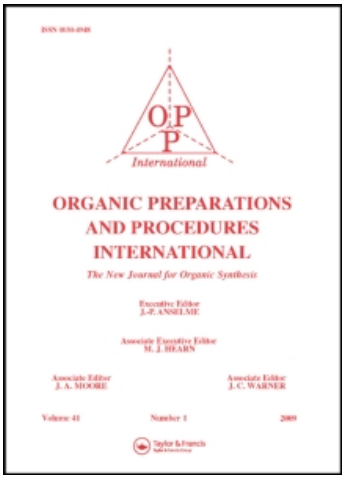

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Gao, Hongwu(1997) 'APPROACHES TO PARTIAL SYNTHESES OF 11-OXO STEROIDS. A BRIEF REVIEW', Organic Preparations and Procedures International, 29: 5, 499 — 539
To link to this Article: DOI: 10.1080/00304949709355229
URL: http://dx.doi.org/10.1080/00304949709355229

ORGANIC PREPARATIONS AND PROCEDURES INT., 29 (5), 499-539 (1997)

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INTRODUCTION

The introduction of an oxo functional group at the 11-position of steroids remains an area of interest because it provides the activated site for the further elaboration of steroid rings. Estradiol derivatives of general structure **1** (Fig. 1) encompass a variety of interesting and valuable compounds.

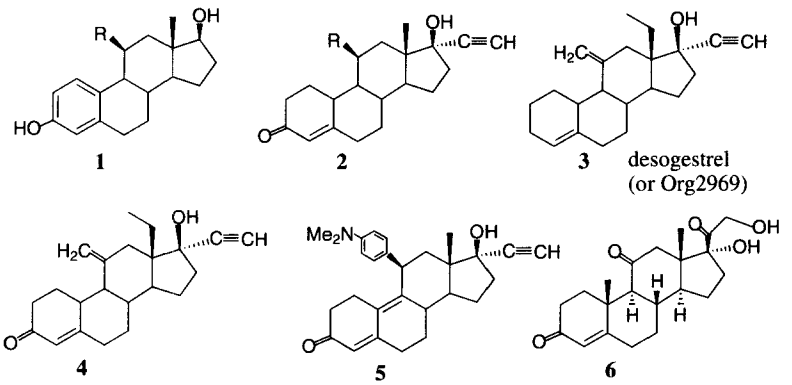


Fig. 1

Those bearing small carbon substituents at the 11β-position (R = ethyl,[1] chloromethyl,[2] vinyl[3], ethynyl,[4] ethenyl,[4] phenyl[4]) are the best known ligands for the estrogen receptor, their affinity being more than 10 times higher than that of estradiol, the natural ligand. Thus, in the synthesis of estradiol derivatives designed as probes for the estrogen receptor, the inclusion of one of such groups (particularly the ethyl and chloromethyl) is often used to secure high binding affinities.[5, 6] In addition to these functions, appropriate 11β-substitution results in compounds endowed with pure anti-estrogenic activity.[7] The synthesis of 11β-substituted estradiol derivatives involves the addition of lithium or Grignard reagents to 11-carbonyl group of an estradiol derivative, followed by the acid-catalyzed dehydration and catalytic hydrogenation (R = ethyl,[1] chloromethyl,[2] vinyl[3]) or the stereoselective

deoxygenation of the resulting 11-hydroxy steroids by means of an ionic hydrogenation (R = ethynyl,[4] ethenyl,[4] phenyl[4]).

Since some 11-substituted 19-nor-steroids **2** (Fig. 1), particularly 11β-chloro[8] and 11β-methyl[9] derivatives, were found to be the very biologically active compounds, studies of ovulation inhibitory activity of 11-substituted 19-nor-steroids have been carried out.[10] The differences in biological activity could reasonably be correlated with two steric effects introduced by the 11β-substituent. These were a change in the overall shape of the 11β-substituent and the angular methyl group, and direct steric hindrance of the steroid-receptor protein binding. The resulting study[11] of 11-alkylidene 19-nor-steroids led a powerful progestogen widely used in oral contraceptives, desogestrel (**3**, Org2969),[12] and its active metabolite-3-keto-desogestrel **4**.[13] The 11-methylene group could be introduced from 11-oxo-19-nor-steroid in three ways: 1) the addition of methylmagnesium iodide or methyllithium followed by dehydration in formic acid 2) Wittig reaction 3) Peterson olefination.[10]

The other stereospecific introduction of 11β-carbon substituents, such as in mifepristone (**5**, RU-486), [14, 15] could be completed by the copper-catalyzed conjugate addition of organometallic reagents to vinyloxirane which could be synthesized from the intermediate of 11-oxo-19-nor-steroid.[16]

On account of its dramatic influence on chronic rheumatoid arthritis and acute rheumatic fever,[17] cortisone (**6**) is produced commercially. Numerous partial and total syntheses of this compound have been performed by chemical and microbiological methods. A common feature of all of the partial syntheses of cortisone from deoxycholic acid devised by Kendall and co-workers is the multi-step method to shift the oxygen function from C-12 to C-11.[18]

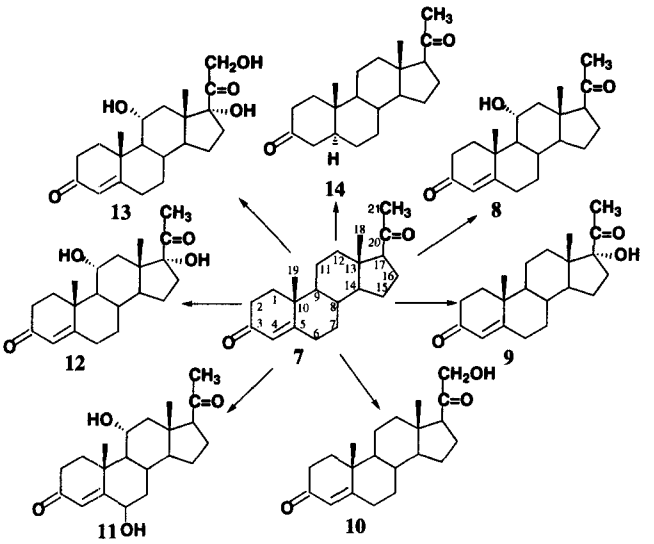
I. SYNTHETIC APPROACHES TO 11-OXO STEROIDS WITH 4-EN-3-ONE

1. Microbiological Transformation

a) Fermentation of Progesterone

11α-OH-progestrone

Incubation of *Aspergillus ochraceus* on progesterone **7** yielded the corresponding 11α-hydroxyprogesterone **8** as the main product, together with 6β,11α-dihydroxy derivative **11** (*Scheme 1a*).[19-30] Gaitonde and co-workers[25] explored the effect of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (NTG) on ability of spores of *Aspergillus ochraceus* to transform progesterone and obtained 85-90% of **8** and 5-10% of **11**. Chopra and Somal[26] developed a mutant of *Aspergillus ochraceus* to convert progesterone to 11α-hydroxyprogesterone in high yield (**8**: 90%; **11**: minimal). The action of *Aspergillus ochraceus* TS on progesterone only gave 11α-hydroxyprogesterone.[30] C-11 Hydroxylation of progesterone with *Aspergillus niger* led to the corresponding 11α-hydroxyprogesterone along with five by-products (*Scheme 1b*).[31-39] Paper chromatographic analysis of the mixture indicated that the progesterone was transformed to 11α-hydroxyprogesterone in 47-62%.[35] The other species like *Aspergillus phoenicis*[40-42], *Aspergillus fischeri*[43, 44], *Aspergillus nidulans*[45] also could transform progesterone to 11α-hydroxyprogesterone and other related by-products.



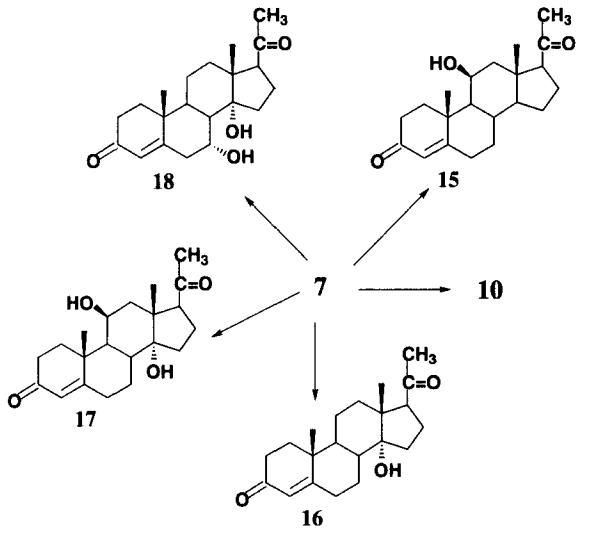
Reagents and Results: a) *Aspergillus ochraceus*: **8** and **11**; b) *Aspergillus niger*: **8**, **9**, **10**, **11**, **12** and **13**; c) *Rhizopus nigricans*: **8**, **9**, **10**, **11** and **14**; d) *Rhizopus Arrhizus*: **8**, **9**, **10** and **11**.

Scheme 1

The conversion of progestrone to 11α-OH-progestrone by *Rhizopus nigricans*, was first reported by Peterson and co-workers in 1952.[46, 47] In this microbiological transformation, 11α-hydroxyprogestrone is the main product formed (**8**: 85-95%). In addition, small amounts of a dihydroxyprogestrone (**11**: 0.5%) and 11α-hydroxyallopregnane-3,20-dione (**14**: 0.5-5%) were also isolated (*Scheme 1c*). The other studies revealed that two additional by-products were formed in this oxidation.[48-58] The yield of 6β,11α-dihydroxyprogesterone could be diminished by the addition of 0.02M ascorbic acid to the reaction mixture.[53] The nonsterile fermentation of progesterone using a strain of *Rhizopus nigricans* gave a yield of more than 80%.[49] The rate of 11α-hydroxylation of progesterone with *Rhizopus nigricans* could be accelerated by glucose.[57] Peterson's further studies[47] revealed that *Rhizopus arrhizus* produced a lower yield (50%) of **8** and higher yields (5-15%) of **11**. The other two by-products were reported later (*Scheme 1d*).[59] Recent investigations showed that supplementation of the medium with critical micelle concentration (CMC) resulted in the production of *Rhizopus arrhizus* mycelium with an increased specific capacity to transform progesterone to 11α-hydroxyprogesterone.[60] Special species like *Rhizopus stolonifer*[61], *Penicillium*[62], *G. Khaki and G. Lagenarium*[63] could also transform progesterone to 11α-hydroxyprogesterone with some by-products. Aside from the 11α-position, the microbial introduction of hydroxy groups into positions 6, 17 and 21 are chemically activated by carbonyl groups.

