHEA in a 17% overall yield.[144] DHEA was first converted in three steps (protection at C-3, reduction at C-17 and esterification of the resulting alcohol) in 82% yield into the steroid **207**. The ester chain at C-17 had to be long because the 7β-hydroxy-Δ4-3-ketone functionality was very sensitive to a variety conditions used for ester hydrolysis. Allylic oxidation

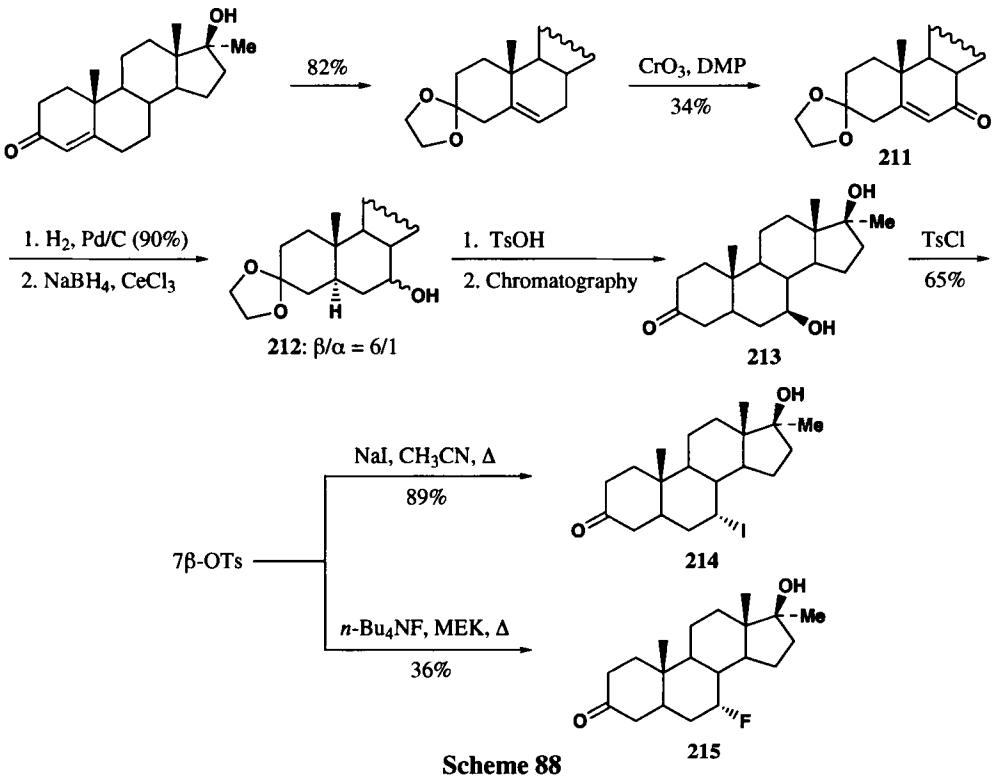
of **207** gave the ketone **208** that was then reduced stereoselectively using $NaBH_4$, $CeCl_3$. The steroid **209** was obtained in 70% yield from **208** after desilylation. Enzymatic oxidation of **209** at C-3, followed by an enzymatic hydrolysis of the ester function afforded the desired 7β-hydroxytestosterone (*Scheme 87*).



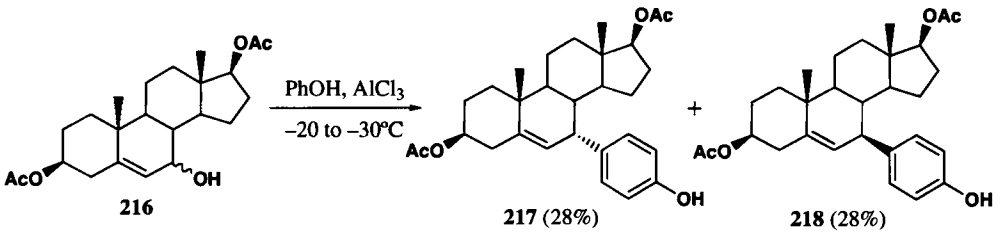
Scheme 87

The allylic oxidation at C-7 of a Δ^5-steroid using CrO_3-3,5-dimethylpyrazole (DMP) followed by a stereoselective reduction of the 7-ketosteroid with $NaBH_4$, $CeCl_3$ has also been used to prepare other 7β-hydroxysteroids. Higher yields were reported for the oxidation step.[34,121] The allylic oxidation at C-7 has also beeen performed with pyridinium dichromate and *tert*-butyl hydroperoxide.[100] This reaction may give 5-ene-4,7-diones as by products. 7α-Iodo **214** and 7α-fluoro-17α-methyl-dihydrotestosterones **215** were prepared from 7β-hydroxy compounds *via* the corresponding tosylate.[145] Ketalization of 17α-methyltestosterone followed by allylic oxidation (34% yield) gave enone **211**. Hydrogenation of **211** followed by reduction of the 7-ketone gave a 1:6 mixture of 7α- and 7β-epimeric alcohols **212**. After removal of the C-3 ketal, the desired 7β-alcohol was isolated in 70% yield from **212** by flash chromatography. The tosylate reacted with NaI or nBu_4NF to afford the target compounds in good or low yields (*Scheme 88*). 7α-Fluoro-DHT was also prepared, in 23% yield, by fluorination of the corresponding tosylate.[145,146]

The synthesis of the 7α- and 7β-arylandrostenes **217** and **218** was achieved through Friedel-Crafts reaction on the 7-hydroxy compound **216**.[147] The reaction of **216** with phenol in the presence of of anhydrous $AlCl_3$ at –20 to –30°C gave a (1:1) isomeric mixture of the stereoisomers which could be separated into pure **217** and **218** by chromatography (*Scheme 89*).



Scheme 88

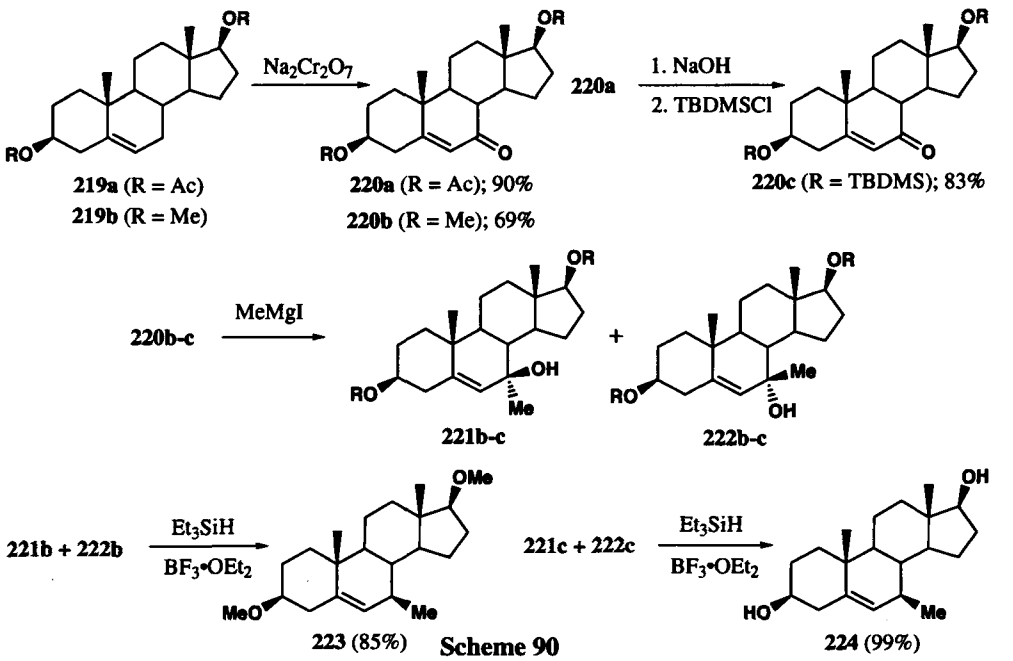


Scheme 89

c) Synthesis and Reactions of 7-Ketosteroids

Due to the environmentally hazardous nature of chromium, new methods for allylic oxidation of Δ^5-steroids have been developed based on catalyzed *tert*-butyl hydroperoxide (TBHP) oxidation with metal or metal salts as catalysts. The following catalysts were reported: $RuCl_3$,[148] Cu(II) and Cu(I) salts or Cu metal,[149] cobalt acetate (in homogeneous or heterogeneous forms)[150] and Co(II) alkyl phosphonate modified silica.[151] The allylic oxidation products were generally obtained in high yields (70 to 89%) and selectivity in the presence of a 17β-hydroxy function was observed.[149,150] The reactions were best performed either at room temperature in non polar solvent ($RuCl_3$ as catalyst) or at 50-55°C in acetonitrile (other catalysts). The

synthesis of 7β-methyl-androst-5-enes **223** and **224** (*Scheme 90*) was achieved from 7-ketosteroids **220a-c**.[152] These ketosteroids were prepared either by oxidation with sodium dichromate of the corresponding 5-ene compounds **219a-b** (in 90 and 69% yields respectively) or by alkaline hydrolysis of **220a** followed by silylation of the resulting diol, in 83% overall yield. The addition of MeMgI to ketosteroids **220b-c** gave equal amounts of of the addition products **221** and **222** in quantitative yields. The mixture of addition products was then reduced by ionic hydrogenation with $Et_3SiH/BF_3{\cdot}OEt_2$ to afford **223** in 85% yield or **224** in 99% yield, the silyl ether groups being removed under deoxygenation conditions in the latter case. The approach of relatively bulky triethylsilane to the 7-carbocation formed during the deoxygenation process occurred from the α-side.

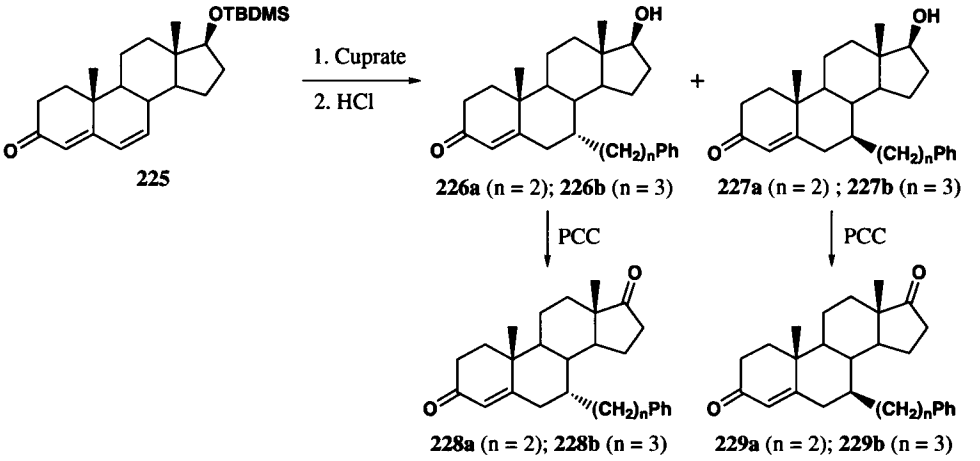


Scheme 90

d) 1,6-Conjugate Addition of Cuprates

7-Substituted androstenediones **228a,b** and **229a,b** were synthesized *via* a 1,6-conjugate addition of the appropriate cuprate reagent to steroid **225** (*Scheme 91*), which was prepared in two steps from testosterone (6,7-dehydrogenation with chloranil followed by silylation of 17-hydroxy function in 88% yield).[14,153] The cuprate was formed either by reacting tetrakis [iodo-(tri-*n*-butylphosphine)copper(I)] with the lithium reagent[153] or by reaction of this lithium reagent with CuI followed by addition of n-Bu_3P, the yields being higher in this latter case.[14] The conjugate addition resulted in a mixture of α- and β-epimers which were separated after deprotection. The mixture of α:β **226** and **227** were obtained in overall yields of 70-80%, the epimer ratios being of α/β = 2/1 (n = 2) or 1/1 (n = 3). The four androstenediones were

then obtained in quantitative yields by oxidation with PCC. A similar approach was utilized for synthesis of 7-benzyl androstenediones.[153] The Grignard reagent of benzyl bromide and catalytic amount of tetrakis [iodo-(tri-*n*-butylphosphine) copper(I)] were used in this case. The overall yield of epimers was lower (33%), due to competing 1,2-addition of the benzyl group, but the stereoselectivity was higher (α/β = 5/1).



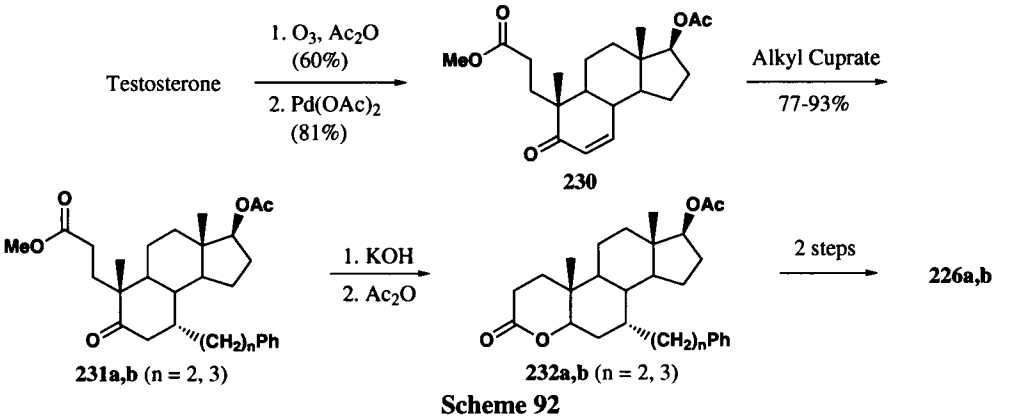
225

226a (n = 2); **226b** (n = 3) **227a** (n = 2) ; **227b** (n = 3)

228a (n = 2); **228b** (n = 3) **229a** (n = 2); **229b** (n = 3)

Scheme 91

An alternate approach has been developed to improve the α/β ratio, that involved oxidation of the A ring of testosterone to yield a seco-A-ring enone **230** (48% yield), followed by 1,4-conjugate addition (77-93% yields) and subsequent A ring closure (*Scheme 92*).[154,155] The intermediate enol lactones **232a,b** (66-71% yields) were transformed to testosterones **226a,b** by treatment with $LiCH_2P(O)(OMe)_2$ followed by hydrolysis of the 17-acetoxy group (67-88% yields). The overall yield of this synthetic approach was approximately the same but stereoselectivity was raised, a 7/1 mixture of α/β isomer being produced.