11β-OH-progestrone

11β-Hydroxylation of progesterone by *Curularia lunata* was first described by Kita and Shull.[64] These workers did not determine the chemical structures of four other transformation products that were produced. In later studies,[65, 66] structural details were provided (*Scheme 2*). The yields of



Reagents and Results: *Curvularia lunata*, **15**, **10**, **16**, **17** and **18**.

Scheme 2

products oxidation at C 11β- and 21-positions were markedly improved in the presence of Mg^{2+}, Fe^{2+}, Mn^{2+}, Zn^{2+} and Ca^{2+}.[67] C-11 Hydroxylation of 19-norprogesterone with *Curularia lunata* led to the corresponding 11β-hydroxy analog.[68]

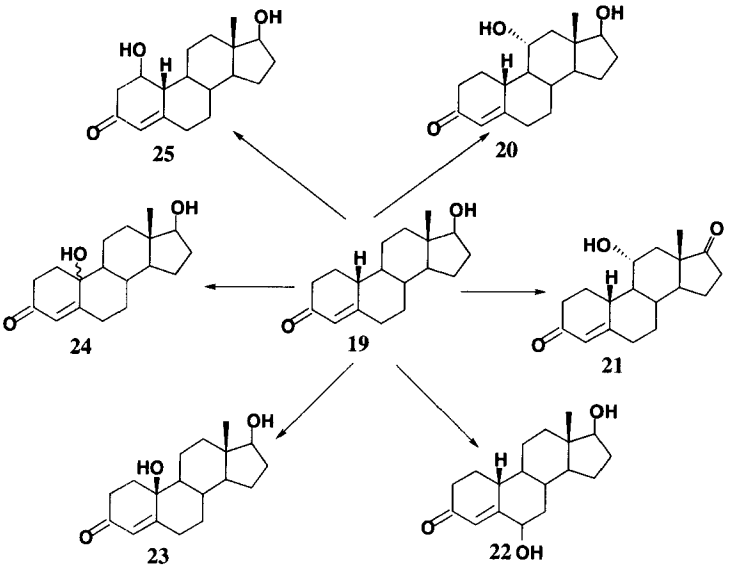
b) Fermentation of 19-Nortestosterone

11α-OH-19-nortestosterone

In 1956, Peterson and co-workers[69] reported the preparation of a 10ξ-hydroxy-19-nortestosterone by the microbiological action of *Rhizopus nigricans* on 19-nortestosterone (*Scheme 3a*). Hydroxylation proceeded mainly at the 6β-position (**22**: 18%), while reaction at the 11α- and 10ξ-positions (**20**: 4% and **24**: 1.2%) occurred only to a minor extent. Thus, this mold contained an enzyme which could hydroxylate 19-nortestosterone at a tertiary position. *Aspergillus ochraceus* fermentation of racemic 19-nortestosterone yielded *l*-10β-hydroxy derivative (**23**: 13%), together with *d*-11α-hydroxy (**20**: 37%), *l*-1β-hydroxy (**25**: 0.3%), *dl*-6β-hydroxy (**22**: 0.07%) derivatives (*Scheme 3b*).[70] Similarly, the fermentation of *d*-19-nortestosterone with *Aspergillus ochraceus* led to a different product mixture, a 72% yield of 11α-OH-19-nortestosterone and a small amount of 11α-hydroxy-estr-4-ene-3,17-dione (**21**: 10%) were obtained (*Scheme 3c*). In an additional example, the microbiological attack of *Aspergillus ochraceus* on 19-nortestosterone gave the same mixture of products (**20**: 34% and **21**: 20%) (*Scheme 3d*).[71] Compound **21** (the by-product from the microbiological conversion of 19-nortestosterone with *Aspergillus ochraceus*) can be obtained by fermentation of 19-norandrost-4-ene-3,17-dione with *Aspergillus ochraceus* in a good yield (**21**: 68%) (*Scheme 4*).[71]

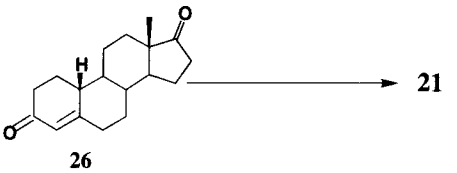
11β-OH-19-nortestosterone

By fermentation of 19-nortestosterone with *Curvularia lunata*, Szpilfogel and co-workers[71] obtained 10β-OH-19-nortestosterone as the major product (**23**: 36%) with the 11β-OH- (**27**: 3.2%),



Reagents and Results: a) *Rhizopus nigricans*, **20**: 4%; **22**: 18%; **24**: 1.2%;
b) *Aspergillus ochraceus*, *d*-**20**: 37%; *dl*-**22**: 0.07%; *l*-**23**: 13%; *l*-**25**: 0.3%;
c) *Aspergillus ochraceus*, **20**: 72%; **21**: 10%; d) *Aspergillus ochraceus*, **20**: 34%; **21**: 20%.

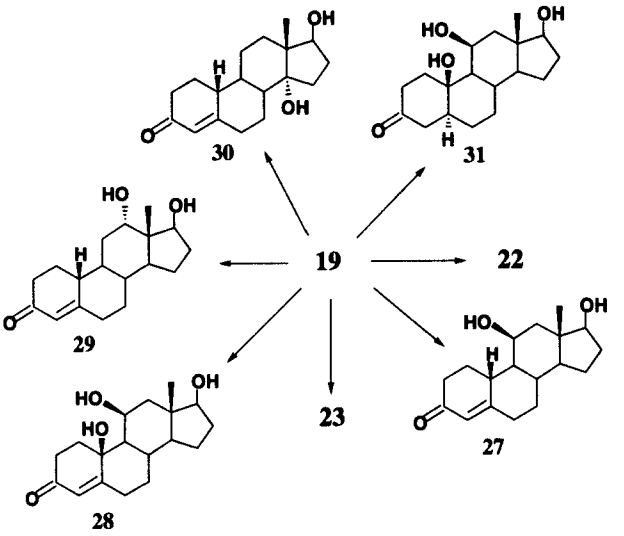
Scheme 3



Reagents and Results: *Aspergillus ochraceus*, **21**: 68%.

Scheme 4

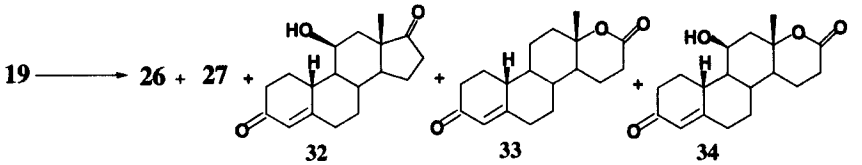
10β,11β-dihydroxy- (**28**: 0.7%) and 14α-OH-derivatives (**30**: 2.3%) being isolated as minor products (*Scheme 5a*). Smith and co-workers[72] carefully reexamined the transformation of *d*-**19** and *dl*-**19** by *Curvularia lunata* and confirmed that the 10β-hydroxy derivative is the major product (*d*-**23**: 55% and 50%), with diminished amounts of the 11β-hydroxy (*d*-**27**: 17% and *dl*-**27**: 6%), 14α-hydroxy (*d*-**30**: 13% and 7.3%), and 10β,11β-dihydroxy products (*d*-**28**: 0.8% and *dl*-**28**: 10%) being produced (*Schemes 5b* and *5c*). In addition to these products, they isolated 6β-hydroxy product (*d*-**22**: 4% and *dl*-**22**: 4.8%), not reported by Szpilfogel.[71] Garrett and co-workers[73] found that incubation of 19-nortestosterone with *Aspergillus tamarri* for 72 h gave five transformation products; the major reaction pathway produced 19-nortestololacetone (**33**: 70%). The consecutive steps to the D-ring δ-lactone involve the initial interaction of the steroid substrates with 17-ketodehydrogenase followed by the action of a lactonase enzyme system. An 11β-hydroxylase enzyme system was also found to be operative on the 19-nortestosterone substrate since 11β-hydroxy-19-nortestosterone (**27**: 1.8%), 19-norandrost-4-en-



Reagents and Results: a) *Curvularia lunata*, **27**: 3.2%; **23**: 36%; **28**: 0.7%; **30**: 2.3%;
b) *Curvularia lunata*, **27**: 17%; **22**: 4%; **23**: 55%; **28**: 0.8%; **30**: 13%;
c) *Curvularia lunata*, *dl*-**27**: 6%; *dl*-**22**: 4.8%;*d*-**23**: 50%; *dl*-**28**: 10%; *l*-**29**: 1.4%; *d*-**30**: 7.3%; *l*-**31**: 4.8%.

Scheme 5

11β-ol-3,17-dione (**32**: 2.3%), and 11β-hydroxy-19-nortestololactone (**34**: 3.4%) were obtained (*Scheme 6*).



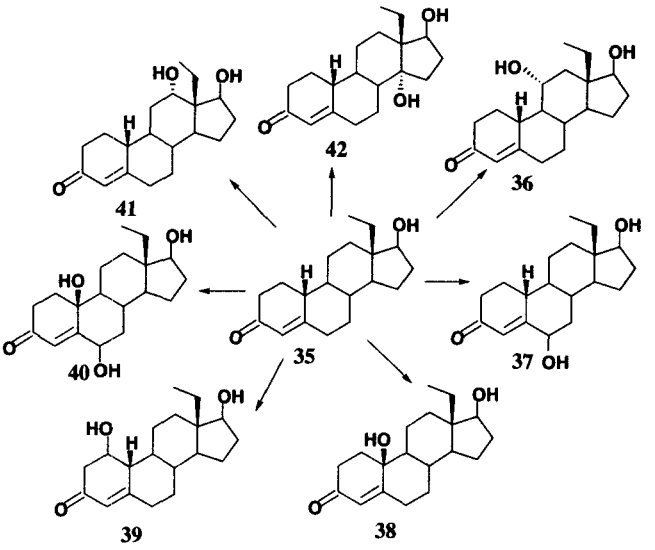
Reagents and Results: *Aspergillus tamarri*, **26**: 3.2%; **32**: 2.3%; **33**: 70%; **34**: 3.4%; **27**: 1.8%.