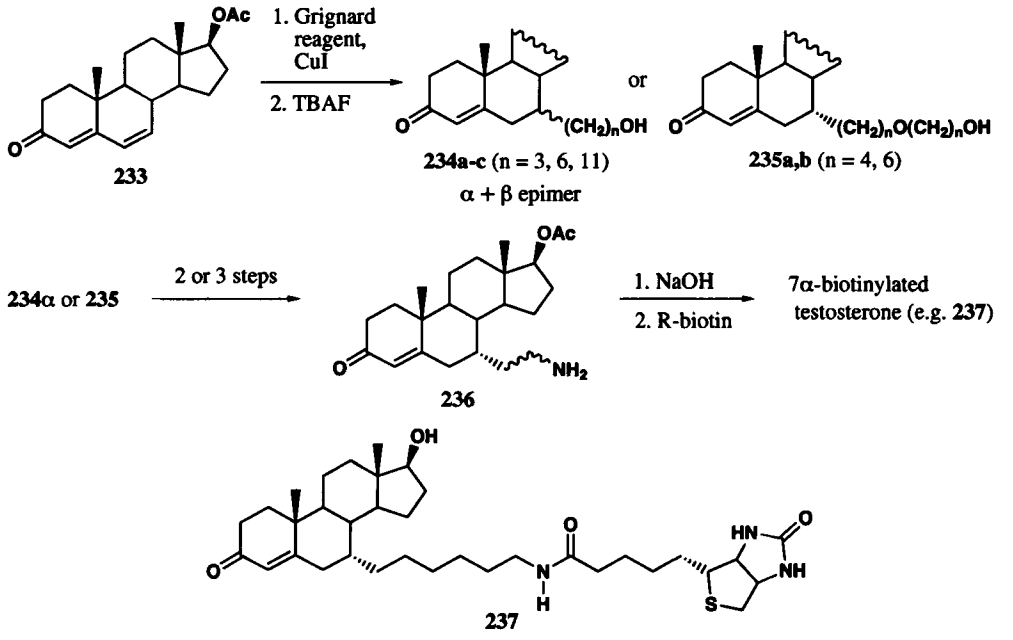


230

231a,b (n = 2, 3) **232a,b** (n = 2, 3) **226a,b**

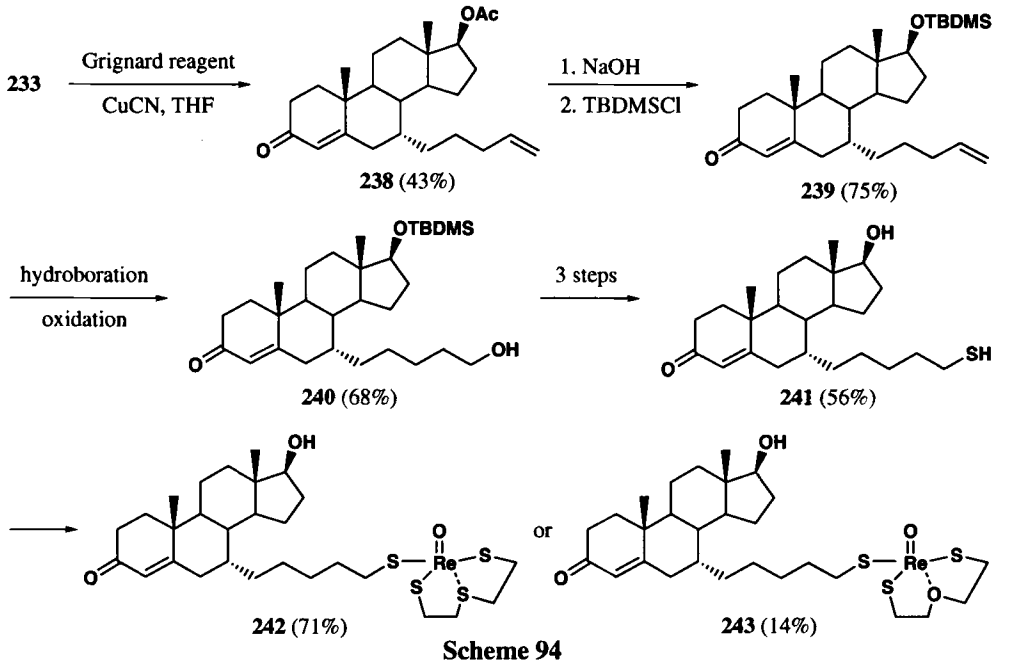
Scheme 92

Various 7α-biotinylated testosterones (*e. g.* **237**, *Scheme 93*) were prepared *via* copper-catalyzed 1,6-addition of alkyl Grignard reagents to the 6,7-dehydrotestosterone **233**.[48,156] The addition provided either α/β-mixtures (α/β = 1.7-2) of 7-substituted testosterones **234** (77-89% yields) or α-epimers **235** (46-51% yields). The various amino derivatives **236** were then prepared in high yields either *via* oxidation of the alcohol **234a** (α-epimer) followed by a reductive amination of the resulting aldehyde[156] or by functional groups interconversions (mesylation of the α-epimers of **234** or of **235** followed by conversion into azides which were converted into amines by the Staudinger reaction with PPh_3 in boiling wet THF).[48] The synthesis was completed by amidation with various biotins after hydrolysis of the 17-acetoxy group (*Scheme 93*).



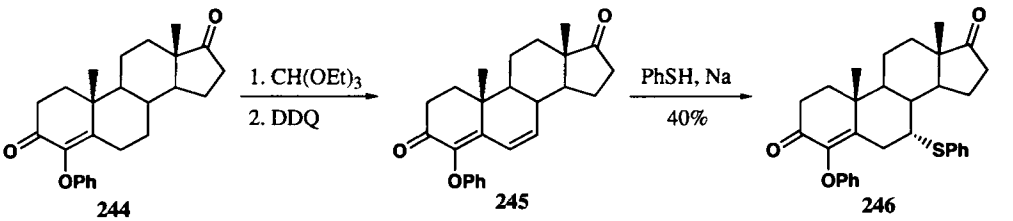
Scheme 93

The copper-catalyzed α-selective 1,6-Michael addition of a Grignard reagent to steroid **233** was also the key step in the synthesis of the oxorhenium(V) complexes **242, 243** containing a testosterone moiety (*Scheme 94*).[157] The use of THF and CuCN for the Michael addition provided the α-epimer **238** in 43% yield that was separated from its β-epimer (10% yield) by chromatography. The protective group at C-17 was then changed in two steps (75% yield) followed by a hydroboration/oxidation to afford the alcohol **240** in 68% yield. The thiol **241** was then prepared in 56% overall yield from **240** (12% from **233**) *via* a thiobenzoate by the Mitsunobu reaction followed by cleavage of the protective groups. The complexes **242, 243** were respectively obtained in 71% and 14% yields by reaction of the thiol with appropriate rhenium derivatives.



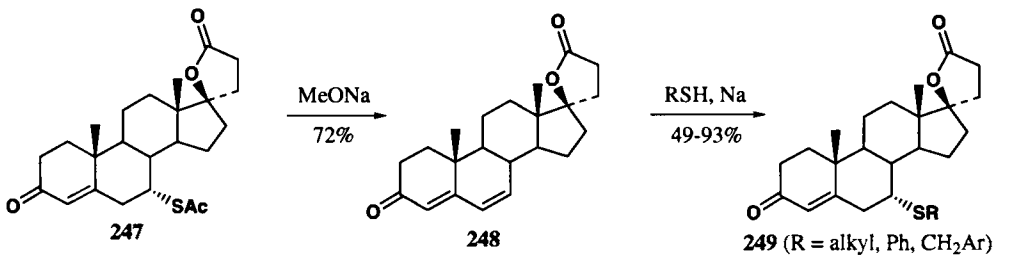
Scheme 94

The 7α-phenylthioandrostene **246** was obtained in 40% yield by base-catalyzed 1,6-Michael addition of thiophenol to steroid **245**, that was prepared in two steps from **244** (50% yield). Introduction of the 6,7-double bond involved an enol ether that was dehydrogenated with DDQ (*Scheme 95*).[158]



Scheme 95

The sodium-mediated 1,6-conjugate addition of various thiols was also used to synthesize a series of 7α-substituted spirolactones **249** in 49-93% yields (*Scheme 96*).[159] The

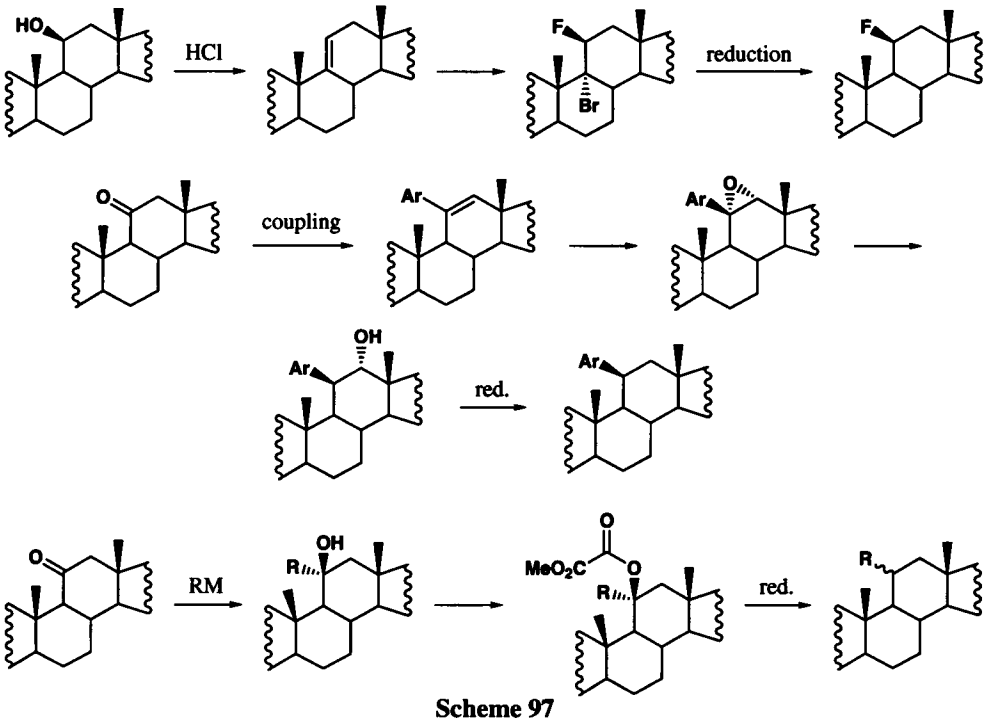


Scheme 96

6,7-dehydrosteroid **248** was prepared in 72% yield from spirolactone **247** by a retro-Michael elimination of the thioacetyl group.

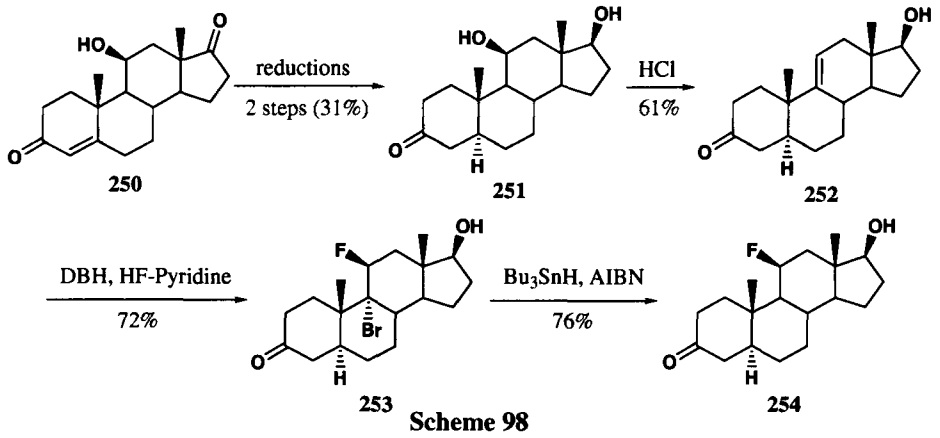
III. MODIFICATIONS OF RING C

Teutsch[160] showed that a lipophilic pocket of the progesterone receptor protein fits very well for flat unsaturated 11β-substituents in steroids and his group has described numerous synthesis in norsteroids series. Little work has been done however to prepare 11-substituted compounds in androstane or androstene series, due to the poor reactivity at C-11. The various approaches are summarized in *Scheme 97*.



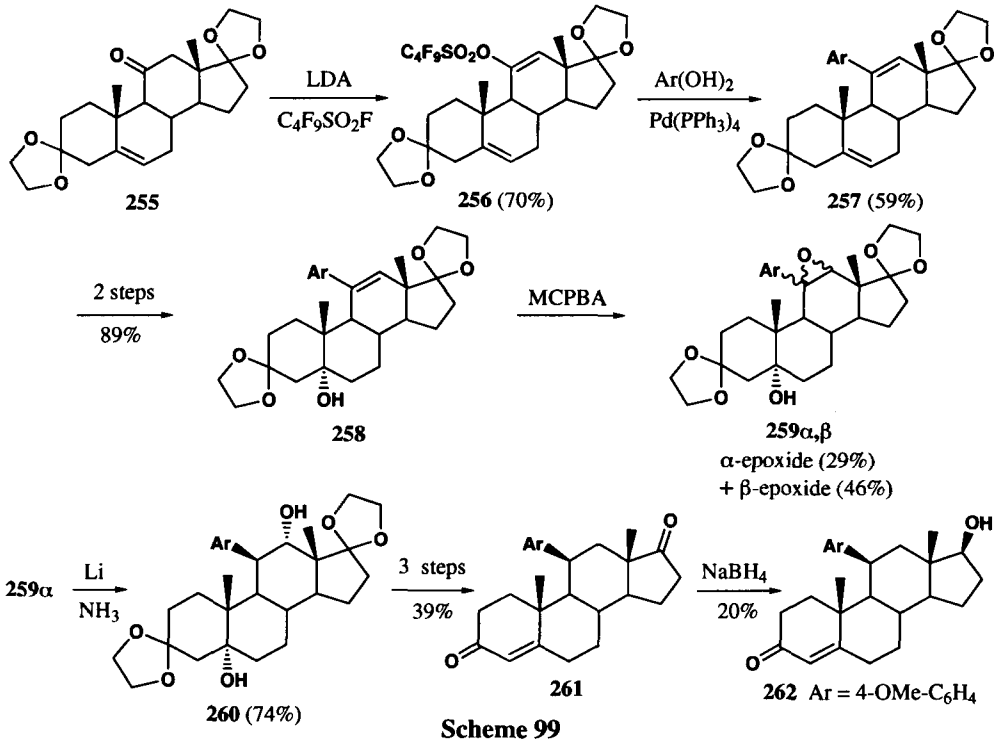
Scheme 97

The synthesis of 11β-Fluoro-dihydrotestosterone **254** was based on halofluorination of a 9,11-alkene precursor **252** (*Scheme 98*).[161] The two-step reduction of compound **250** gave 11β-hydroxydihydrotestosterone **251** with an overall yield of 31%. Treament of this diol with acid afforded the alkene **252** exclusively (61% yield). Halofluorination of the alkene with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and HF-pyridine resulted in axial attack by fluoride ion on the 9,11-bromonium ion. This bromonium ion was formed on the α-side to avoid steric hindrance from the 18- and 19-methyl groups on the β-side. The desired product was then obtained by reductive debromination of **253**. The in vivo properties of **254** in rats are favorable for imaging of prostate cancer.



Scheme 98

The synthesis of the 11β-aryltestosterone **262** started with the protected adrenosterone **255** (*Scheme 99*)[162] The aryl introduction was performed by Suzuki cross-coupling (59% yield) of

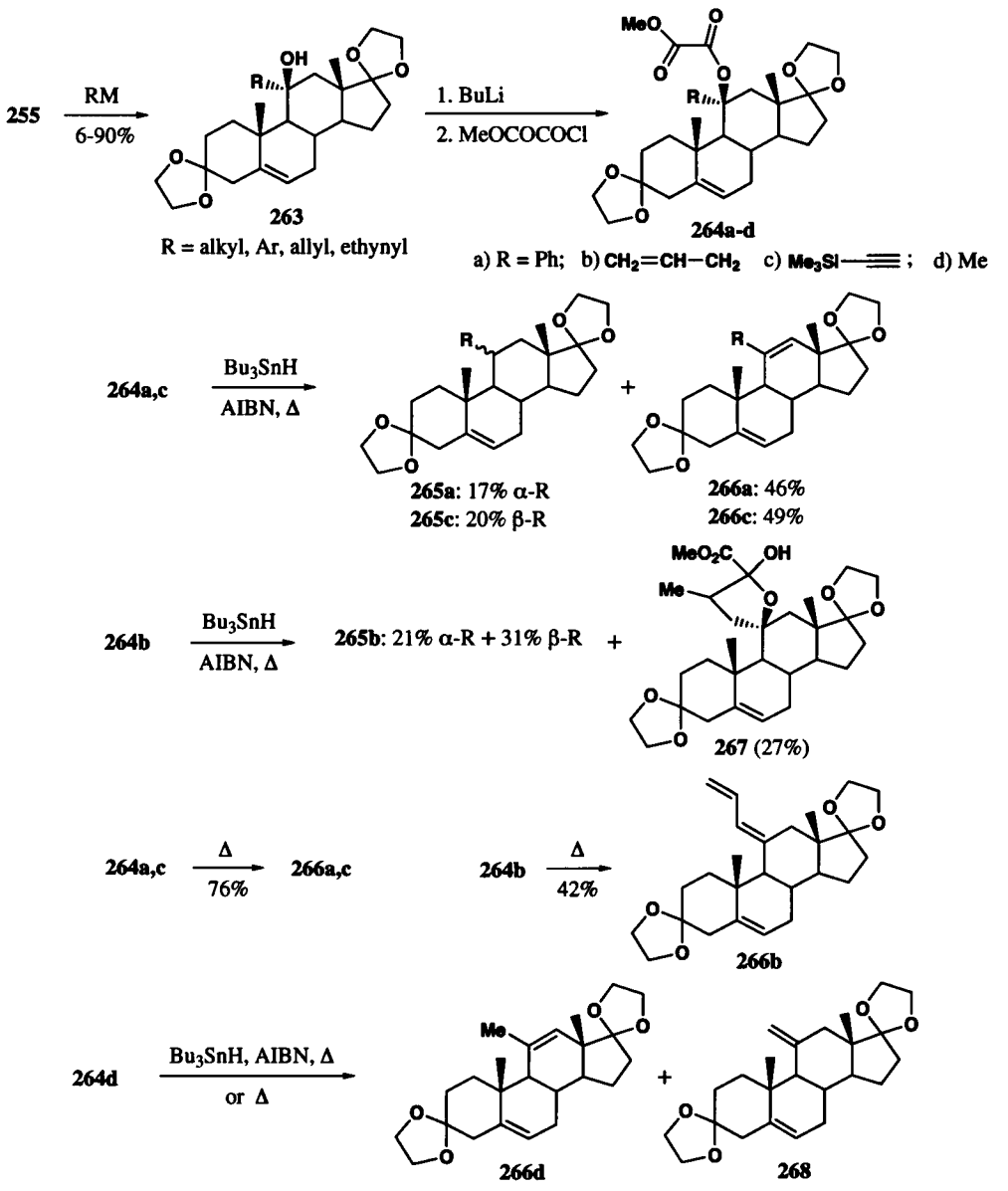


Scheme 99

the kinetically controlled nonaflate **256** with a tenfold excess of arylboronic acid. The reduction of the 11-double bond in **257** was effected neither by dissolved metal in ammonia nor by hydrogenation. A 11,12-epoxide **259** was then prepared with prior protection of the 5-double bond by α-epoxidation followed by reduction to **258** (89% yield). A 3/2 mixture of β/α-epoxides **259** was obtained in overall 75% yield. The 11β-arylandrostane **260** was then prepared by stereospecific

reduction of **259α** in 74% yield. The deprotection of both carbonyl groups followed by removing of the 12α-hydroxy function afforded the androstenedione **261** in 39% overall yield from **260**. The reduction of this dione to 11β-aryltestosterone **262** displayed only low 3,17-selectivity (20% yield in **262**). The overall yield of this synthesis was very low.

Various C-11 modified androstenes were prepared from the oxalates derivatives of 11β-hydroxy compounds **263**, these latter steroids being synthesized by organometallic reagents addition to the 11-ketosteroid **255** (*Scheme 100*)[163-168] The addition of aryl- and alkyl



Scheme 100

lithium derivatives to **255** was better achieved in non-polar or low-polar media to produce addition compounds **263** in medium (50% yield for R = Ph) to high yields (84-88% yields for R = alkyl).[163-165] The 11α-allyl compounds **263** were prepared by a Barbier-Grignard reaction in low (17% yield for R = cinnamyl) to high yields (80-90% for R = allyl, crotyl).[166] The 11α-alkynyl steroids **263** were obtained by addition of lithium or sodium alkynyl derivatives to **255** with low to moderate yields (6-34%).[168] The oxalates **264a-d**, which were quantitatively prepared by deprotonation of **263** and treatment with methyl chlorooxoacetate, were then deoxygenated under free-radical conditions to afford a mixture of 11-substituted androstenes **265a-c** and elimination products **266a-d** or **268**.[167,168] The androstenes **265** were obtained in moderate to medium yields either as pure α- (**265a**) or β-epimer (**265c**) or as a mixture of α/β epimers (**265b**), the product distribution depending of steric factors.[168] The elimination compounds **266** may be prepared by thermolysis (at 110°C) of the oxalates in 42-76% yields, a mixture of isomers **266** and **268** being obtained for thermolysis of the 11α-methyl oxalate **264d**. The 11-tetrahydrofuran **267** was formed in 27% isolated yield during the course of the deoxygenation of the 11α-allyl oxalate **264b**.

IV. MODIFICATIONS OF RING D

1. 16- and 16,17-Modifed Steroids

C-16 and C-16,17-modified compounds were generally prepared from 17-keto-, α-substituted 17-keto- or Δ^{16}-steroids (*Fig. 8*).

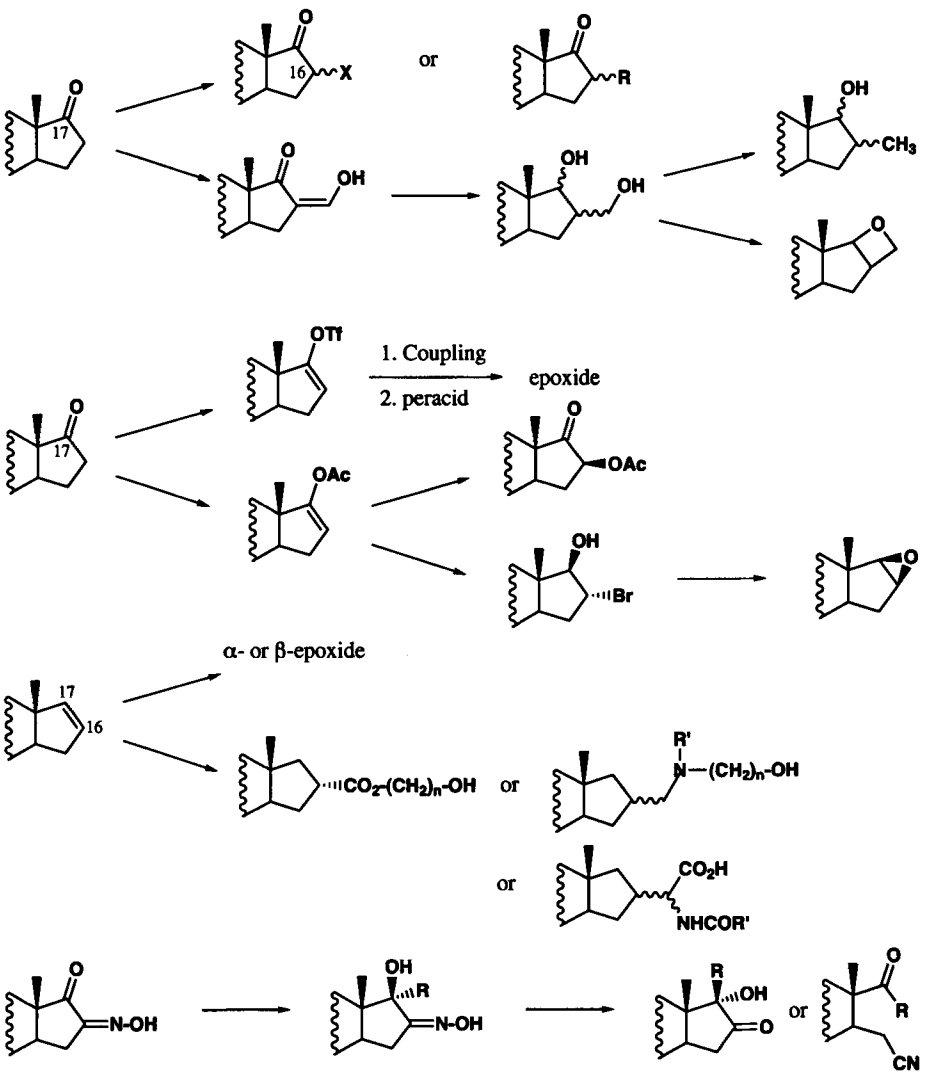
a) Synthesis from 17-Ketosteroids

A direct α-fluorination of ketones, using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2] octane *bis*(tetrafluoroborate) was used to prepare the 16α-fluorosteroid **269** (*Scheme 101*).[169]

A [4 -^{14}C] labeled 16α-bromosteroid **272α** was prepared in good yield from a labeled testosterone (*Scheme 102*).[170] Birch reduction of the testosterone followed by Jones oxidation afforded the dione **270** that was selectively reduced at C-3 with lithium tri-*tert*-butoxy aluminum hydride (LATH) to **271**. Selective bromination of **271** with $CuBr_2$ gave 75% of the target compound and the 16β-isomer (20%).

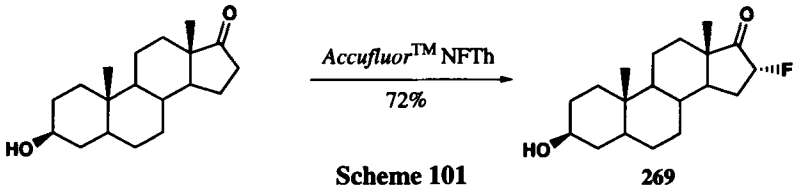
16-Substituted androsterone derivatives **277** and **279** were synthesized from the protected ADT **273** (*Scheme 103*).[171] The enolate of **273** was alkylated by allyl bromide at low temperature to afford a 88/12 mixture of α/β-allyl compounds **274** in 70% yield. The hydroboration/oxidation of this mixture afforded the 16α-compound **275** in 65% yield after chromatography. Substitution of the primary alcohol lead to bromide **276** (70%) that was hydrolized to the diol **277** in 68% yield. The steroid **276** was also oxidized to 17-keto compound **278** (86% yield) followed by deprotection with HCl in methanol. An epimerization occured at C-16 and the two stereoisomers **279α** an **279β** were obtained in a 3 to 1 proportion (92% global yield). Dialkylated ADT were also prepared from **273** using NaH and halides or dihalides.

The treatment of enol acetates **280a-c** with lead (IV) acetate in acetic acid containing Ac_2O gave 16β-acetoxy-17-ketosteroids **281a-c** in 54-62% yields, along with steroids **282a-c**



Access to 16- and 16,17-Modified Steroids

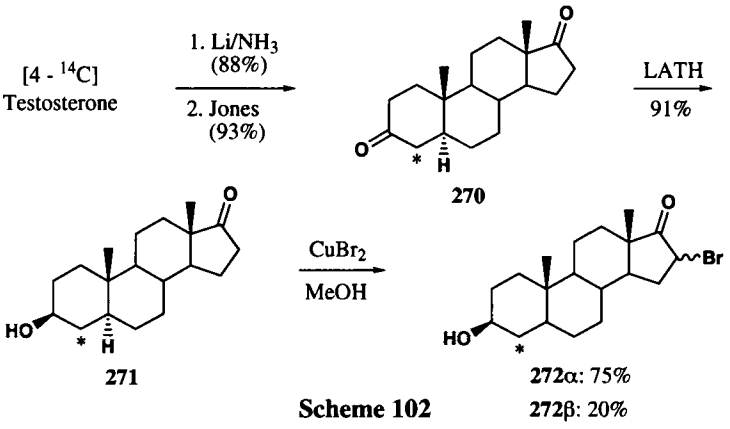
Fig. 8



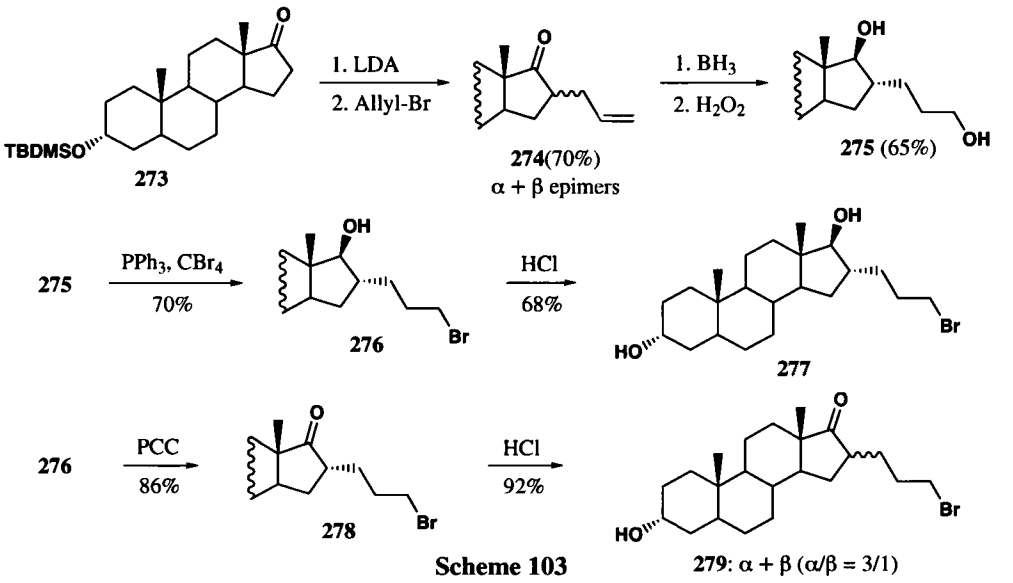
Scheme 101 **269**

as minor products (*Scheme 104*).[172] The alkaline hydrolysis of **282c** afforded 17β-hydroxy-16-keto **283** (55%) the most thermodynamically stable 16,17-ketol. Isotopes labelling experiments were performed, which seemed to show that the compounds **282a-c** are produced through a

migration of the 17-acetyl group on the enol acetate to the 16β-position followed by attack of an acetoxy anion.