Scheme 6

c) Fermentation of 13β-Ethyl-17β-hydroxygon-4-en-3-one

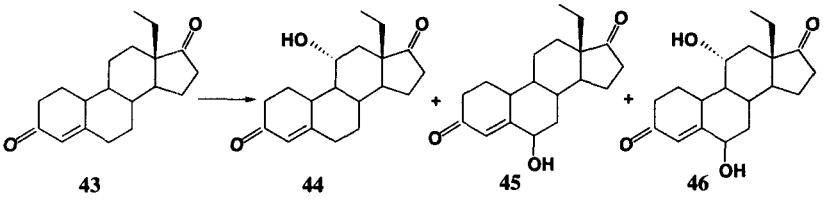
11α-OH-derivative

Aspergillus ochraceus converted 13β-ethyl-17β-hydroxygon-4-en-3-one into a major product (**39**: 52%), together with a series of minor polar components (*Scheme 7a*).[70] A trace of 13β-ethyl-11α,17β-dihydroxygon-4-en-3-one was isolated (**36**: 0.12%). After racemic 13-ethyl-17β-hydroxygon-4-en-3-one was transformed by *Curvularia lunata*, the gas chromatographic pattern of transformation products showed that two major products (*dl*-**38**: 30% and *l*-**41**: 38.5%) were produced (*Scheme 7b*);[72] none of the 11-hydroxy derivative was detected. In 1983, Ulrich and co-workers[74] used *Aspergillus ochraceus* on 13β-ethyl-4-ene-3,17-dione **43** and successfully isolated the 11α-derivative (**44**: 40%). In later work,[75, 76] the process was repeated and the 6β- (**45**: 7%) and 11α,6β-dihydroxy (**46**: 13%) derivatives were isolated as well (*Scheme 8*).



Reagents and Results: a) *Aspergillus ochraceus*, 36: 0.12%;37: 3.9%; 38: 2.9%; 39: 52%;
b) *Curvularia lunata*, *dl*-37: 6.5%; *dl*-38: 30%;*d*-40: 1.7%; *l*-41: 38.5%; *d*-42: 14%.

Scheme 7

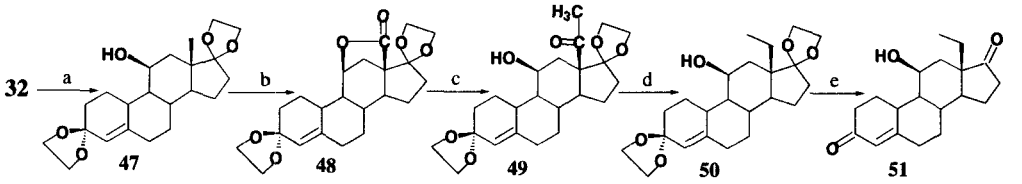


Reagents and Results: *Aspergillus ochraceus*, **44**: 42%; **45**: 7%; **46**: 13%.

Scheme 8

11β-OH-derivative

A partial synthesis of the 13β-ethyl-11β-hydroxygon-4-ene-3,17-dione **51** was reported by Zeelen and co-workers in 1988.[77] The key step in the synthesis is the intramolecular hypoiodite reaction which allows the functionalization of the angular 18-methyl group. Conversion **32** to **51**, required a total of four steps and the overall yield was 33.2% (*Scheme 9*).

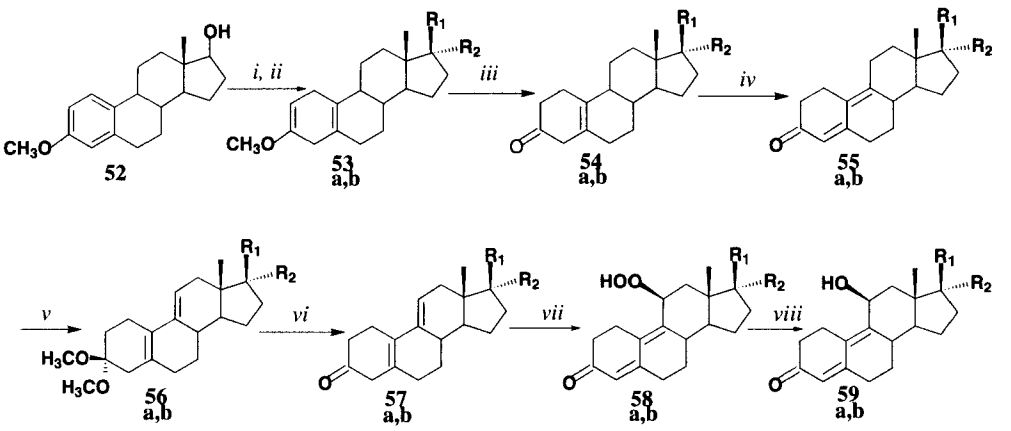


Reagents and Results: a) $HC(OEt)_3$, $(CH_2OH)_2$, *p*-TsOH; b) $Pb(OAc)_4$, I_2, azobisisobutyronitrile, 40%;
c) CH_3MgBr, ether, quantitative yield; d) Wolff-Kishner reduction 83%; e) *p*-TsOH, acetone, quantitative yield

Scheme 9

2. Oxygen Peroxidation

The oxygen peroxidation of 5(10),9(11)-dien-3-one steroids under the basic condition was first reported by Joly and co-workers.[78] The intermediate peroxides were unstable and were immediately reduced to hydroxides. Later investigation demonstrated that this is an effective method of introduction 11β-OH into steroids.[79-82] The process starting from 3-methoxy-estra-1,3,5(10)-trien-17-ol (**52**) included eight steps (*Scheme 10*). Birch reduction of compound **52** gave the 3-methoxy-2,5(10)-diene steroid **53a**;[83-86] subsequent Oppenauer oxidation yielded **53b**. Selective hydrolysis of



a) R_1 = OH, R_2 = H; b) R_1 = R_2 = O

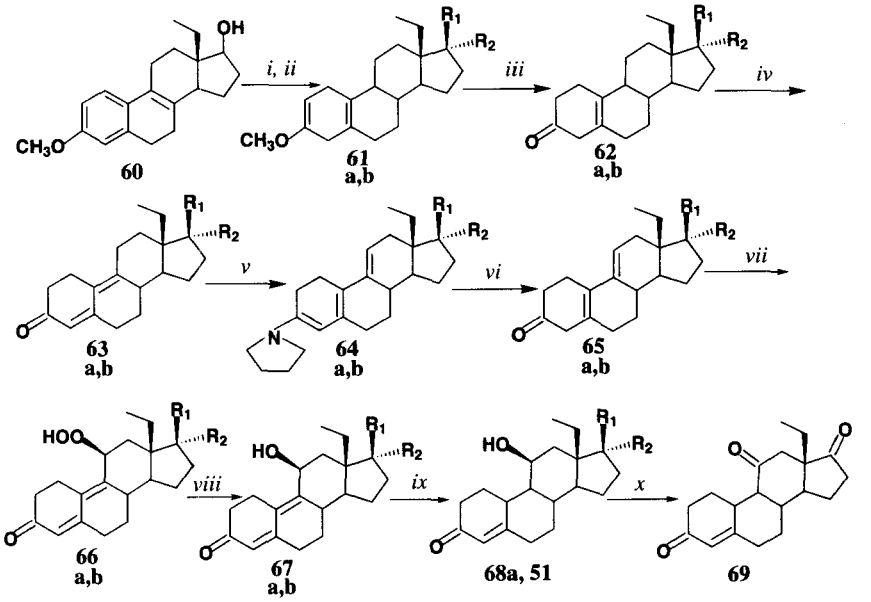
Reagents and Results: i) Li, liq NH_3, ethanol, THF, **53a**: 90%.
ii) (*i*-PrO)$_3$Al, cyclohexanone, toluene, **53b**: 87%. iii) Oxalic acid, acetone, **54a:** 83%, **54b:** 85%.
iv) Pyridinium hydrobromide perbromide (PBP), pyridine, **55a:** 89%, **55b:** 49%.
v) CH_3COCl, MeOH, **56a:** 95%, **56b:** 97.5%. vi) 8% H_2SO_4, acetone, **57a**: 98%, **57b**: 93%.
vii) O_2, MeOH (1% Et_3N), **58a**: 100%, **58b**: 92%.
viii) NaI, HOAc-dioxane, **59a:** 45%; $(MeO)_3P$, MeOH, **59b:** 82%.

Scheme 10

3-methoxy-2,5(10)-diene steroids (step iii) could be accomplished by using acid catalysts, such as aliphatic acids (e. g. acetic (86%)[85] and propanedioic acid (100%)[87]) or mineral acids (e. g. perchloric[88] and sulfuric acid[85]). The most common catalyst was oxalic acid.[83, 84, 87a, 89] Jones' oxidation of **54a** gave **54b** in a 41% yield.[90] The 4,9-dien-3-ones (**55**) was formed in one step *via* bromination and dehydrobromination using pyridinium bromide perbromide (PBP) in pyridine.[89, 91-93] The oxidation of **55** to **55b** could be accomplished with chromic acid;[92] the same method converted estr-4-ene-3,17-dione-19-carboxy acid to **55b**.[94, 95] The conversion of 4,9-dien-3-ones into 5(10),9(11)-isomers could be accomplished *via* selective hydrolysis of an enol ester (73%)[81]or enamine[96], or by tetrachlorosilane ($SiCl_4$)-catalyzed isomerism.[97] Enamination with pyrrolidine followed by formic acid-catalysed hydrolysis was used on **55b**,[95] 17α-ethynyl-17β-hydroxy-19-norandrosta-4,9(10)-dien-3-one[98] or similar compounds.[99] Ketalization with methanol followed by 8% H_2SO_4-catalysed hydrolysis has been used commonly.[80, 93, 100, 101] Ketalization on a similar compound to **55a** with 2,2-

dimethylpropane-1,3-diol gave 74% yield.[102] The 5(10),9(11)-dien-3-ones were unstable and peroxidised on exposure to oxygen[78-82, 95, 96, 103, 104] The resulting 11β-hydroperoxide could be reduced by $(MeO)_3P$,[78, 79, 104] NaI[80, 81, 95] or Na_2SO_3 (86%).[105] in methanolic acetic acid to give **59**.