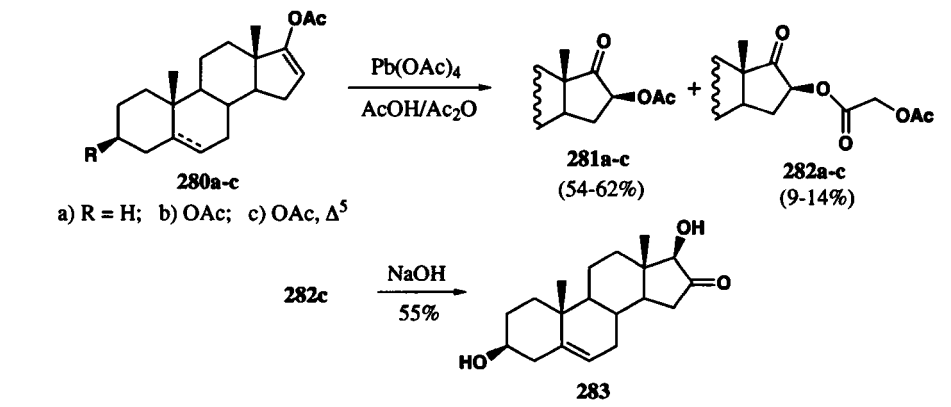


Scheme 102

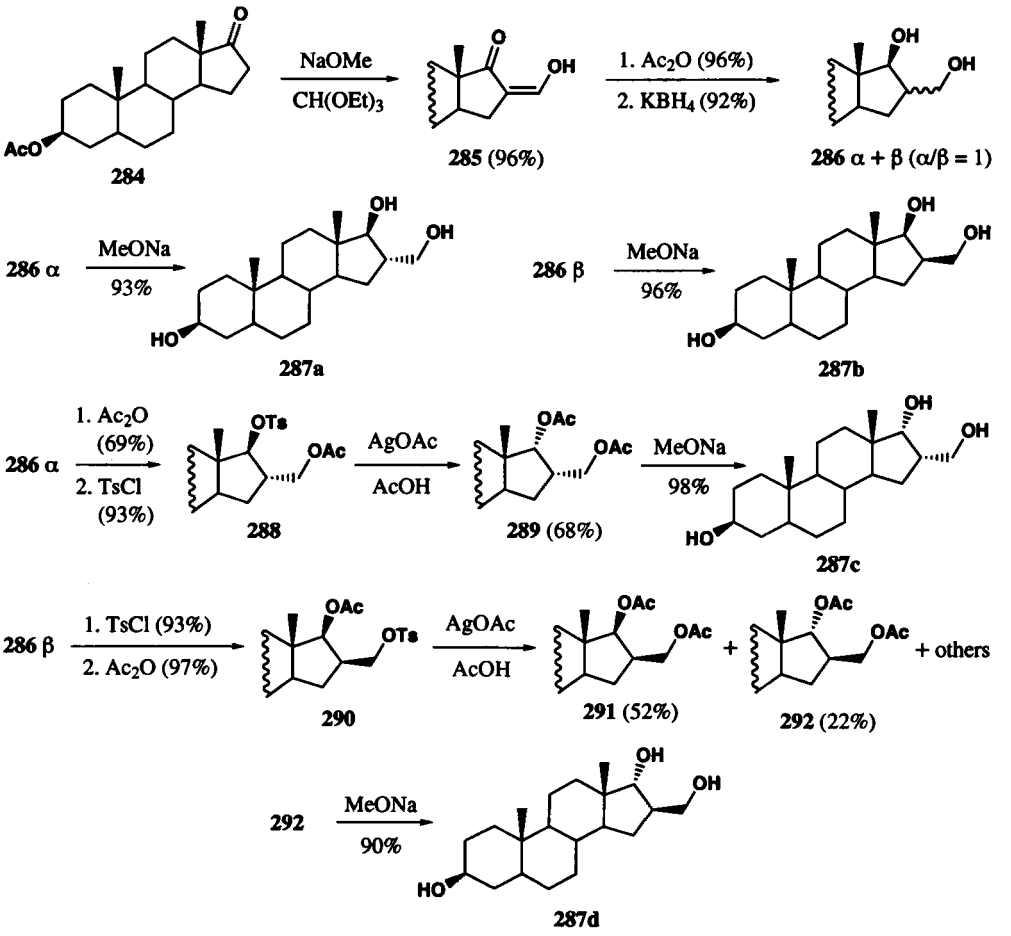


Scheme 103

The four stereoisomers of 16-hydroxymethyl-androstane-3β,17-diol **287a-d** were synthesized from 17-ketosteroid **284** (*Scheme 105*).[173] Formylation of **284** gave diketo compound **285** in 96% yield. The acetyl derivative of **285** was then reduced with KBH_4 (92%) to a 1/1 separable mixture of epimeric 16-hydroxymethylsteroids **286α** and **286β**. The androstane-diols **287a,b** were then prepared in high yields by saponification of the 3-acetates. The epimeric **286α** and **286β** were separately converted in good yields to compounds **288** and **290**, which were subjected to acetolysis in the presence of AgOAc in AcOH. These reactions involved carbocation formation and resulted in mixture of products. The triacetates **289** and **292**, which were obtained in moderate to good yields, were then converted to stereoisomers **287c** and **287d**.

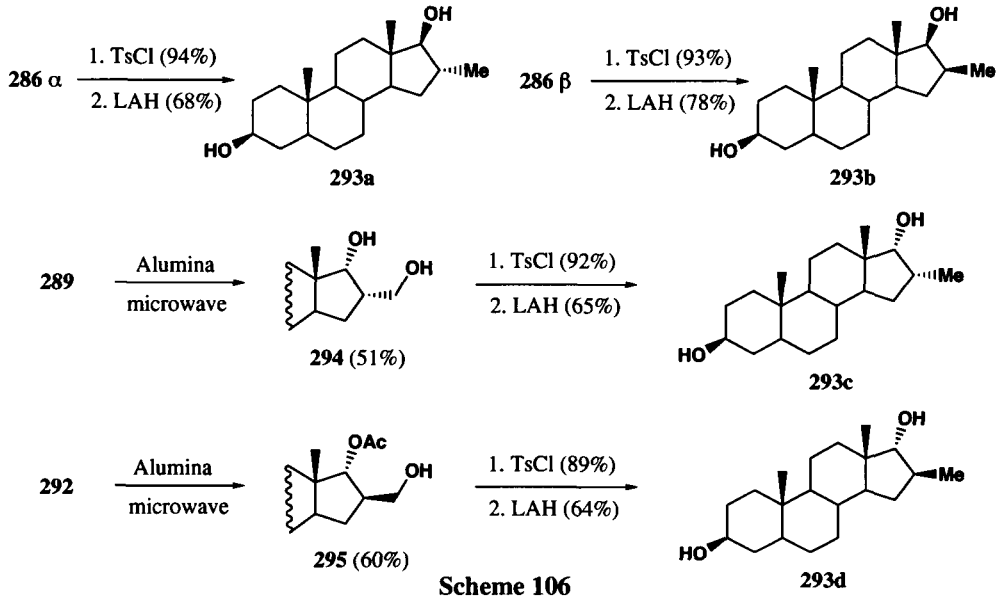


Scheme 104



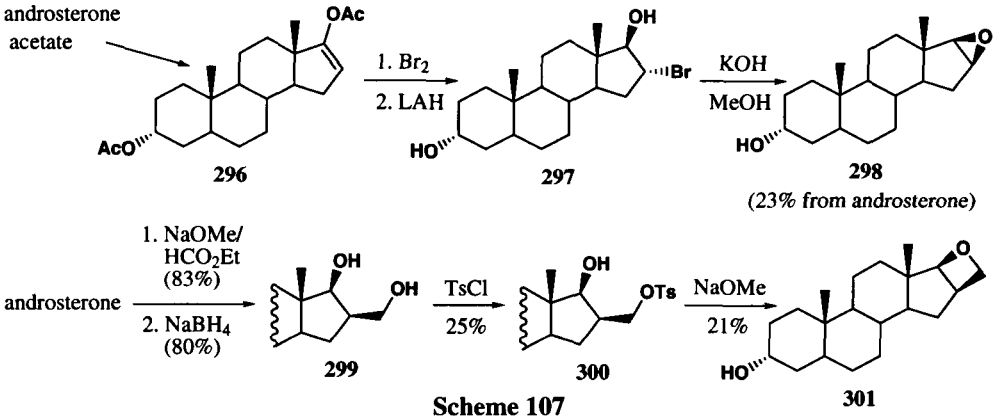
Scheme 105

The four isomers **293a-d** of 16-methyl-androstane-3β,17-diol were synthesized from some of the preceding steroids (*Scheme 106*).[174] The triacetates **289** and **292** were deacetylated respectively to diol **294** (51%) and diacetate **295** (60%) by microwave irradiation on alumina.[42] The four steroids **286α, 286β, 294** and **295** were then converted into tosylates (89-94%) which were reduced in 64-78% yields to 16-methyl compounds **293a-d**.



Scheme 106

Cyclic 16,17-ethers were prepared from androsterone (*Scheme 107*).[175] Androsterone acetate was first converted to the enol ester **296** and brominated to give 16α-bromo ketone which was reduced to the 17β-ol **297**. The halohydrine **297** was then treated with base to



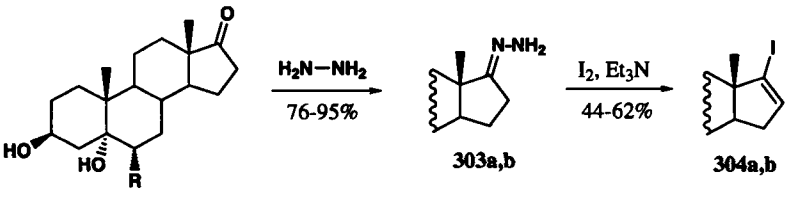
Scheme 107

afford the β-epoxide **298** in 23% yield from androsterone. The fused oxetane **301** was prepared by formylation of androsterone (83%) followed by stereoselective borohydride reduction (80%) to give the triol **299**. Selective tosylation of the primary alcohol afforded **300**

in low yield (25%). The oxetane **301** was then formed in 21% yield by cyclization with sodium methoxide.

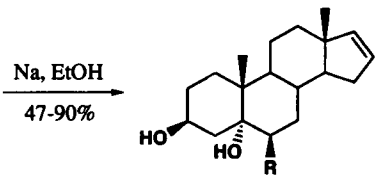
b) Synthesis and Reactions of Δ^{16}-Steroids

The 16-ene steroids **305a,b** have been synthesized from 17-keto compounds **302a,b** *via* the iodides **304** (*Scheme 108*).[108] The iodides were reduced by sodium in EtOH to the target steroids **305** in 47-90% yields.



302a,b
a) R = H; b) OH

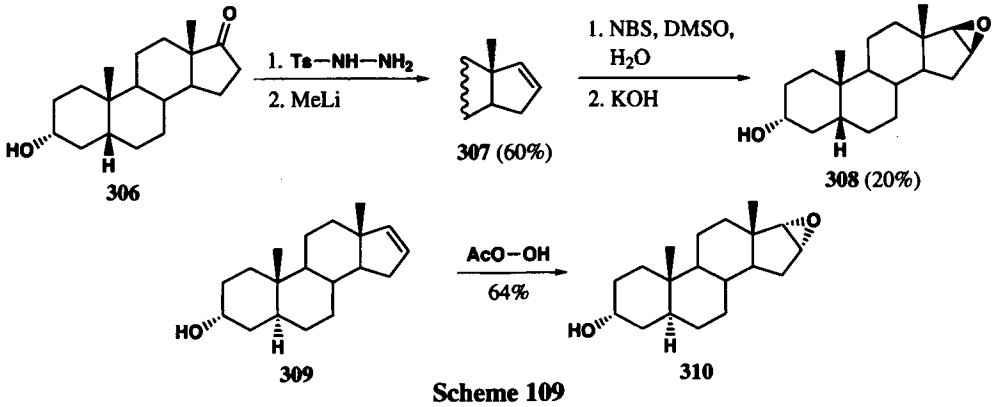
303a,b **304a,b**



305a,b

Scheme 108

The 16-ene steroid **307** was prepared from 17-one **306** *via* the tosylhydrazone in 60% yield (*Scheme 109*).[175] Epoxidation of **307** afforded the β-epoxide **308** in low yield. The diastereoisomeric epoxide **310** was prepared in better yield from 5α-H-16-ene steroid **309**.

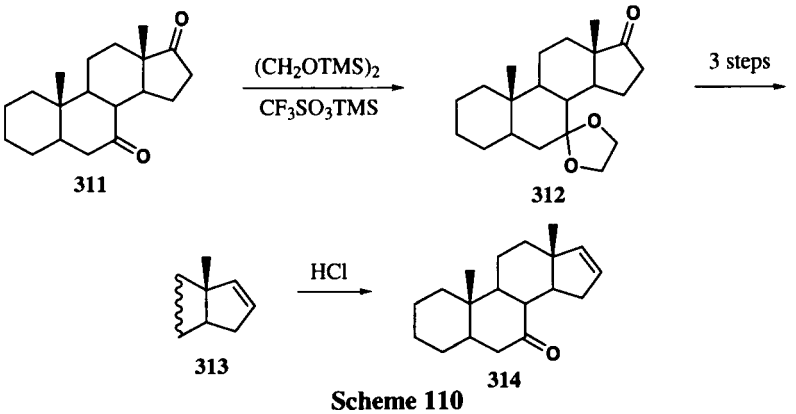


306 **307** (60%) **308** (20%)

309 **310**

Scheme 109

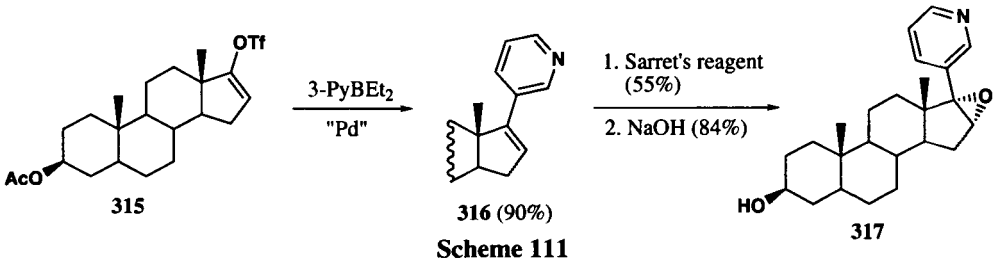
Androst-16-en-7-one **314** was prepared from dione **311** (35% overall yield) in a five-steps sequence, *via* selective ketalization at C-7 with *bis*-trimethylsilyloxyethane and trimethylsyliltriflate as the key step (*Scheme 110*).[176] The introduction of the Δ^{16} bond involved reaction of the 17-hydrazone with iodine followed by deiodination (see *Scheme 108*).



311 312 313 314

Scheme 110

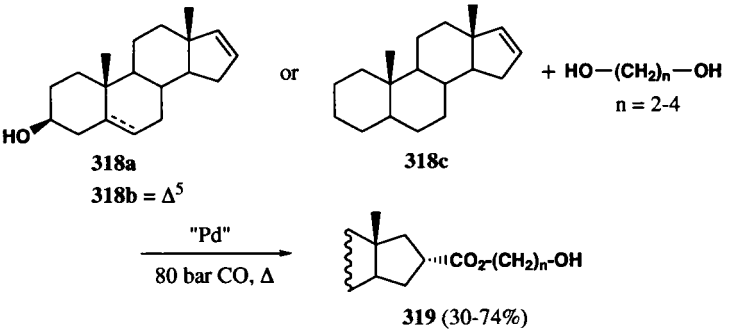
The enol triflate **315** of epiandrosterone acetate coupled with a pyridinylborane to afford the 16-ene **316** in high yield (*Scheme 111*)[177] The α-epoxidation of **316** was performed with Sarret's reagent (55%) followed by hydrolysis to the target compound **317**.



315 **316** (90%) **317**

Scheme 111

Δ^{16}-steroids **318a-c** were converted in medium to good yields to 16α-hydroxyesters **319** by palladium-catalyzed carbonylation in the presence of diols (*Scheme 112*).[178] the 16,17-dihydrosteroids (0.6-12%) and the minor 16β isomer (2.7-6.7%) were formed as by-products.

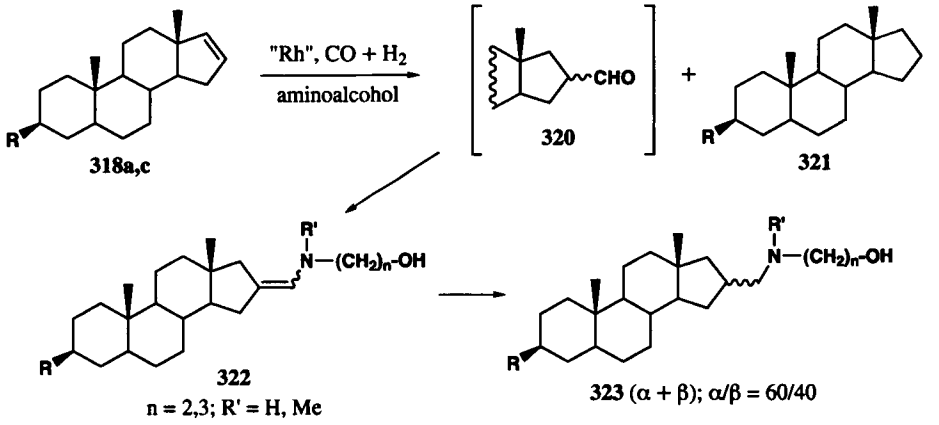


318a
318b = Δ^5
318c
319 (30-74%)

Scheme 112

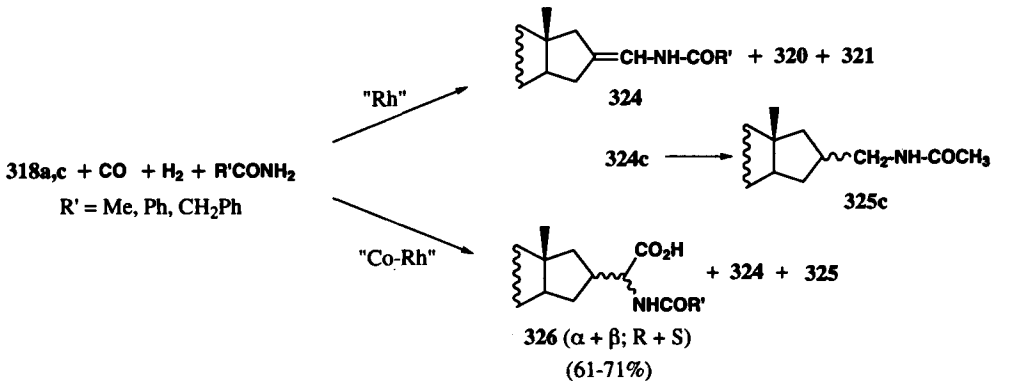
The rhodium-catalyzed carbonylation of **318a,c** in the presence of aminoalcohols afforded 16-substituted androstanes **323** in 50-85% yields with a 60/40 α/β isomers ratio

(*Scheme 113*).[179] The compounds **321** (6.5-19.6%) and **322** (0-17.4%) were observed as by products.



Scheme 113

Hydroformylation-amidocarbonylation of steroids **318a-c** afforded various compounds according to the catalyst (*Scheme 114*).[180] Working with the Rh-PPh_3 catalyst, steroids **324** were the major product (yields not given) accompanied by hydroformylation and



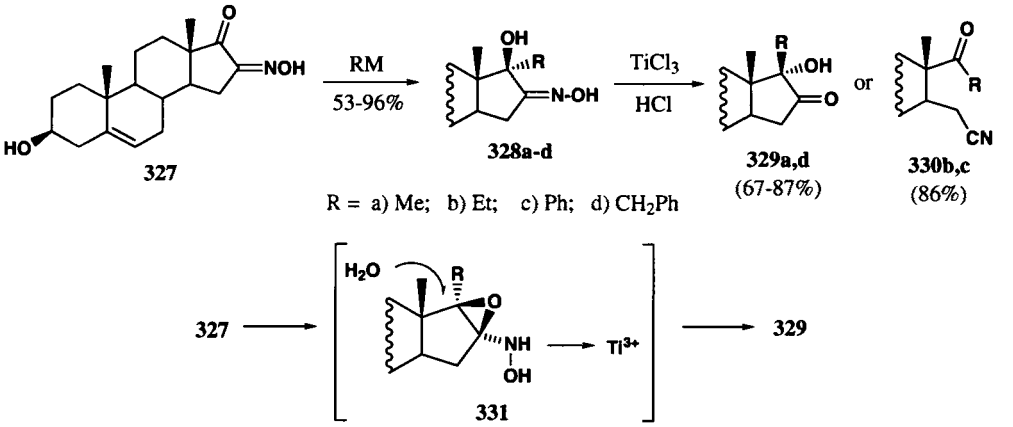
Scheme 114

hydrogenation products **320** and **321**. In the presence of PBu_3 ligand, the hydrogenation of **324c** was observed for R' = Me. Switching to a binary rhodium-cobalt catalyst system, N-acyl-α-amino acids **326** became the major products (61-71% yields). Four diastereoisomers should be formed. The α/β ratio at C-16 depended on the phosphine ligand and the Co/Rh ratio. The best result (α/β = 10/90) was obtained with PPh_3 as ligand at sixfold cobalt excess.

c) Miscellaneous

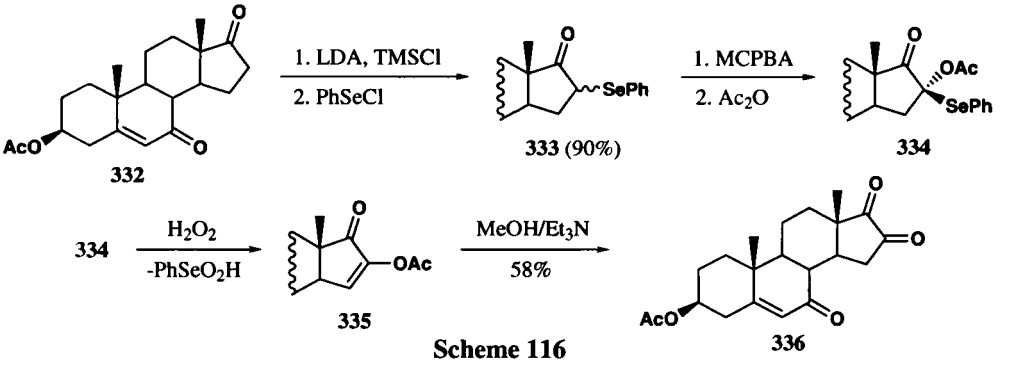
17β-Hydroxy-16-oximino steroids **328a-d** were prepared in 53-96% yields by addition of large excess of Grignard reagents (R = Me, Et) or organolithium compounds (R = Ph, CH_2Ph)

to ketosteroid **327** (*Scheme 115*).[181,182] These adducts were then subjected to the reaction of fragmentation using $TiCl_3$ in acidic medium. Whereas **328b,c** gave Beckmann rearrangement compounds **330b,c** in high yields the major reaction was the hydrolysis of the 16-oximino function for **328a,d** accompanied by inversion of the configuration at C-17. This inversion may resulted of nucleophilic attack of water from the α-side on an intermediate oxiran **331**.



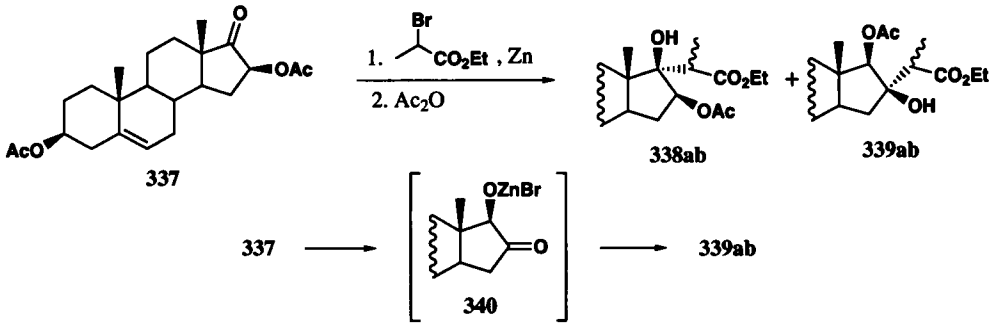
Scheme 115

The 16,17-dione **336** was synthesized from 17-ketosteroid **332** *via* a seleno-Pummerer reaction (*Scheme 116*).[183] The silyl enol ether of **332** was selenylated in high yield to 16α-selenide **333** followed by seleno-Pummerer reaction to afford the 16-acetoxyselenide **334** as a 85/15 mixture of diastereoisomers. Oxidative elimination formed the enol acetate **335** in 60% yield from **333**. This enol acetate was then hydrolyzed to 16,17-dione **336** in 58% yield. Secosteroids and D-ring lactones were also prepared respectively from **336** and **333**.



Scheme 116

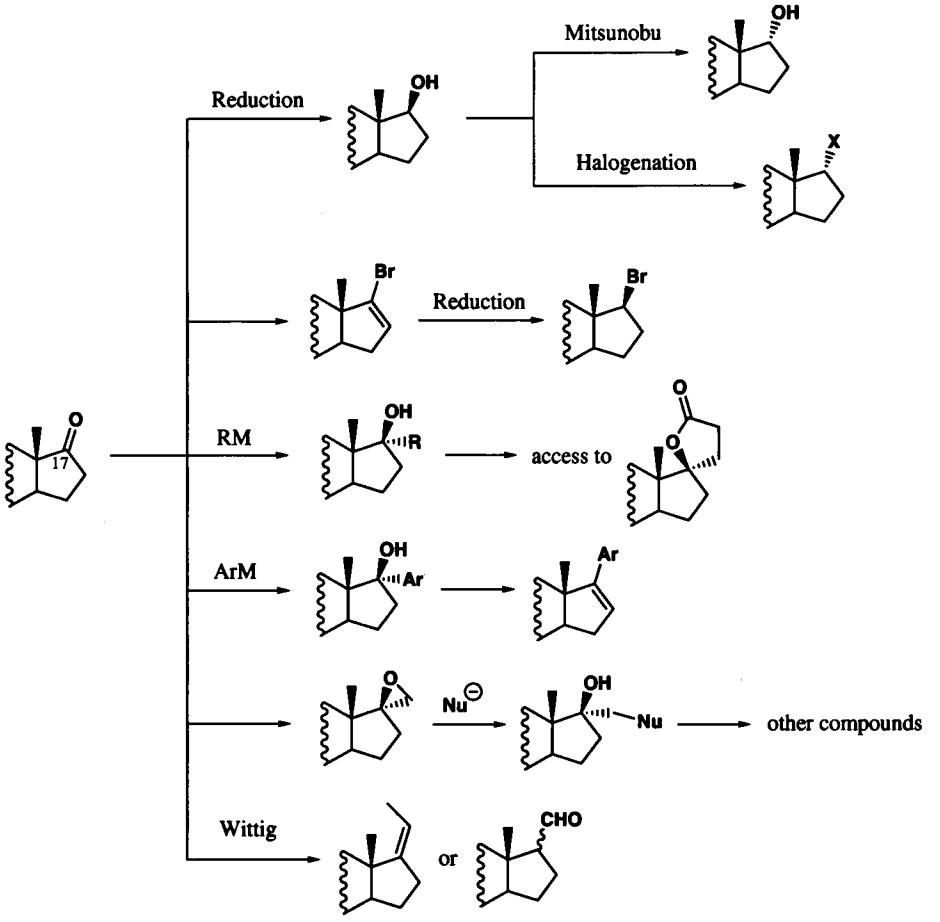
The addition of a Reformatsky reagent on 16β-acetoxy-17-ketosteroid **337** gave a mixture of four different β-hydroxy esters **338a,b** and **339a,b** (yields not given). The formation of **339a,b** was rationalized by calling for an isomerization of **337** to a 17β-hydroxy-16-keto system **340** (*Scheme 117*).[184] The specific addition on C-17 was achieved by using lithium enolate of *tert*-butyl propionate at low temperature.



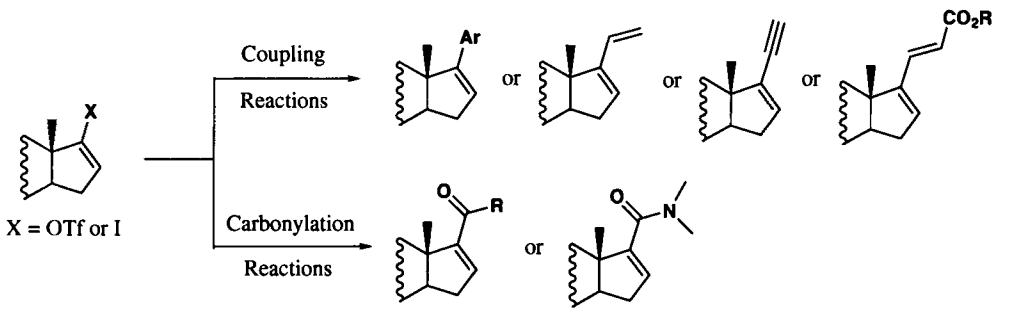
Scheme 117

2. 17-Modified Steroids

The methods used for synthesis of 17-modified steroids are very similar to those that were involved to prepare 3-modified compounds (see *Fig. 3*) as shown in *Schemes 118* and *119*.



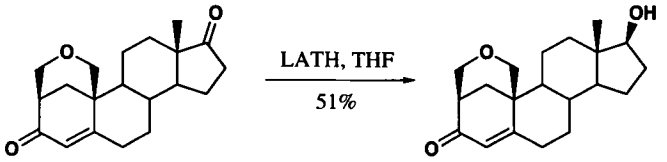
Scheme 118



Scheme 119

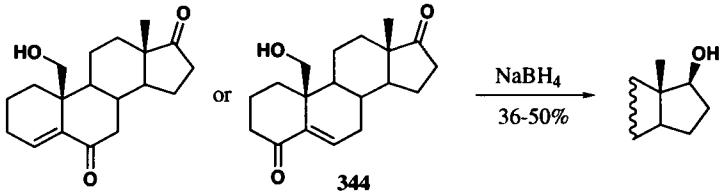
a) Regioselective Reduction of 17-Keto Group

The regioselective reduction of a 17-keto function in the presence of other keto groups is not so easy. Some regioselective reductions of 3,17-diketo Δ^4-steroids at C-17 have been previously cited, which used lithium tri-*tert*-butoxy aluminum hydride (LATH)[161] or $NaBH_4$[162] as reducing reagents with varying results (*Scheme 98, 99*). A high yield (91%) regioselective reduction of 4-androstene-3,17-dione at C-17 has been performed with $NaBH_4$ in aqueous medium using bovine serum albumin as regio auxilliary.[185] A selective reduction of steroids **341** to alcohol **342** (51% yield) with LATH as reducing reagent was also reported (*Scheme 120*).[186]



341 **Scheme 120** **342**

Moderate to medium yields were reported for the reduction of diketo compounds **343** and **344** at C-17 (*Scheme 121*).[187] The reaction was performed with limited amount of $NaBH_4$ in MeOH at 0°C.