During the synthesis of desogestrel and its derivatives, Liu and co-workers[106] successfully applied the same strategy to synthesize 13β-ethyl-gon-4-ene-3,11,17-trione **69** with the total yield of 44% starting from 13β-ethyl-17β-hydroxy-3-methoxy-gona-2,5(10)-diene (*Scheme 11*). Hydrolysis of 3-methoxy-2,5(10)-diene steroids (**61a-b**) *via* oxalic acid in presence of silica gel[107] was developed as a rapid and selective synthetic method to produce the corresponding 5(10)-en-3-ones (**62a-b**) in good yields (87-94%).[106, 108] Steps v and vi could be accomplished simply and in high yields (94-95%) by enamination with pyrrolidine followed by formic acid-catalyzed hydrolysis. Selective hydrogenation of 17-substituted 13β-ethyl-11β-hydroxy-gon-4,9-dien-3-ones (**67a-b**) with a

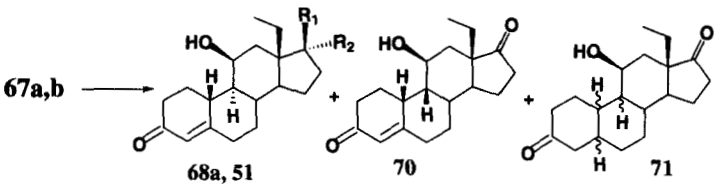


a) R_1 = OH, R_2 = H; b) R_1 = R_2 = O

Reagents and Results: (i) Li, liq NH_3, ethanol, THF, **61a**: 63.2%.
(ii) (*i*-PrO)$_3$Al, cyclohexanone, toluene, **61b**: 85%.
(iii) Oxalic acid on silica gel, CH_2Cl_2, **62a**: 94%, **62b**: 87%.
(iv) Pyridinium hydrobromide perbromide (PBP), pyridine, **63a**: 92%, **63b**: 57%.
(v) Pyrrolidine,MeOH,**64a**: 94%,**64b**: 95%. (vi) 86%HCOOH. (vii) O_2, MeOH (1% Et_3N).
(viii) NaI, HOAc-dioxane, over-all yield of vi, vii, viii **67a**: 70%, **67b**: 46%
(ix) H_2, 5% Pd/$SrCO_3$, pyridine, **68a**: 81%, **51**: 45%. (x) Jones' reagent, **69**: 95%.

Scheme 11

Pd(0)/$SrCO_3$-pyridine medium gave the corresponding 11β-hydroxy-gon-4-en-3-ones (**68a, 51**) (*Scheme 11* and *12*).[106, 109] Complete assignments of ^1H and ^{13}C NMR spectra of the main products (**68a, 51**) were made by one and two dimensional NMR techniques, such as J-MOD or ATP, ^1H-^1H COSY, HETCOR and COLOC.[109]



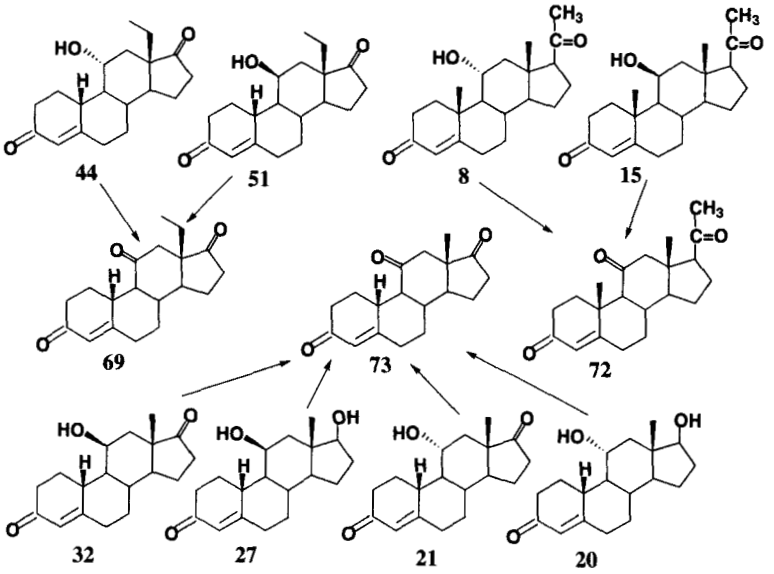
a) R_1 = OH, R_2 = H; b) R_1 = R_2 = O

Reagents and Results: H_2, 5% Pd/$SrCO_3$, pyridine, **68a**: 81%; **51**: 45%; **70**: 4%; **71**: 4%.

Scheme 12

3. Oxidation of 11-OH Steroids with 4-En-3-ones

Jones' oxidation of 11-OH-steroids (**8**[46, 47, 110], **15**[111], **20**[70, 71], **21**[71, 11], **32**[70], **27**[73], **44**[75, 76], **51**[77]) yielded the corresponding 11-oxo-steroids (*Scheme 13*). Jones' reagent can effectively oxidize both



Reagents and Results: Jones' reagents (8*N* chromic acid), acetone, 0-5°, 15 min. **8**: 67%; **15**: 70%; **20**: 57%; **21**: 82%; **27**: 63%; **32**: 74%; **44**: 83%; **51**: 95%.

Scheme 13

11α-OH and 11β-OH. In the meantime, the 17-OH was oxidized to the 17-one. Thus, compounds **8** and **15** gave the same compound **72**; compounds **20**, **21**, **27** and **32** gave the same compound **73**; compounds **44** and **51** gave the same compound **69**. Oxidation of 11α-hydroxyprogesterone with $Na_2Cr_2O_7$ gave a 61% yield of 4-pregnene-3,11,20-trione (*Scheme 14a*).[112] 11α-Hydroxyprogesterone was oxidized to 11-oxoprogesterone (60%) by treatment with *N,N*-diethylamino-1-propyne and DMSO in presence of phosphoric acid (*Scheme 14b*).[113] In 1965, Moffatt and Pfitzner[114] reported that the oxidation of many different types of hydroxy groups, particularly in the steroid area, could be carried out by reaction with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the

Table 4. Oxidation of Estra-1,3,5(10)-trien-11-ol Derivatives

Compd.	substituents R1	R2	R3	R4	Reagents and Conditions	Prod.	yield (%)	ref.
75b		CH_3	CH_3	α-OH, β-H	1. DCC, DMSO, $Cl_2CHCOOH$;	**75c**	100	120
					2. PCC/CH_2Cl_2	**75c**	28	121
77b	β-OCH_2Ph	C_2H_5	CH_3	α-OH, β-H	1. PCC/CH_2Cl_2;	**77c**	64	129
					2. DCC/DMSO	**77c**		131
80b	β-OCH_2Ph	CH_3	$PhCH_2$	α-OH, β-H	1. PDC/DMF;	**80c**	16	136
					2. PCC/CH_2Cl_2	**80c**	57	4
81a	β-OCH_2Ph	C_2H_5	$PhCH_2$	α-OH, β-H	1. PDC/DMF	**81b**		136
82a	=O	CH_3	OH	β-OH, α-H	1. CrO_3/H_2SO_4	**82b**	38	135
83a		CH_3	$PhCH_2$	α-OH, β-H	1. PCC/CH_2Cl_2	**83b**	64	123

Additional applications of PCC to the oxidation of very similar compounds showed the satisfactory results (**83b**: 64%,[123] **80c**: 57%,[4] **77c**: 64%[129]). Coombs and co-workers[120] oxidized **75b** with dicyclohexylcarbodiimide and DMSO in presence of dichloroacetic acid to 11-one with 100% yield. The Moffatt oxidation reaction was also used on compound **77b** but there were difficulties in purification of the products because of DCC and DCU residues.[131, 137]

b) Hydroboration-Chromic Acid Oxidation

The chromic acid oxidation of organoboranes to yield ketones was first reported by Brown and Garg.[138] Wang and Li used the same method on 13β-ethyl-3-methoxygona-1,3,5(10),9(11)-tetraene-17β-ol **76a** and isolated four products (*Scheme 19*).[139, 140] The ^1H NMR data for these compounds are summarized in Table 5. For the compound **76h**, MS and elemental analysis showed the molecular formula of $C_{20}H_{27}BO_4$. The IR spectrum showed two peaks for hydroxy groups (3496 cm^{-1} and 3306 cm^{-1}) and one peak for a ketone (1718 cm^{-1}). The ^{13}C NMR showed the same carbon number as that of **76a**. With DEPT technique, there were still multiple peaks at 24.60 ppm. According to the mechanism suggested,[138] **76h** was supposed to be 11-boron derivative. ^{11}B NMR gave a peak at 15.62 ppm (B_2H_6 as standard). After alkaline peroxide oxidation, the product was identified with **76g**. Thus, the structure of **76h** was 13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one-11α-boron acid. For the compound **76i**, MS gave the molecular weight of 294. ^1H NMR showed five aromatic protons: 7.88 (1H, d, J = 9 Hz, 6-H), 7.64 (1H, d, J = 8.5 Hz, 1-H), 7.18 (1H, d, J = 9 Hz, 7-H), 7.15 (2H, m, 2,

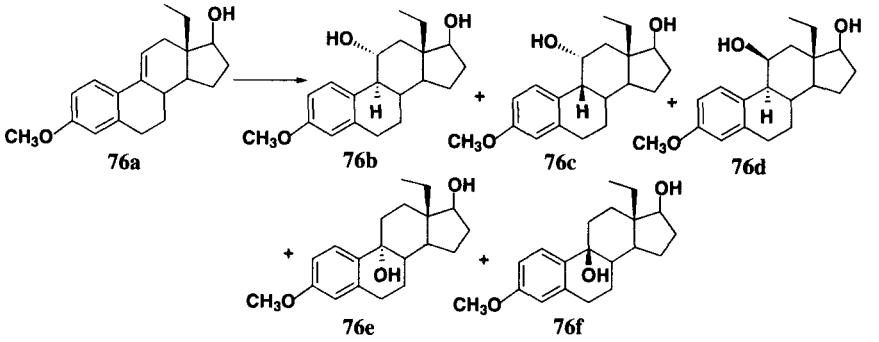
II. SYNTHETIC APPROACHES TO 11-OXO STEROIDS WITH AROMATIC A-RING

1. Hydroboration/Oxidation

a) Hydroboration-Alkaline Peroxide Oxidation

Hydroboration

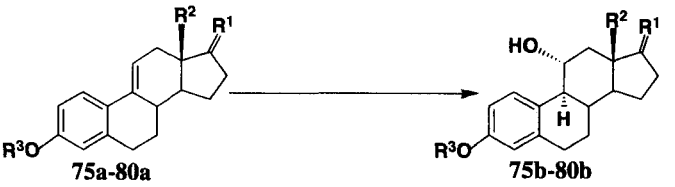
After treating 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10),9(11)-tetraene **75a** (Table 1) with diborane in the usual way[119], Coombs and co-workers isolated a product formulated as the 11α-hydroxy-derivative **75b**.[120] The process was repeated successfully later and **75b** was obtained in 61% yield.[121] Using the same strategy on 13β-ethyl-3-methoxygona-1,3,5(10),9(11)-tetraene-17β-ol **76a**, Smith isolated two products (**76b** and **76e**) (*Scheme 16*).[122] In 1985, Li and co-workers[123] isolated a



Reagents and Results: BH_3/THF, H_2O_2-NaOH, **76b**: 56%; **76c**: 10%; **76d**: 2%; **76e**: 0.4%; **76f**: 3%.