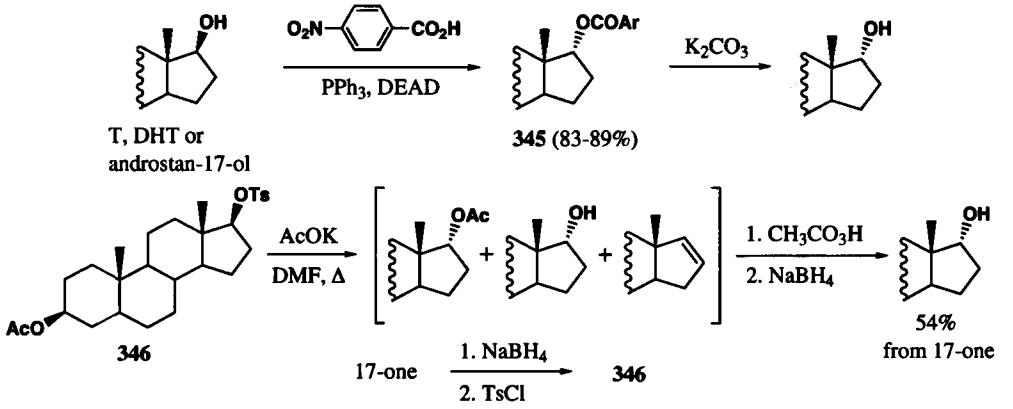
343 **344**

Scheme 121

b) Reactions of 17-Hydroxysteroids

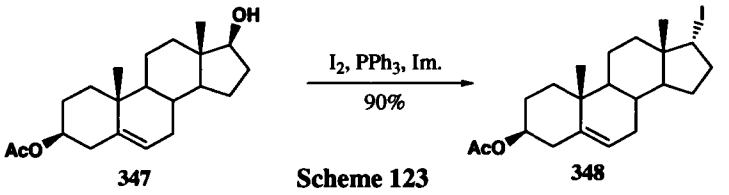
Various 17β-hydroxysteroids like **342** or testosterone were converted into vinyl ethers in 73-75% yields.[186] Alcohol inversion of 17β-hydroxy compounds has been accom-

plished in two ways (*Scheme 122*). The Mitsunobu reaction with 4-nitrobenzoic acid as the acidic component afforded esters **345** in high yields, followed by hydrolysis to 17α-alcohols.[188] A second approach involved the conversion of tosylate **346** into a mixture of 17α-ol, 17α-acetate and 16-ene compounds by treatment of **346** with AcOK. This mixture was then converted into another mixture containg an α-epoxide (from 16-ene compound), this latter mixture being then treated with $NaBH_4$ (to convert the epoxide into 17α-ol) in the presence of sodium hydroxide. Androstane-3β,17α-diol was obtained in 54% yield from 17-ketosteroid using this somewhat complicated methodology.[189]



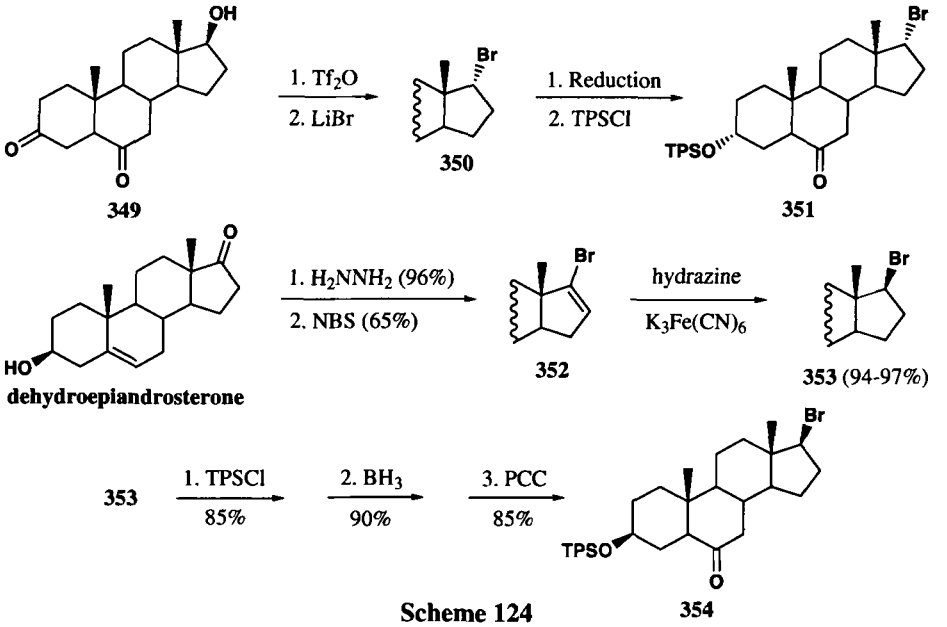
Scheme 122

17β-Hydroxysteroid **347** was converted in high yield into 17α-compound **348** by the convenient reaction of the secondary alcohol with iodine to give iodides with inversion of configuration (*Scheme 123*).[177]



347 **Scheme 123** 348

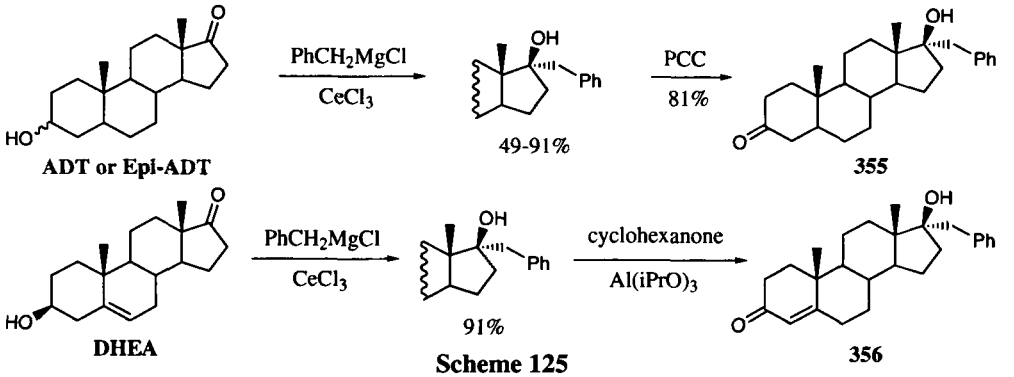
The 17α-bromosteroid **350** was synthesized in two steps from 17β-hydroxy **349** *via* S_N2 reaction on its triflate and then converted into steroid **351** by selective reduction at C-3 followed by silylation (*Scheme 124*).[190] The diastereoisomeric compound **354** was prepared in six steps from DHEA as outlined in *Scheme 124*. The vinylbromide **352** was obtained in good yield from intermediate hydrazone and selectively reduced in ring D to **353** (94-97% yields). **353** was then silylated at C-3 (85%) followed by $\Delta^{5,6}$ hydroboration on the α-side (>90%) and oxidation at C-7 (85%) to afford **354**.[190]



Scheme 124

c) Organometallic Additions to 17-Ketosteroids

17α-Benzylated steroids **355, 356** were synthesized from 17-keto compounds (*Scheme 125*).[89] Androsterone (ADT), epiandrosterone (Epi-ADT) or DHEA were alkylated using an excess of $PhCH_2MgCl$. The use of anhydrous $CeCl_3$ as catalyst gave higher yields. PCC oxidation of the secondary alcohol gave the 3-ketosteroid **355** in 81% yield whereas Oppennauer oxidation conditions were used for preparation of 17-substituted testosterone **356** (88% yield).

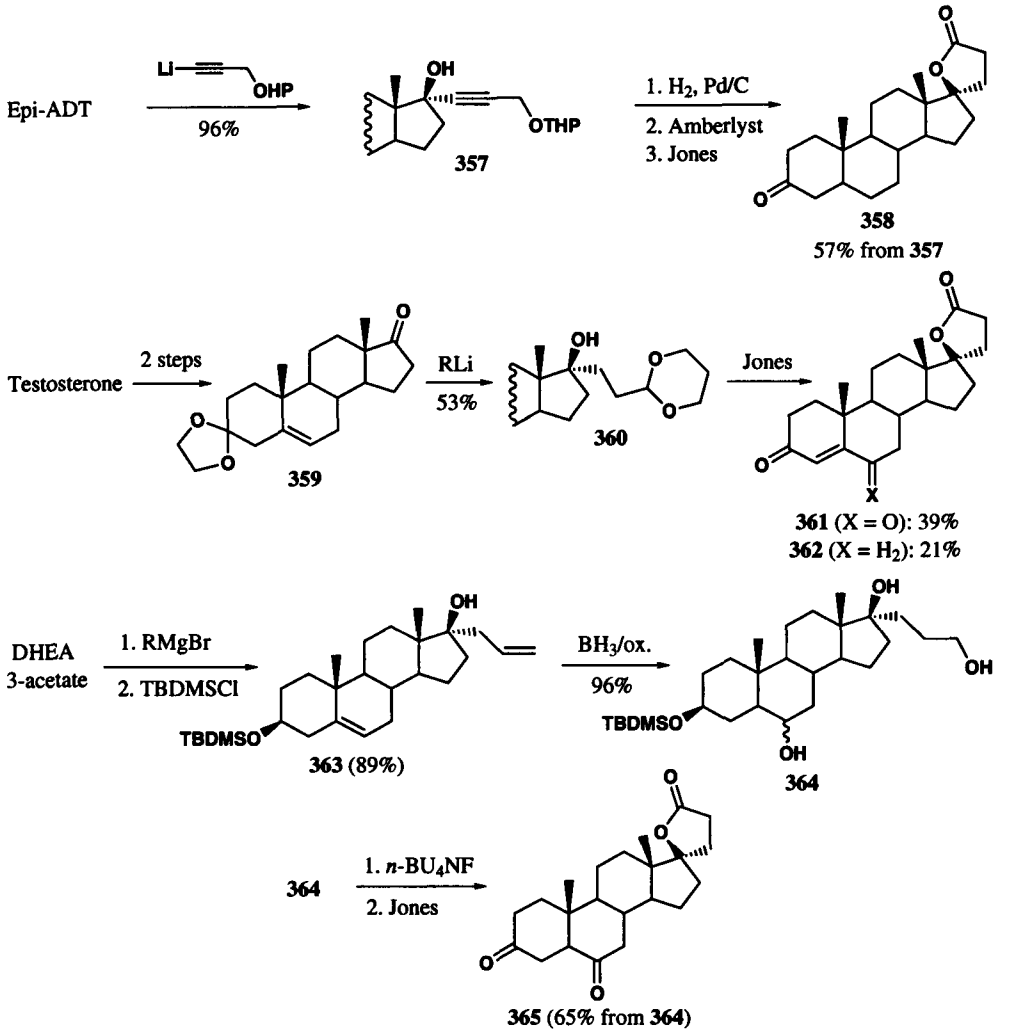


Scheme 125

The *Scheme 126* shows the synthetic pathways to obtain various spiro-γ-lactones **358, 361** and **365**.[191] Epiandrosterone was first alkylated to give the diol **357** in high yield. Then a three-step sequence (catalytic hydrogenation of the triple bond, cleavage of the THP group and Jones'oxidation) was used to transform **357** to lactone **358** in 57% global yield. A similar pathway was used to prepare a 3,17-dispirolactone from 3,17-androstanedione. The synthesis of lactone **361** from testosterone involved first a classic two-step sequence to prepare ketone **359** in

good yield. This ketone was then alkylated by primary alkylhalide lithium interchange to afford **360** in 53% yield. Treatment of **360** with Jones'reagent gave lactone **361** in 39% yield and lactone **362** in 21% yield. The saturated analog of lactone **361** was also synthesized. The synthetic route began by alkylation of DHEA 3-acetate at the 17α-position with allylmagnesium bromide. A diol intermediate was formed (without acetate group) that was silylated to **363** (89% yield). Oxidative hydroboration of double bonds generated then two additional hydroxyl groups to afford triol **364** in 96% yield. Cleavage of the silyl group at C-3 followed by oxidation gave the lactone **365** in 65% yield.

The addition of 2-lithiofuran and 2-lithiothiophene to a protected DHEA gave steroids **366a,b** in medium to good yields (*Scheme 127*).[192] This latter compounds were then dehydrated in good yields to **367a,b**. In similar fashion were prepared the 3-furanyl (**369a**) and 3-thienyl (**369b**) isomers. **368a** was deprotected using Bu_4NF to provide diol **370** in 50% yield.

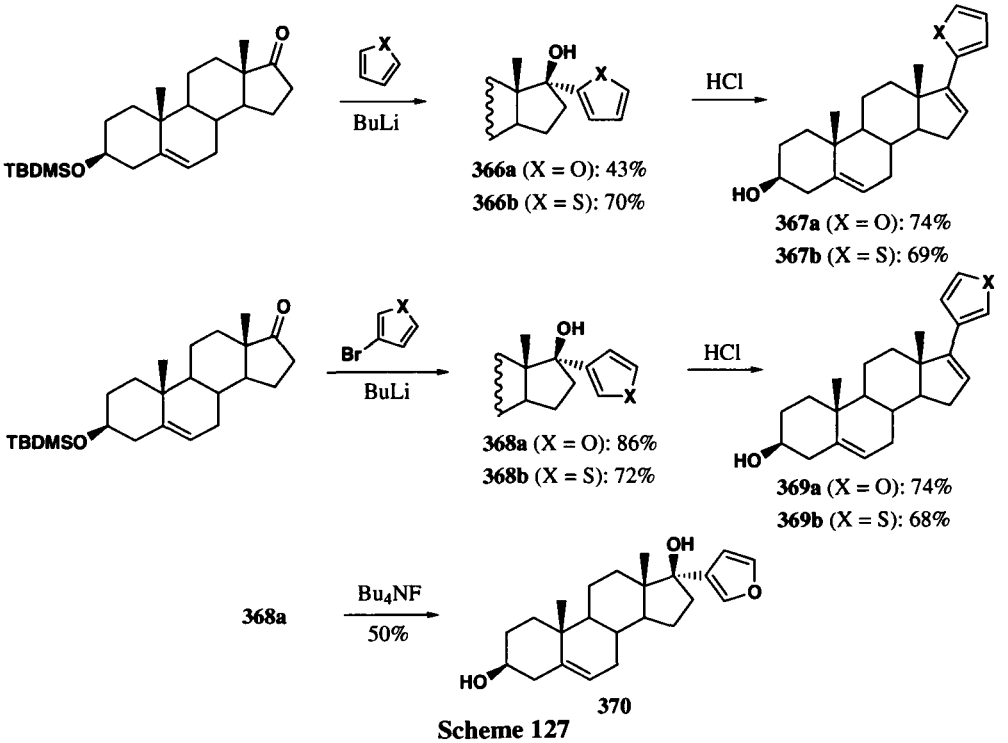


Scheme 126

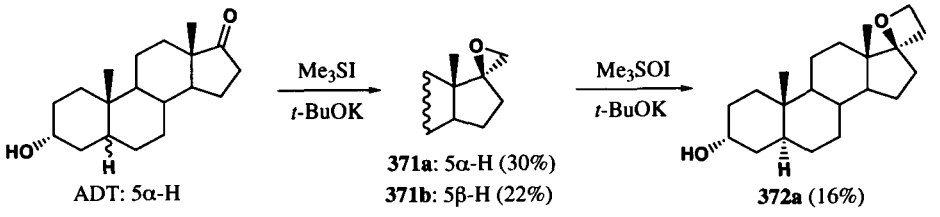
d) Synthesis and Reactions of 17-Spiro-oxiranes

Synthesis of spiro-epoxides **371a,b** was accomplished in low yields by treating ADT and it 5β-epimer with a sulfonium ylide (*Scheme 128*).[175] Further reaction of epoxide **371a** with sulfoxonium ylide gave the spiro-oxetane **372a** in 16% yield.