Scheme 16

Table 1. Hydroboration-Alkaline Peroxide Oxidation of Estra-1,3,5(10),9(11)-tetraene Derivatives



Compd	substituents R1	R2	R3	Reagents and Conditions	Prod.	yield (%)	ref
75a		CH_3	CH_3	1. BH_3/THF 2. H_2O_2-NaOH	**75b**	35, 61	121
76a	β-OH, α-H	C_2H_5	CH_3	1. BH_3/THF 2. H_2O_2-NaOH;	**76b**	56	122
				1. $NaBH_4/BF_3$ Et_2O 2. H_2O_2-NaOH	**76b**	75	132
77a	β-OCH_2Ph	C_2H_5	CH_3	1. BH_3/THF 2. H_2O_2-NaOH	**77b**	49	129
78a	=O	C_2H_5	CH_3	1. BH_3/THF 2. H_2O_2-NaOH	**78b**	a	131
79a	=O	CH_3	CH_3	1. $NaBH_4$-$AlCl_3$ 2. H_2O_2-NaOH	**79b**	a	133
80a	β-OCH_2Ph	CH_3	$PhCH_2$	1. $LiAlH_4/BF_3$ Et_2O 2. H_2O_2-NaOH;	**80b**	a	134
				1. $LiBH_4$/catecholborane 2. H_2O_2-NaOH	**80b**	72	4

a) Yields were not reported.

third isomer **76d** in the same reaction mixture. Three years later, Zhou and Li[124] carefully reexamined the same reaction mixture and isolated all five isomers by column chromatography. The ^{1}H NMR data and the ^{13}C NMR data of the five isomers (**76b-76f**) are summarized in Tables 2 and 3, respectively.

Table 2. Partial ^{1}H NMR Spectra of **76b**, **76c** , **76d** , **76e** and **76f**

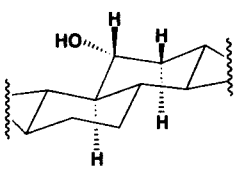
Cmpd	3-OCH_3	17α-H	C_{11}-H	C_4-H	C_2-H	C_1-H
76b	3.75(s)	3.73(s)	4.04(td)	6.60(d)	6.75(dd)	7.82(d)
76c	3.79(s)		4.52(dt)	6.68-7.02(m)	6.68-7.02(m)	7.11(d)
76d	3.73(s)		4.72(broad)	6.62(d)	6.75(dd)	7.16(d)
76e	3.80(s)			6.67, 6.68(m)	6.67, 6.68(m)	7.16(d)
76f	3.79(s)			6.65-6.77(m)	6.65-6.77(m)	7.19(d)

Table 3. ^{13}C NMR Spectra of **76b**, **76c** , **76d** , **76e** and **76f**

Assignment	**76b**	**76c**	**76d**	**76e**	**76f**
C-1	127.1	129.4	125.9	126.5	125.5
C-2	110.9	112.6	112.2	111.6	111.6
C-3	157.7	157.7	157.7	157.4	157.8
C-4	113.7	113.1	114.7	113.5	113.7
C-5	139.0	135.1	139.9	137.7	136.4
C-6	28.6	34.2	28.9	30.3	29.7
C-7	27.0	30.2	26.7	27.4	26.9
C-8	37.0	43.7	33.0	39.4	39.6
C-9	(50.9)	49.0	(51.8)	85.7	72.2
C-10	132.5	133.1	127.7	132.0	132.7
C-11	70.4	68.9	67.4	25.3	25.9
C-12	43.5	41.5	44.1	31.7	41.3
C-13	45.4	43.8	37.7	51.9	47.3
C-14	(50.2)	44.7	(50.1)	43.8	45.3
C-15	22.5	24.9	22.3	22.8	24.7
C-16	30.8	30.7	30.8	30.9	31.0
C-17	83.1	84.4	84.8	79.7	83.3
C-18	18.4	19.1	20.3	16.7	17.6
C_{18}-CH_3	9.7	10.0	11.1	8.4	9.3
C_3-OCH_3	55.1	55.2	55.1	55.1	55.2

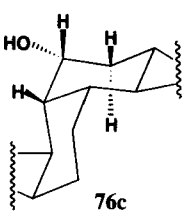
Compound **76b**, **76c** and **76d** were identified by their melting points and ^{1}H NMR spectra data.[122, 125] When 11-OH is at the α-position (**76b**), the 11β-H is deshielded to 4.04ppm. Among the 11β-H, 9α-H, 12α-H and 12β-H, the first three hydrogens are axial and the last one is equatorial.

Thus, both $J_{9\alpha,\ 11\beta}$ and $J_{11\beta,\ 12\alpha}$ are10Hz which is larger than $J_{11\beta,\ 12\beta}$ (5Hz). The 11β-H shows a triple-doublet (Fig. 2). When the 11-OH is α oriented and the 9-H is β oriented (**76c**), the 11β-H is shifted to 4.52ppm. Among the 11β-H, 12α-H, 9β-H and 12β-H, the first two hydrogens are axial and the last



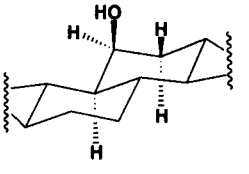
76b

4.04 ppm (1H, td, 11β-H)
$J_{9\alpha,\ 11\beta}=J_{11\beta,\ 12\alpha}$=10 Hz
$J_{11\beta,\ 12\beta}$[a]



76c

4.52 ppm (1H, dt, 11β-H)
$J_{9\beta,\ 11\beta}=J_{11\beta,\ 12\beta}$=4.5 Hz
$J_{11\beta,\ 12\alpha}$=8.5 Hz



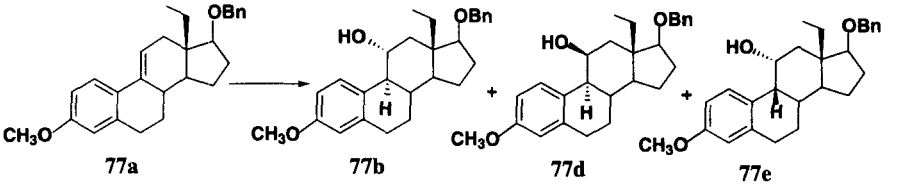
76d

4.72 ppm
(1H, Broad, J=2.5Hz, 11α-H)

Fig. 2 ^{1}H NMR coupling configuration determination of **76b**, **76c** and **76d**.

two are equatorial. Thus, $J_{9\beta,\ 11\beta}$ and $J_{11\beta,\ 12\beta}$ are 4.5Hz which is smaller than $J_{11\beta,\ 12\alpha}$ (8.5Hz). The 11β-H shows a double-triplet. When 11-OH is at β-position (**76d**), the 11α-H deshields to 4.72ppm and shows a broad peak with J = 2.5Hz. This is due to 60^0 angle between 11α-H and each of 9α-H, 12α-H and 12β-H. For compound 76e, ^{1}H NMR spectrum did not show any peaks between 4 ppm and 5 ppm, and it easily dehydrated in HCl-CH_3OH at room temperature to give $\Delta^{9(11)}$. There was positive Cotton effect at 228 nm. All these data demonstrated that **76e** had a 9-OH at the α-position. In the ^{13}C NMR, the two tertiary carbon peaks appeared at C-17 (79.7 ppm) and C-9 (85.7 ppm). For compound **76f**, the elemental analysis and MS spectra were consistent with the formula $C_{20}H_{28}O_3$. In ^{1}H NMR, there were no peaks between 4 ppm and 5 ppm which indicated there was no other CH(OH) grouping in the molecule except 17β-OH. Refluxing **76f** in HCl-CH_3OH produced a $\Delta^{9(11)}$ double bond and showed that a second hydroxy group was connected to C-9. In ^{13}C NMR, the two tertiary carbon peaks assigned to C-17 (83.3 ppm) and C-9 (72.2 ppm). The negative Cotton effect at 228 nm determined the 9-OH to be in the β-configuration.[126, 127] The introduction of the 9-OH is clearly activated by the A-ring aromatic system. The assignment of C, CH, CH_2 and CH_3 was accomplished by INEPT technique based reference compounds and substituent effects.[128] For compound **76d**, there is γ relationship between C-11β-OH and C-8, C-13 with cross conformation. Compared with **76b**, $\delta_{c\text{-}8}$ and $\delta_{c\text{-}13}$ were more shielded (4.0 and 7.7 ppm respectively). The three tertiary carbons (C-8, C-9 and C-14) in **76c** were assigned by conformation. Because the C-14H approached the C-6H, $\delta_{c\text{-}14}$ was deshielded to higher field (44.7 ppm). The relationship between C-8H and C-6H changed from axial-axial to axial-equatorial causing $\delta_{c\text{-}8}$ to be deshielded (43.7 ppm). Because 9α-OH of compound **76e** showed γ effect, $\delta_{c\text{-}12}$ and $\delta_{c\text{-}14}$ were more shielded (9.6 and 1.5 ppm respectively) compared with compound **76f**. In the synthesis of 3-oxo desogestrel, Gao and co-workers applied the same method on the similar compound **77a** and isolated three products with 11α-hydroxy derivative (**77b**: 49%) as the major product (*Scheme 17*).[129, 130] This method has also been used on the related compound with a 17-one

group **78a**.[131] To avoid the complexity in the preparation of diborane solution in THF, other more convenient methods such as $NaBH_4$-BF_3•Et_2O[132], $NaBH_4$-$AlCl_3$[133], $LiAlH_4$-BF_3•Et_2O[134], $LiBH_4$-catecholborane[4] gave better yields (Table 1).

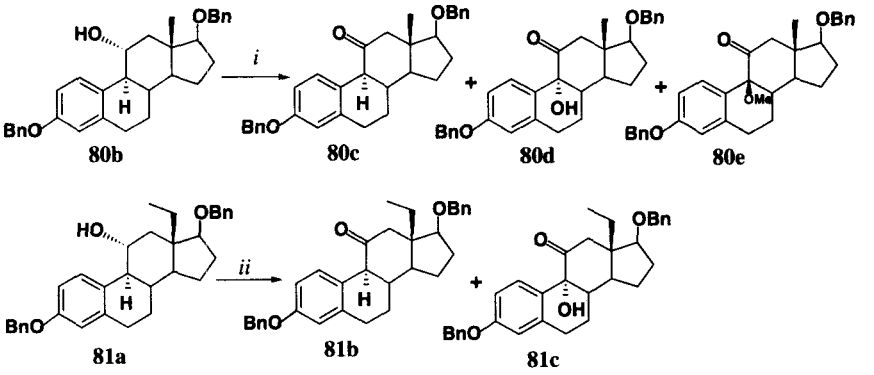


Reagents and Results: BH_3/THF, H_2O_2-NaOH, **77b**: 49%; **77d**: 4%; **77e**: 16%.

Scheme 17

Oxidation

The proper oxidant should be selected to oxidize estra-1,3,5(10)-trien-11-ol derivatives. Because C-9 is adjacent to C-11 and is also benzylic, 9α-OH-11-ketone may be obtained along with the anticipated 11-ketone. Oxidation 11β-hydroxyestrone **82a** with Kiliani's reagent gave a 38% of 11-ketoestrone **82b** (Table 4).[135] In 1985, Hanson and co-workers[136] reported that the oxidation of 3,17β-dibenzyloxy-11α-hydroxyestra-1,3,5(10)-triene **80b** with pyridinium dichromate (PDC) yielded the corresponding 9α-hydroxy-11-ketone **80d** as well as the anticipated 11-ketone **80c**. The 9β-methyl ether **80e**, obtained as a result of a methanolic work-up and shown to arise by an acid-catalyzed methanolysis of the 9α-alcohol, had its stereochemistry confirmed by X-ray crystallographic analysis (*Scheme 18i*). When the alcohol **81a** containing a 13-ethyl substituent was subjected

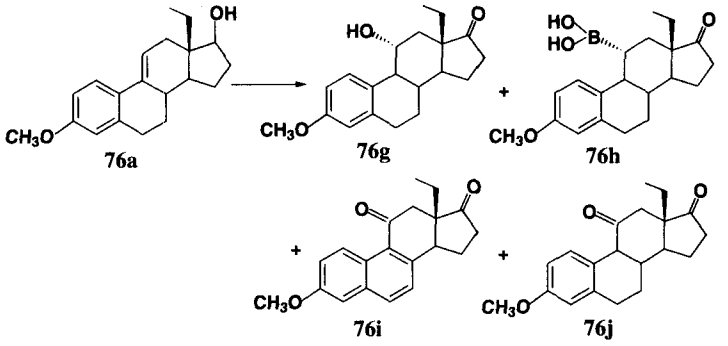


Reagents and Results: i) DCC, DMF, MeOH, **80c**: 16%; **80d**: 1.2%; **80e**: 41%; ii) DCC, DMF, **81b** and **81c**.

Scheme 18

to the same oxidation sequence but without treatment with methanol, the corresponding ketone **81b** and ketol **81c** were obtained (*Scheme 18ii*). Oxidation of 17,17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-trien-11α-ol **75b** with pyridinium chlorochromate (PCC) afforded the non-crystalline 11-ketone **75c** (Table 4).[121]

4-H). ^{13}C NMR showed five aromatic carbons between 100 and 200 ppm. Thus, the structure of **76i** was 13β-ethyl-3-methoxygona-1,3,5(10),6,8-pentaen-17-one. The anticipated product **76j** showed two



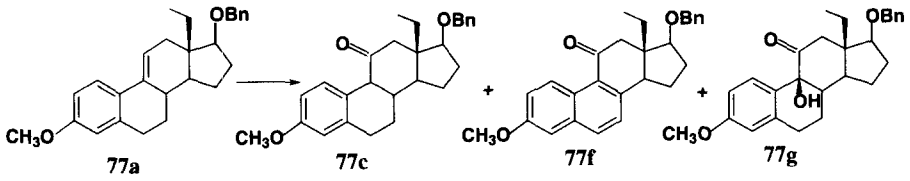
Reagents and results: a) BH_3/THF, rt., 48 h; b) H_2CrO_4, rt., 5h.**76g**: 9%, **76h**: 32%, **76i**: 13%, **76j**: 28%.

Scheme 19

Table 5. Partial ^1H NMR Spectra of **76g**, **76h** , **76i** and **76j**

Cpd.	3-OCH_3	C_{11}-H	C_4-H	C_2-H	C_1-H	C_6-H	C_7-H
76g	3.78(s)	4.02(td)	6.64(m)	6.64(m)	7.99(d)	——	——
76h	3.70(s)	6.62(m)	6.62(m)	7.18(d)	——	——	
76i	3.94(s)	——	7.15(m)	7.15(m)	7.64(d)	7.88(d)	7.18(d)
76j	3.78(s)	——	6.60-6.84(m)		7.27(d)	——	——

carbonyl absorptions at 1736 cm^{-1} and 1714 cm^{-1}. The C_9-H showed a doublet ($J_{8,9}$ = 9.8 Hz) at 3.52 ppm. The 9.8 Hz coupling constant confirmed the 9α-configuration.[141] In this reaction, a TLC analysis showed that **76h** and **76i** were formed at the very beginning of the reaction. With the different molar ratios of oxidant and reaction temperatures, compound **76h** was still the major product. Using the same method on the compound **77a**, the yield of anticipated product **77c** was improved to 47% (*Scheme 20*).[139, 142] For the compound **77g**, the result of MS and elemental analysis indicated a molecular formula $C_{27}H_{32}O_4$. ^1H NMR did not show the peaks typical of 9H-11-one structure between 3.40 and 3.60 ppm. The three peaks in ^{13}C NMR between 70 and 100 ppm demonstrated 9-OH structure while the other two peaks belonged to 17-OCH_2- and C-17. The earlier study showed that 9β-hydroxy



Reagents and Results: a) BH_3/THF, rt., 48h; b) H_2CrO_4, rt., 2h. **77c**: 47%, **77f**: 13%, **77g**: 17%.

Scheme 20

group resulted in *cis*-B/C rings and formed hydrogen bond with 11-one (Fig. 3 A).[143] This resulted in C_1-H being shielded to the higher field. The chemical shift of C_1-H (6.60-6.67 ppm, 3H, m, 1, 2, 4-H) in ^{1}H NMR and IR frequency of 9-OH group (3432 cm^{-1}) confirmed the 9β-OH configuration.

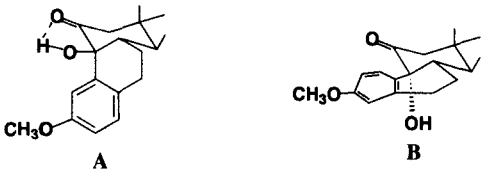


Fig. 3

2. Epoxidation

The epoxidation of 9(11)-dehydroestrone acetate **84a** with perbenzoic acid in chloroform afforded a mixture of an epoxide.[144] The epoxide obtained as the major product (72%) was identified to have the 9α,11α-epoxide configuration, whereas the minor product (12%) has the 9β,11β-epoxide configuration (Table 6). Liang and co-workers[145] used *m*-chloroperbenzoic acid to epoxidise **85a** and got an epoxide mixture with 80% yield. Upon epoxidation of **75a** by the two-phase dichloromethane/aqueous potassium carbonate procedure of Anderson and Veysoglu,[146] Collin and co-workers[121, 147] obtained a 70% yield of crystalline but extremely acid-sensitive 9α,11α-epoxide **75d**. Suitable precautions were necessary for its recrystallization and spectroscopic examination.[121]

Table 6. Epoxidation of Estra-1,3,5(10),9(11)-tetraene Derivatives

84a-75a **84b-75d**

Compd	substituents R^1	substituents R^2	Reagents and Conditions	yield (%) 9a,11a	yield (%) 9b,11b	yield (%) 9z,11z	ref
84a	=O	AcO	1. $PhCO_2OH$, $CHCl_3$, 0°, 24 h	**84b**: 72	**84c**: 12		144
85a	β-OAc, α-H	AcO	1. *m*-$ClPhCO_2OH$, $CHCl_3$, 0°, 2 h			**85b**: 80	145
75a		OCH_3	1. *m*-$ClPhCO_2OH$, $NaHCO_3$, $CHCl_3$	**75d**: 70-72			121

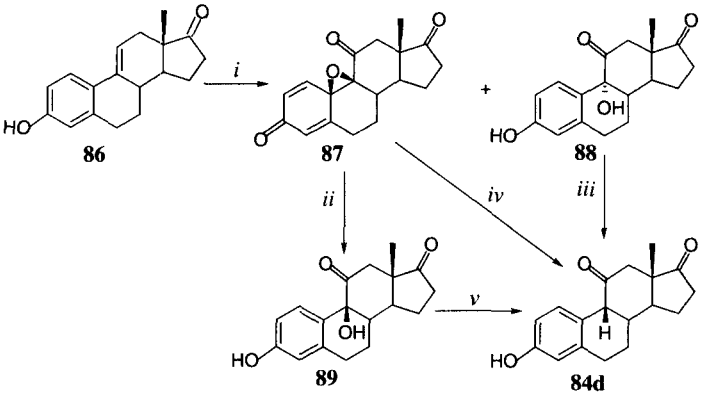
Treatment of 9α,11α-epoxides with dry hydrogen chloride in methanol[141] or 5% KOH in methanol[145] afforded the corresponding 3-hydroxy-9β-estra-1,3,5(10)-trien-11-one derivatives (Table 7) *via* a pinacol-pinacolone-like mechanism. A solution of **75d** in benzene containing a trace of anhy-

drous lithium perchlorate was heated under reflux for 3 hours to give a nearly quantitative yield of the non-crystalline 9β-ketone **75e**.[121, 147]

Table 7. Conversion of 9a,10a-Epoxides to 11-Ones

Compd	substituents R1	substituents R2	Reagents and Conditions	substituents R1	substituents R2	Prod.	yield (%)	ref
84b	=O	AcO	1. HCl, MeOH, -5°, 1.5 h	=O	HO	**84d**	80	141
85b	β-OAc, α-H	AcO	1. KOH, MeOH, reflux, 30 min.	β-OH, α-H	HO	**85c**	66	145
75d		OCH_3	1. $LiClO_4$, benzene, reflux, 3 h		OCH_3	**75e**	98-100	121

Hasegawa and Tsuda's further work demonstrated that the treatment of $\Delta^{9(11)}$-estrone **86** with three molar equivalents of perbenzoic acid in chloroform afforded an epoxydienone **87** in 40-50% yields and a phenolic compound **88** in 3-10% yields (*Scheme 21*).[143] When **87** was treated with zinc in



Reagents and Results: (i) $PhCO_2OH$, $CHCl_3$, 0°, 24 h, **87**: 44%, **88**: 4.7%;(ii) H_2, 5% Pd-C, **89**: 50%;
(iii) Zn/HOAc, reflux, 4 h, **84d**: 21%; (iv) Zn/HOAc, reflux, 2 h, **84d**: 15%;
(v) Zn/HOAc, reflux, 19 h, **84d**: 22%.