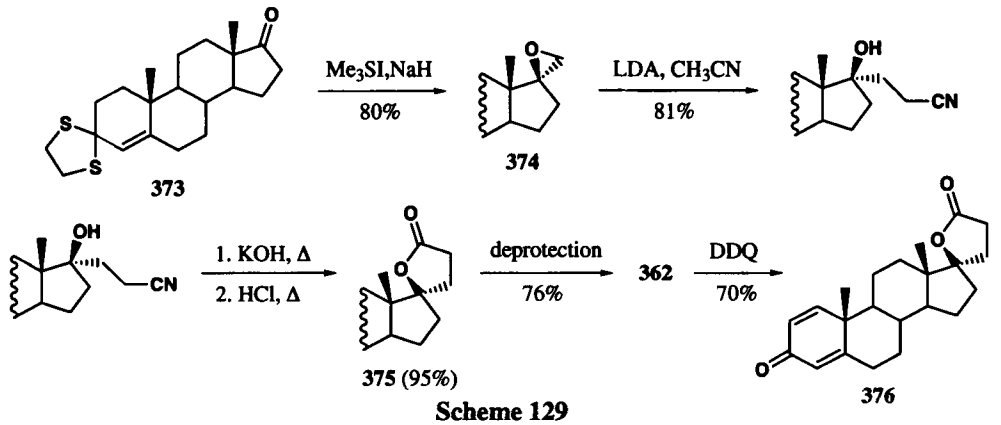
The lactone **362** (see *Scheme 126*) was also synthesized in good yield *via* a 17-spiro-oxirane (*Scheme 129*).[191] The epoxide **374** (80% yield from the ketone **373**) was opened by alkylation with lithium acetonitrile in 81% yield followed by hydrolysis of the nitrile group to afford the lactone **375** in high yield as the result of an intramolecular cyclization. Removal of 1,3-dithiolane group gave lactone **362** in good yield. Dienone lactone **376** was obtained from **362** by dehydrogenation with DDQ (70% yield).



Scheme 127

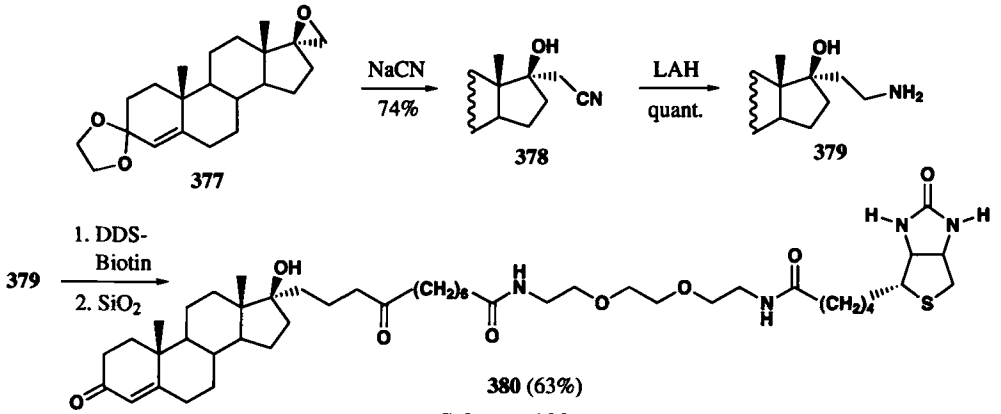


Scheme 128



Scheme 129

The biotinylation of testosterone at 17α-position started with nucleophilic attack of cyanide on the 3-protected 4-androstene-17-epoxide **377** to give 17α-cyanomethyl derivative **378** (*Scheme 130*).[48] The quantitative reduction to amine **379** with LAH, followed by reaction with DDS-biotin and removal of the protecting group at C-3 gave 17α-biotinylated T **380** in good yield.

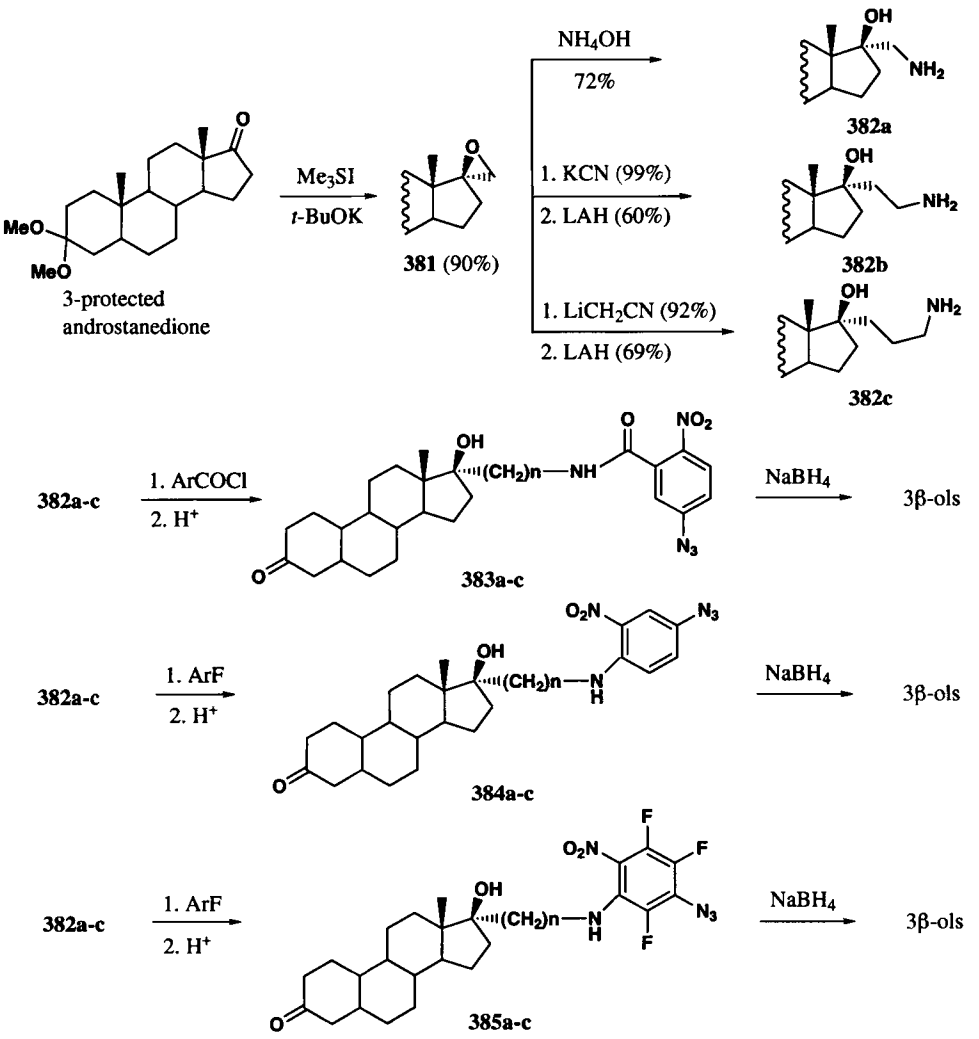


Scheme 130

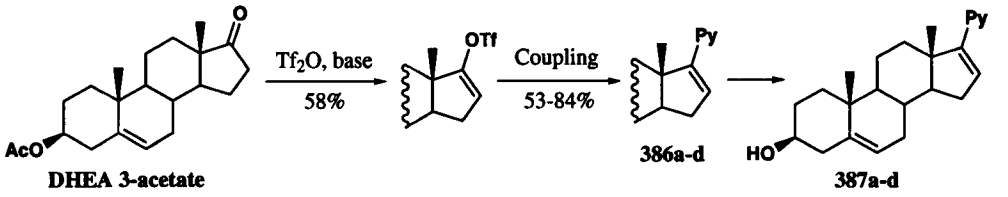
Series of 17α-substituted DHT and 17α-substituted androstane-3,17-diols were synthesized from a 3-protected androstanedione *via* the 17-epoxide **381** (*Scheme 131*).[193] This epoxide was obtained in high yield by condensation of the ketone with dimethylsulfonium methylide reagent and opened by reaction with various nucleophiles (NH_4OH, KCN and $LiCH_2CN$) to afford 17α-substituted steroids **382a-c**, either directly (**382a**) or after reduction with LAH, in good yields. The three amines were then acetylated (56-72%) to give amides or condensed with appropriated arylfluoro compounds to give arylaminoalkyl compounds (33-91%). Removing of the 3,3-dimethoxy groups by mild acidolysis regenerated the corresponding 3-oxosteroids series **383a-c**, **384a-c** and **385a-c** in high yields (84-97%). These 3-oxo compounds were also reduced in mild conditions with $NaBH_4$ to generate the corresponding 3β-hydroxysteroids in moderate yields (42-66%).

e) Palladium-Catalyzed Cross-Coupling Reactions of Enol Triflates or Iodo Alkenes

The palladium-catalyzed cross-coupling of 17-enol triflates with suitable pyridyl-containing nucleophilic coupling partners was used for introducing a 17-pyridyl 16,17-ene functionality into ring D (*Scheme 132*).[194] The 17-pyridyl steroids **386a-d** were prepared in 53-84% yields by reacting the enol triflate of DHEA 3-acetate with respectively diethyl (3-pyridyl) borane, 2-pyridyl- and 2-picolylzinc chloride, lithium trimethoxy (4-pyridyl)boronate and using generally $Pd(PPh)_3Cl_2$ as catalyst. The acetyl group of **386a-d** was removed either *in situ* or by hydrolysis to afford **387a-d** in good yields. Other 17-pyridinyl steroids were prepared from AD or adrenosterone using the same coupling reaction.

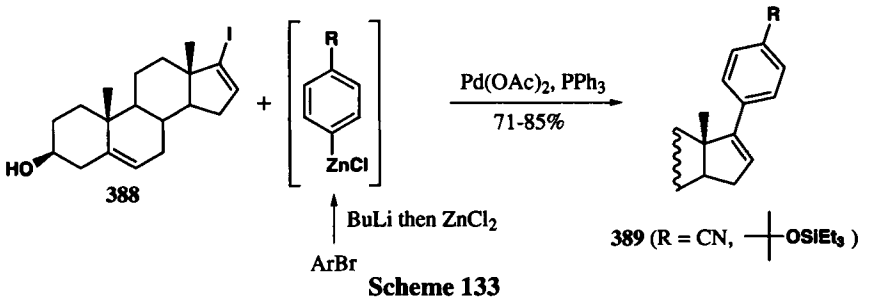


Scheme 131



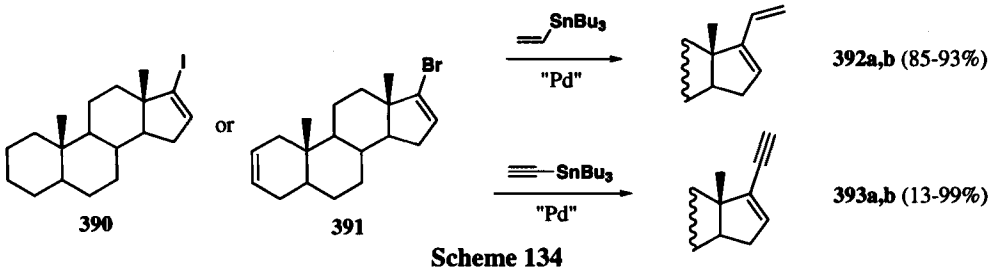
Scheme 132

The palladium-catalyzed cross-coupling of vinyl iodide **388** with an excess arylzinc chlorides afforded steroids **389** in good yields (*Scheme 133*).[195]



Scheme 133

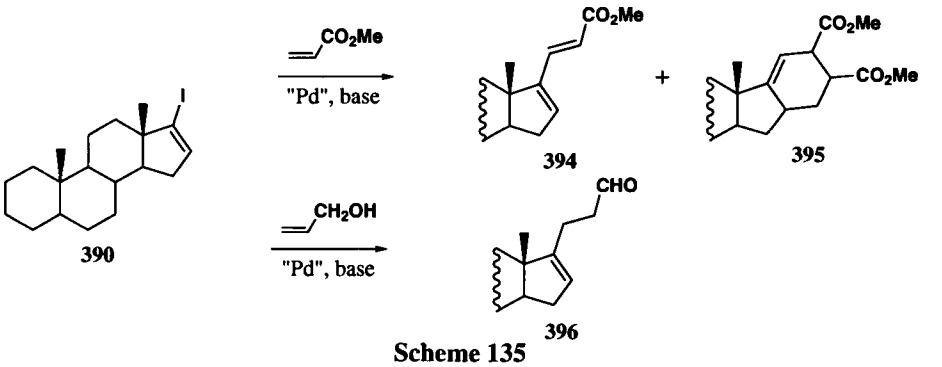
The Stille-coupling of 17-halo steroids **390** or **391** and vinyl- or ethynyl-tributyltin afforded 17-modified compounds **392** and **393** (*Scheme 134*).[196] High yields were generally observed with $Pd(PPh_3)_4$ as catalyst, an exception being the coupling reaction of 17-bromo **391** and ethynyltributyltin (13% yield). The coupling of **390** with vinyltributyltin was also carried out using microwave irradiation.[197] The reaction was complete in minutes rather than in hours.



Scheme 134

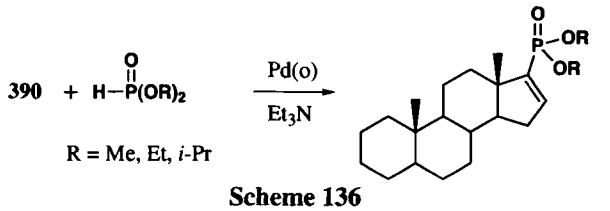
The Heck reaction of **390** was carried out in the presence of palladium catalysts using various olefins as coupling partners (*Scheme 135*).[198] The reaction with methyl acrylate afforded a mixture of **394** and **395**, this latter compound being formed by Diels-Alder reaction of **394** with the starting olefin. This side reaction may be limited at moderate temperature (88/12 ratio of **394/395** at 60°C for 97% conversion). The reaction with allylic alcohol

afforded exclusively the aldehyde **396** (98% conversion) which may result of an isomerization of the alcohol.