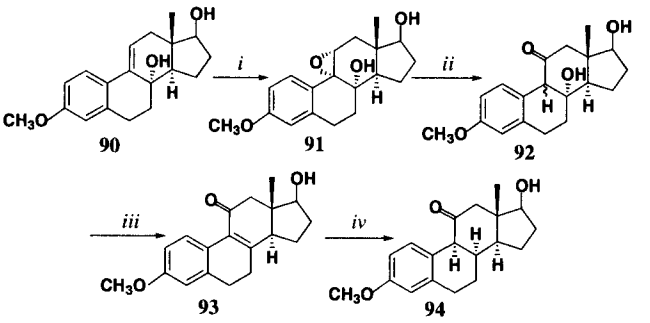
Scheme 21

acetic acid, 3-hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione **84d** was obtained. On hydrogenation with 5% palladium-charcoal **87** readily consumed one molar equivalent of hydrogen to afford in high yield a phenolic compound determined to be 3,9-dihydroxyestra-1,3,5(10)-triene-11,17-dione (**89**). Elemental analysis indicated that **88** was isomeric with **89**.

The hydroxy group of **88** was resistant to oxidation by chromic anhydride in pyridine and thus might be tertiary. Reduction of **88** with zinc in acetic acid resulted in hydrogenolysis to yield **84d**

as did **87**. The configurations of the hydroxy groups of **88** and **89** was assigned by measurement of intramolecular hydrogen bonding in the infrared spectra. The hydroxy and carbonyl absorption bands in dilute carbon tetrachloride solution (c = 0.0004 M, l = 50 mm) of **88** and **89** were observed at 3609, 1730 and 3843, 1713 cm^{-1}, respectively. The later frequencies indicated the presence of intramolecular hydrogen bonding between C_9-hydroxyl and C_{11}-carbonyl group, while the former did not. Inspection of Dreiding Model as shown in Fig. 3 indicates that the 9β-hydroxy isomer (A) should exhibit hydrogen bonding, while the 9α-hydroxy isomer (B) cannot. Thus the α- and β-configuration were assigned to the hydroxy group of **88** and **89** respectively.

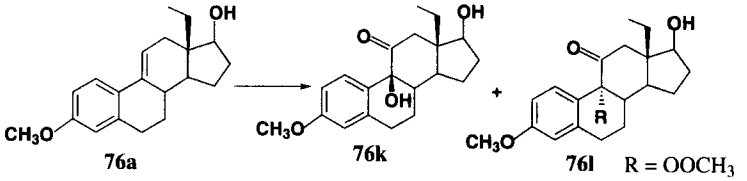
When *m*-chloroperbenzoic acid was used on the diol **90** in benzene-hexane, the epoxydiol **91** was obtained (*Scheme 22*).[148] Methanolic HCl at or below room temperature transformed **91** to 11-oxo-estratetraene **93**, probably through formation and dehydration of the ketol **92**. The overall yield for the three stage sequence *i-iii* was 52%. Catalytic hydrogenation over palladized charcoal in dimethylformamide converted **93** to an estratriene **94**.



Reagents and Results: (i) m-ClPhCO$_2$OH, benzene-hexane; (ii)-(iii) HCl/MeOH, rt., **90-93**: 52%; (iv) H_2/Pd-C, DMF

Scheme 22

During the synthesis of 3-oxo desogestrel, Wang and Li[139, 149] attempted a *m*-chloroperbenzoic acid epoxidation on 13β-ethyl-3-methoxygona-1,3,5(10),9(11)-tetraen-17β-ol **76a** (*Scheme 23*).



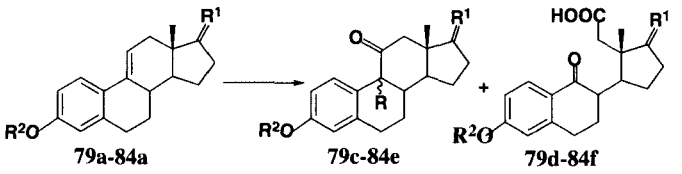
Reagents and Results: (i) m-ClPhCO$_2$OH, $CHCl_3$, 0°, 2 h; (ii) KOH, MeOH, reflux, 30 min. **76k**: 39%; **76l**: 15%.

Scheme 23

Because of the instability of the 9α,11α-epoxide, it was treated with 5% KOH in methanol directly. Column chromatography afforded two compounds. The elemental analysis and MS showed that the compound **76k** had a formula of $C_{20}H_{26}O_4$. The IR spectrum gave two peaks for hydroxy

groups (3458 cm^{-1} and 3440 cm^{-1}) and one ketone peak (1705 cm^{-1}). ^1H NMR spectrum did not give a peak for the C_9-H (δ=3.40-3.60 ppm). ^{13}C NMR showed a new tertiary-carbon peak at δ=85.5 ppm. The above analysis showed the presence of a 9-OH structure. The 9β-configuration was identified like **77g**. The elemental analysis and MS demonstrated that compound **76l** had a formula of $C_{21}H_{28}O_5$. Both ^1H NMR (δ = 3.39 ppm) and ^{13}C NMR (δ = 102.4 ppm) showed the 9-$OOCH_3$. The 9α-configuration was identified by Hasegawa and Tsuda's method.[143]

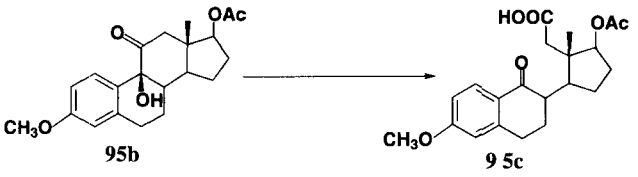
Table 8. Jones' Oxidation of Estra-1,3,5(10),9(11)-tetraene Derivatives



Compd	substituents R1	substituents R2	Reagents and Conditions	yield (%) 79c-84e	yield (%) 79d-84f	ref
79a	=O	CH_3	1. CrO_4-H_2SO_4, rt., 11 h, R = 9β-OH	**79c**: 23	**79d**: 31	153
95a	β-OAc, α-H	CH_3	1. CrO_4-H_2SO_4, rt., 11 h, R = 9β-OH	**95b**: 37	**95c**: 35	153
95a	β-OAc, α-H	CH_3	1. CrO_4-H_2SO_4, 0°, 5 h, R = 9β-OH	**95b**: 32	**95c**: 42	155
96a	H_2	CH_3	1. CrO_4-H_2SO_4, rt., 3 h, R = 9β-OH	**96b**: 1 1	**96c**: 4	154
96a	H_2	CH_3	1. CrO_4-H_2SO_4, rt., 11 h, R = 9β-OH	**96b**: 35	**96c**: 28	153
84a	=O	Ac	1. CrO_4-H_2SO_4, rt., 11 h, R = 9α-OH	**84e**: 28	**84f**: 18	153

3. Jones' Oxidation

Jones' oxidation of estra-1,3,5(10),9(11)-tetraene could yield 9β-OH-11-one (**79c-84e**) and 9-oxo-9,11-seco-11-oic acid derivatives (**79d-84f**) (Table 8).[150-155] It was suggested that the 9β-hydroxy-11-oxo-derivatives were formed *via* a 9(11)-dehydro-derivative. Further oxidation of **95b** with sodium metaperiodate produced **95c** nearly quantitatively (*Scheme 24*).[155] The only 9α-hydroxy-11-oxo derivative was found in the oxidation of 17-oxo-estra-1,3,5(10),9(11)-tetraen-3-yl acetate.[153] The 9α-H-11-oxo and 9β-H-11-oxo derivatives were reported by Aclinou and co-workers.[154]



Reagents and Results: $NaIO_4$, HCl, acetone, reflux, 8 h, **95c**: 98%

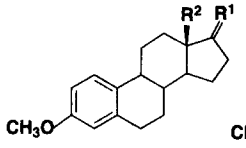
Scheme 24

4. ^{1}H NMR Studies of Estra-3-methoxy-1,3,5(10)-trien Derivatives

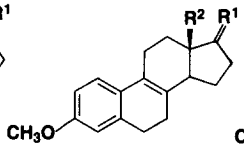
Nuclear magnetic resonance spectroscopy (NMR) is one of the more powerful tools available to the chemist for elucidating the structure of steroids. The steroid skeleton has many aliphatic carbons and protons which show overlapping peaks at high field. However, the special carbons and protons of steroid structures give characteristic NMR signals because of its highly asymmetric structure and distinct chemical environments. In principle, they can be uniquely assigned to give remarkably detailed information on the system.

For the estra-3-methoxy-1,3,5(10)-trien steroids, C_2-H and C_4-H are less deshielded by the aromatic A-ring compared with C_1-H because of back-donation by the 3-methoxy group. Because of the coupling with C_2-H, C_1-H show a doublet (J = 9 Hz). Besides the coupling with C_1-H, C_2-H has a long distance coupling with C_4-H (J = 1.8 Hz) and shows a double-doublet peak. Thus, C_4-H shows a doublet. After the introduction of $\Delta^{9(11)}$, C_1-H is in the plane of A-ring and $\Delta^{9(11)}$. Therefore, it will be deshieled to lower field about 0.45 ppm because the effect from A-ring and $\Delta^{9(11)}$ (Table 9). On the

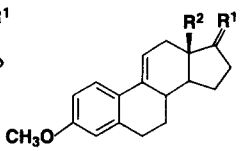
Table 9. ^{1}H NMR Chemical Shifts of Estra-3-methoxy-1,3,5(10)-triene Derivatives



97-101



102-103

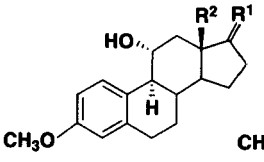


96a-107

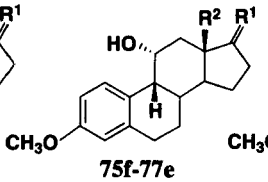
Compd.	substituents R^1	R^2	Chemical Shifts (ppm) C_1-H	C_2-H	C_4-H	C_{11}-H	ref.
97	β-OH, α-H	C_2H_5	7.01	6.53	6.45		131
98	β-OCH_2Ph	C_2H_5	7.02	6.63	6.50		139
99	=O	CH_3	7.12	6.60	6.56		143
100	β-$OC(CH_3)_3$	CH_3	7.20	6.63	6.63		156
101	β-$OC(CH_3)_3$	C_2H_5	7.18	6.68	6.68		156
102	β-OH, α-H	CH_3	7.13	6.66	6.66		156
60	β-OH, α-H	C_2H_5	7.11	6.72	6.60		139
103	β-OCH_2Ph	C_2H_5	7.16	6.66	6.56		139
96a	$=H_2$	CH_3	7.39	6.70	6.61	6.08	154
75a		CH_3	7.47	6.48-6.70	6.48-6.70	6.08	121
104	β-OH, α-H	CH_3	7.53	6.66	6.66	6.11	156
76a	β-OH, α-H	C_2H_5	7.44	6.65	6.54	6.04	139
77a	β-OCH_2Ph	C_2H_5	7.45	6.66	6.56	6.04	139
105	 , α-H	C_2H_5	7.45	6.66	6.54	6.04	139
106	β-$OC(CH_3)_3$	CH_3	7.48	6.58	6.58	6.07	156
107	β-$OC(CH_3)_3$	C_2H_5	7.45	6.63	6.63	6.07	156

other hand, $\Delta^{8(9)}$ cannot become coplanar with A-ring because of the B/C bridge bond. The C_1-H is only deshielded about 0.1 ppm (Table 9). The introduction of 11α-hydroxy group will deshield C_1-H by about 0.8 ppm (Table 10). With 9β-H, there will be *cis*-B/C conformation and longer distance