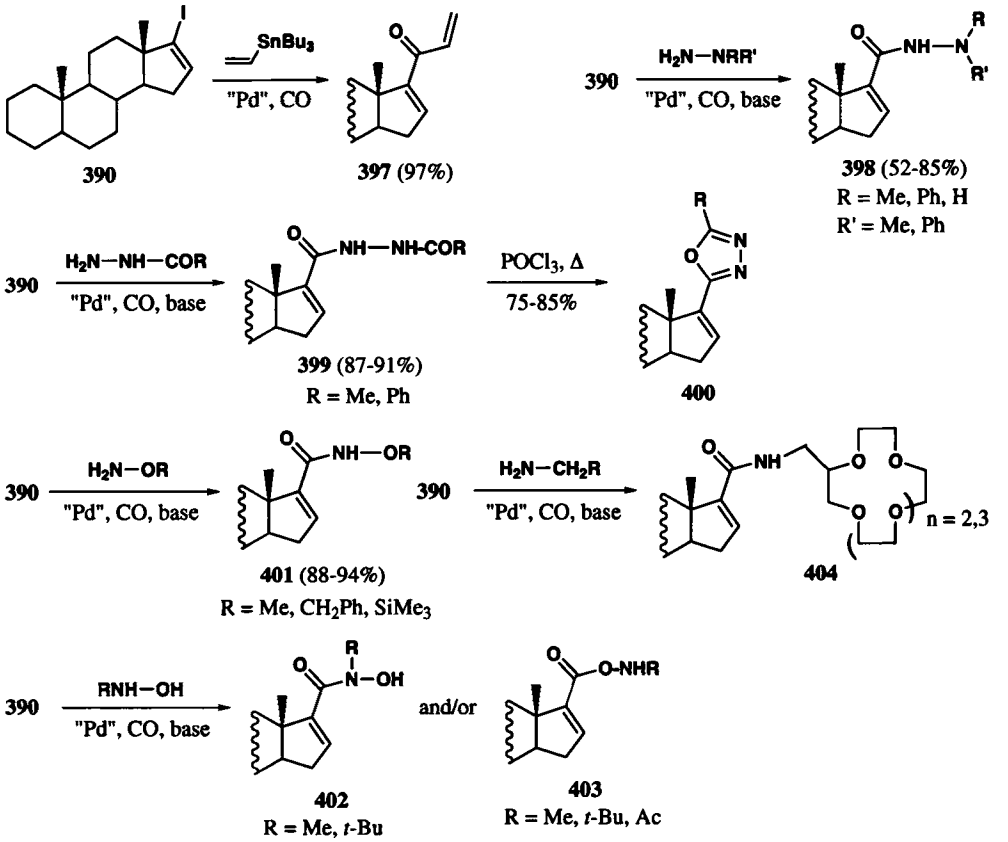
Scheme 135

The palladium-catalyzed coupling of **390** with large excess of dialkyl phosphites afforded the corresponding phosphonates in 47-89% yields (*Scheme 136*).[199]



Scheme 136

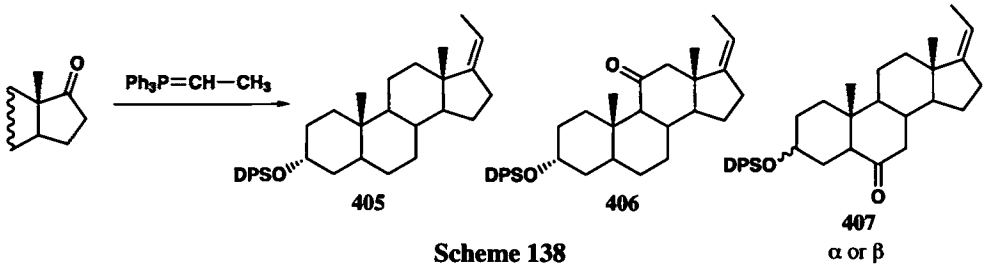
The Stille-coupling of **390** with vinyltributyltin was also carried out under atmospheric CO pressure to afford the vinyl ketone **397** in high yield (*Scheme 137*).[196] Various homogeneous catalytic carbonylation reactions were used for the synthesis of 17-modified androst-16-enes **398-404** (*Scheme 137*). The hydrazinocarbonylation reaction of **390** afforded N-substituted steroidal hydrazides **398** in 52-85% yields from hydrazines[200] and diacyl hydrazines **399** in 87-91% yields from hydrazides.[201] Steroidal oxadiazoles **400** were prepared in good yields from hydrazines **399** using $POCl_3$ as the dehydration agent. Hydroxamic acid derivatives **401** were synthesized in high yields by carbonylation reaction of **390** in the presence of O-substituted hydroxylamines.[202,203] The carbonylation with N-substituted hydroxylamines afforded either N- or O-acylation compounds **402** and/or **403**, the regioselectivity of the reaction being influenced by the structure of the substrate and the solvent.[203] The palladium-catalyzed carbonylation reaction of **390** in the presence of $NaBPh_4$ afforded 17-benzoyl-androst-16-ene in 95% yield.[58] 17-formyl-androst-16-ene was synthesized from the same steroid **390** by formylation, using tributyltin hydride as hydrogen source (yield not given).[204] The steroidal crown-ether **404** was also formed in high yield by a carbonylation reaction.[205]



Scheme 137

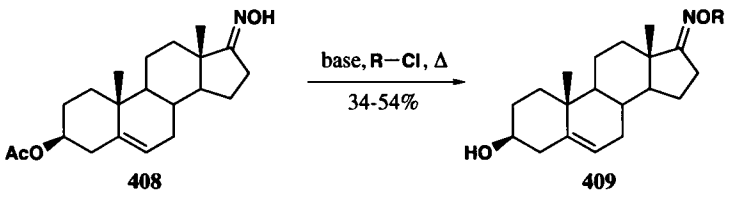
f) Miscellaneous

Various C-17 olefins **405-407** were prepared from 17-ketosteroids by a Wittig reaction (*Scheme 138*).[206] The Wittig reaction on androsterone (71% yield) followed by silylation (80% yield) gave predominantly the Z isomer (97%). The alcohol precursor for **406** was prepared by olefin reduction of adrenosterone (Li/NH_3) followed by regiospecific reduction at C-3. The subsequent Wittig reaction (69% yield) was specific to C-17 due to steric encumbrance of C-11. The synthesis of **407** from testosterone acetate involved allylic oxidation at C-7 and required protections at C-3 and C-7.



Scheme 138

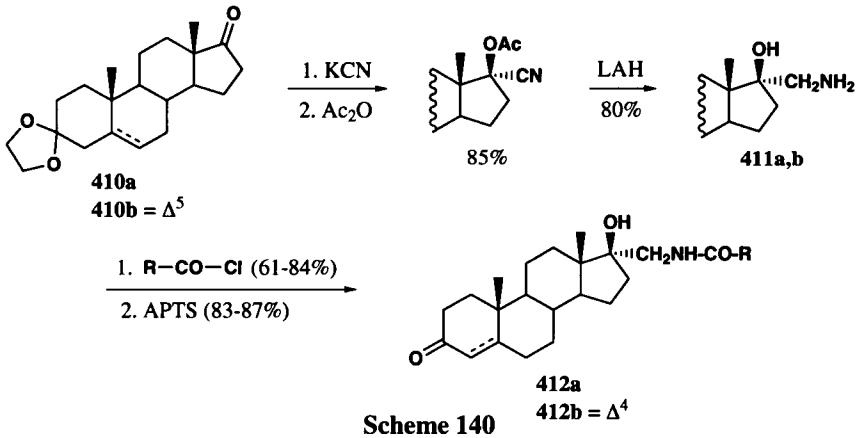
The 17-keto group may also be transformed to an aldehyde function *via* Wittig reaction using (methoxymethyl) triphenylphosphonium chloride. Excess ylide and boiling THF may be required.[63] 17-Oximino steroids **409** were prepared in moderate yields from oxime **408** (*Scheme 139*).[46]



408 **409**

Scheme 139 (R = CH_2—CH_2—NR'R')

17α-Aminomethyl steroids **411** have been prepared in good yields by hydrocyanation of 17-ketosteroids **410a,b** followed by reduction with LAH (*Scheme 140*).[207] The acylation of the amines **411** followed by acid hydrolysis of the 3-ketal group afforded 17α-amidomethyl compounds **412a,b** in good yields.



410a
410b = Δ^5

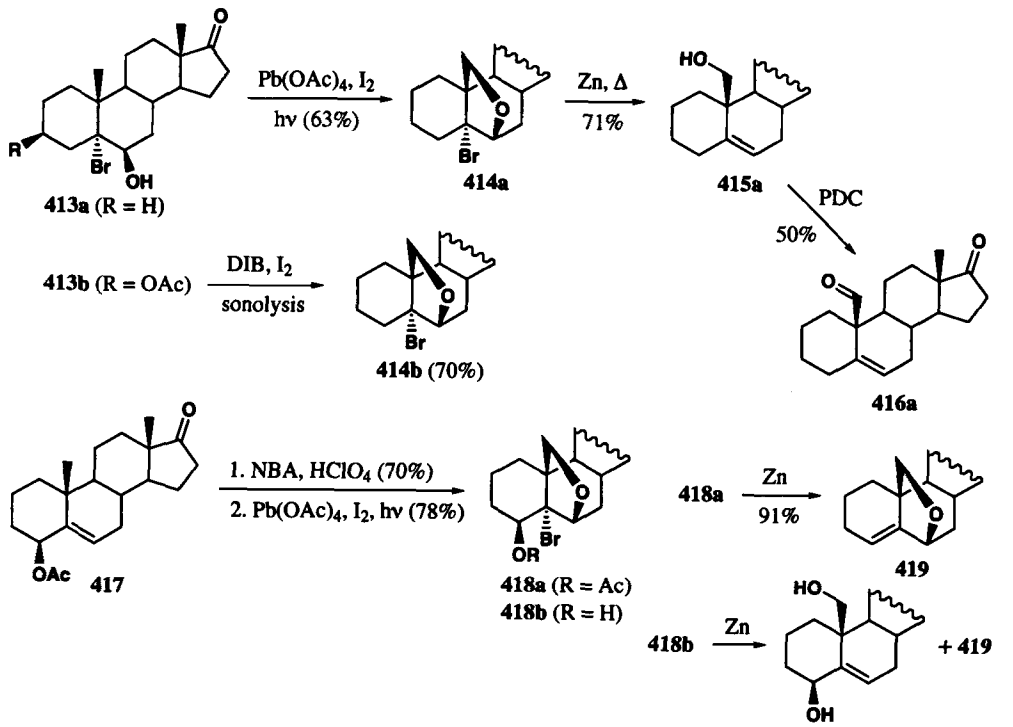
411a,b

412a
412b = Δ^4

Scheme 140

V. 19-MODIFIED STEROIDS

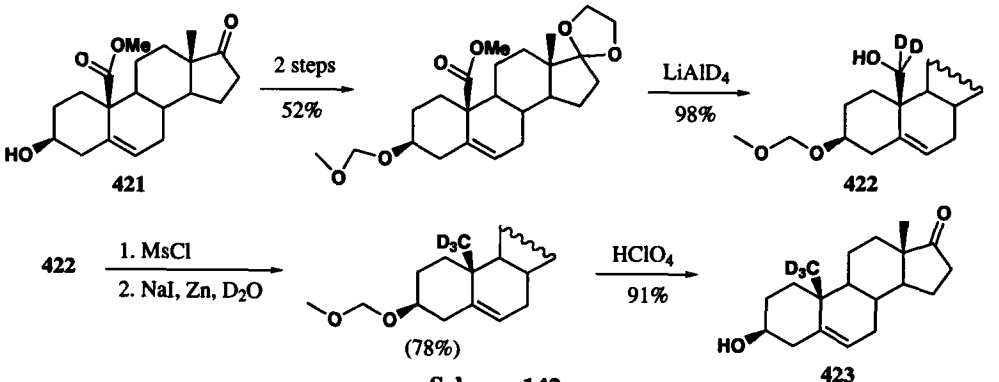
The functionalization at C-19 is commonly achieved through the preparation of tetrahydrofurans as precursors of 19-hydroxysteroids. 19-Hydroxy- and 19-oxosteroids **415a**, **416a** were synthesized from bromhydrin **413a** via tetrahydrofuran **414a** (*Scheme 141*).[120] The cyclic ether was formed in 63% yield via a 6β-alkoxyl radical that allows intramolecular hydrogen abstraction at C-19, the radical being generated by photolytic decomposition of lead (IV) acetate and iodine. Zinc dust reduction of ether afforded the 19-ol **415a** in 71% yield followed by oxidation to aldehyde **416a** in 50% yield. The synthesis of cyclic ether **414b** has been achieved in 70% yield by ultrasonic irradiation of bromhydrin **413b** in the presence of (diacetoxyiodo) benzene (DIB) and I_2.[208] The treament of cyclic ether **418a** (synthesized from **417** in good yield) with zinc dust resulted in the 4-ene steroid **419** (91% yield) as a *trans*-elim



Scheme 141

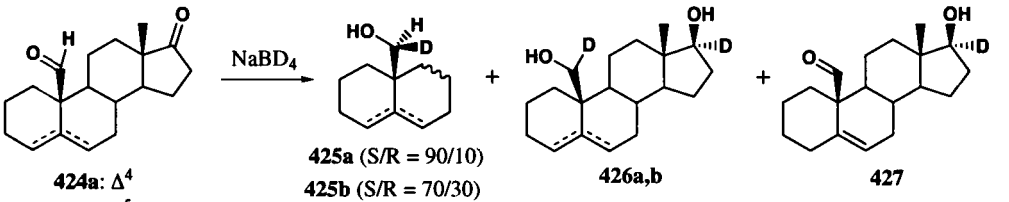
ination product (*Scheme 141*).[209] In contrast, the same treament of the 4-hydroxy analog **418b** gave a mixture of **419** (52%) and **420** (42%). The oxidation of **418b** followed by treatment with zinc gave a 4-oxo-19-hydroxy-steroid in low yield.

d_3-DHEA **423** was synthesized from ester **421** (*Scheme 142*).[39] The protected ester was treated with lithium aluminum deuteride to give dideuterated alcohol **422** in high yield followed by conversion into mesylate, its exchange to deuterium and final deprotection. The three last steps of the synthesis were performed in good to high yields.



Scheme 142

^{3}H-Labeled 19-hydroxy derivatives were also synthesized through $NaBT_4$ reduction of 19-aldehydes and the stereochemistry of this reduction was established, based on experiments with $NaBD_4$ (*Scheme 143*).[210] The stereoselective *si*-face attack of the borohydride reagent gave rise principally to the 19S introduction of the labelled group. [17α, 19-^{2}H] diols **426a,b** were also formed as well as steroid **427** for the reduction of **424b**. The 17-carbonyl function of **424b** appeared to be more reactive than the 19-carbonyl function.



424a: Δ^4
424b: Δ^5

Scheme 143

The biotinylation of testosterone at C-19 was carried out from a 19-carboxymethyl ether precursor that was prepared from 19-hydroxy AD according to known procedures.[48]

VI. CONCLUSION

The present review covers the period 1995-2004. Some results published during the first part of 2005 made use of methods previously presented, such as the synthesis of 3-ether-ADT derivatives,[211] the addition of MeMgBr to a steroidal 4,5-epoxy-3-ketone,[212] the regioselective enzymatic acylation of *vic*-diols of steroids[213] or the aminocarbonylation of 17-iodoandrost-16-ene.[214] Moreover, 4- and 6-aryl substituted AD or androstatriene diones have been prepared in high yields by the Suzuki-Miyaura cross-coupling from the corresponding bromosteroids[215] and a 6α-bromosteroid was synthesized in good yield from a 5-bromo-6β,19-epoxy compound.[216] A 12β-hydroxylation of DHEA has also been performed in moderate yield by a copper-mediated reaction of the 17-(2-iminomethyl)pyridinyl derivative of DHEA with molecular oxygen.[217]

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(Received October 3, 2005; in final form February 21, 2006)