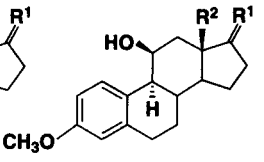
Table 10. ^{1}H NMR Chemical Shifts of Estra-3-methoxy-1,3,5(10)-trien-11-ol Derivatives



75b-76g



75f-77e



76d-77d

Compd	substituents		Chemical Shifts (ppm)				ref.
	R^1	R^2	C_1-H	C_2-H	C_4-H	C_{11}-H	
75b		CH_3	7.80	6.56-6.74	6.56-6.74	4.24	121
76b	**β-OH, α-H**	C_2H_5	7.82	6.75	6.60	4.04	124
77b	**β-OCH₂Ph**	C_2H_5	7.80	6.78	6.72	4.10	129
76g	**=O**	C_2H_5	7.99	6.65	6.61	4.01	139
75f		CH_3	7.76	6.68	6.65	4.45	121
76c	**β-OH, α-H**	C_2H_5	7.11	6.86	6.66	4.52	124
77e	**β-OCH₂Ph**	C_2H_5	7.12	6.78	6.68	4.56	129
76d	**β-OH, α-H**	C_2H_5	7.16	6.75	6.62	4.72	124
77d	**β-OCH₂Ph**	C_2H_5	6.69	6.62-6.75	6.62-6.75	4.51	129

between C_1-H and 11α-OH. The C_1-H are not affected by 11α-OH. From the data, the 11β-hydroxy group do not affect C_1-H either. The introduction of 11-one will deshield C_1-H by about 0.1 ppm (Table 11). On the other hand, C_1-H will be shielded to the higher field about 0.4 ppm with 9β-configuration and overlap with C_2-H and C_4-H.

III. SYNTHETIC APPROACHES TO 11-OXO STEROIDS OF CHOLIC ACID DERIVATIVES

1. Marker-Lawson Method

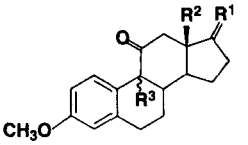
11-Oxo-deoxycholic Acid Derivatives

In 1938, Marker and Lawson[157] brominated 3α-acetoxy-12-ketocholanate and then hydrolyzed the resulting 11α-bromoketone to a ketol acid which contained an oxygen function at C-11. This has become known as the Marker-Lawson acid, which is a useful precursor 11-oxygenated steroid.

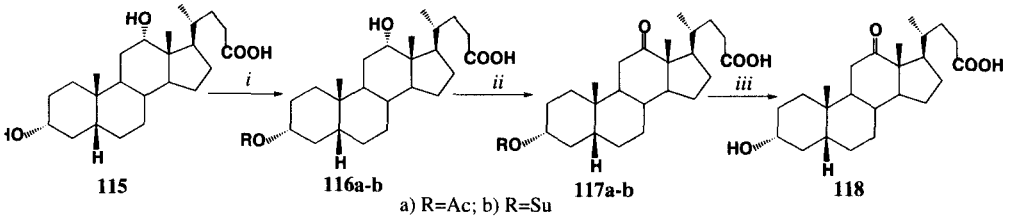
Desoxycholic acid **115** was treated with acetic anhydride[157, 158] or succinic anhydride[159] in presence of acetic acid or pyridine affording the monoacetate **116a** or 3α-succinoxy-12-ketocholanic acid **116b**. Upon chromic acid oxidation followed by alkaline treatment, ketone **118** was easily obtained (*Scheme 25*). The bromination of **117a-117b** with bromine at 65-75° in glacial acetic acid

solution gave a mixture of 11α- and 11β- bromo derivatives (*Scheme 26*).[157-161] Stefanovic and co-workers[162] found that when bromination in presence of HBr was carried out at room temperature (48-72 h) instead at 75°, the pure crystalline equatorial 11α-bromo-derivative **119a** was obtained almost

Table 11. ^{1}H NMR Chemical Shifts of Estra-3-methoxy-1,3,5(10)-trien-11-one Derivatives



Compd.	substituents			Chemical Shifts (ppm)			ref.
	R^1	R^2	R^3	C_1-H	C_2-H	C_4-H	
108	=H_2	CH_3	a-H	7.33	6.81	6.63	154
75c		CH_3	a-H	7.20	6.68	6.56	121
109	=O	CH_3	a-H	7.26	6.82	6.64	143
77c	β-OCH_2Ph	C_2H_5	a-H	7.26	6.74	6.60	129
76j	=O	C_2H_5	a-H	7.28	6.67	6.64	139
110	=H_2	CH_3	a-OH	7.35	6.77	6.62	154
111	=O	CH_3	a-OH	7.33	6.97	6.83	143
112	β-OCH_2Ph	C_2H_5	b-H	6.89	6.66	6.65	139
113	=O	CH_3	b-H	6.72	6.72	6.72	143
75e		CH_3	b-H	6.48-6.92	6.48-6.92	6.48-6.92	121
114	β-OH	C_2H_5	b-OH	6.67	6.72	6.70	139
77g	β-OCH_2Ph	C_2H_5	b-OH	6.68	6.74	6.60	139
79c	=O	CH_3	b-OH	6.80	6.80	6.90	143
96b	=H_2	CH_3	b-OH	6.75	6.75	6.75	154

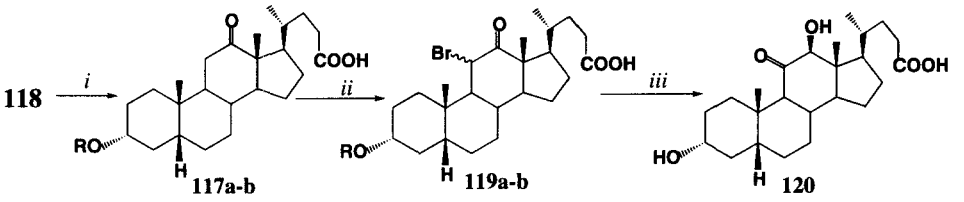


a) R=Ac; b) R=Su

Reagents and Results: (i) Ac_2O, AcOH, reflux, 3 h, **116a**; succinic anhydride,pyridine, rt., overnight, **116b**: 91%; (ii) chromic acid, AcOH, rt., 25 min.,**117a**; CrO_3, AcOH, H_2O, rt., 5 h, **117b**; (iii) **117a**, KOH, H_2O, reflux, 3 h, overall yield **115-118**: 74%; **117b**, alkaline solution, reflux, 3 h, overall yield **115-118**: 90%.

Scheme 25

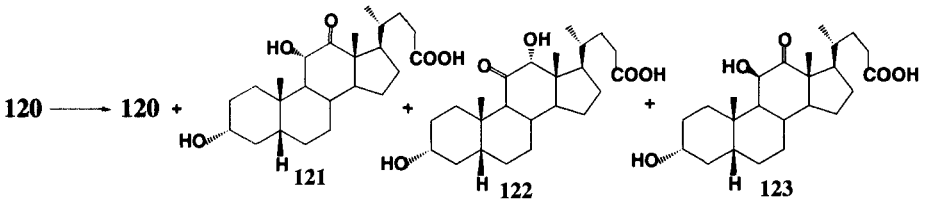
quantitatively. Application of the same bromination on sapogenins also resulted in the formation of 11α-bromo-derivatives.[163] The 11-bromo-derivatives were then refluxed for two hours with a solution of sodium hydroxide in aqueous methanol to effect the rearrangement of the intermediate 11-hydroxy-12-ketone into the 12β-hydroxy-11-ketone (Marker-Lawson acid, **120**).[157, 161, 162] Gallagher[164] showed



Reagents and Results: (i) Ac_2O, AcOH, reflux, 1.5h, **117a**: 77%; succinic anhydride, pyridine, reflux, 1 h, **117b**: 83%; (ii) Br_2, AcOH, HBr, 25°, 48-72h, **119a** (11α-): 100%; Br_2, AcOH, 65°, **119b** (11α- + 11β-): 98%; (iii) **119a**, NaOH, MeOH, reflux, 2 h, **120**: 79%; **119b**, NaOH, MeOH, reflux, 2 h, **120**: 77%.

Scheme 26

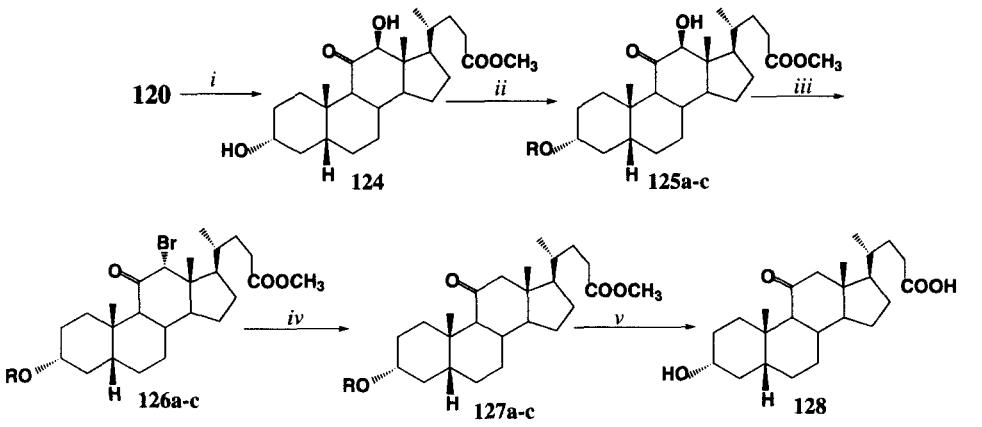
that all four possible ring C ketols were formed. The predominant isomer (60%) was the 12β-hydroxy-11-keto acid **120**, but a substantial amount (33%) of the isomeric 11α-hydroxy-12-keto acid contaminated with trace amounts of the other two isomers, was also present. The alkaline isomerization of 3α,12β-dihydroxy-11-ketocholanic acid also gave the same four possible ketols (*Scheme 27*).[165] Monoacetylation of ester **124** was first described to proceed in a poor yield.[166] Later studies



Reagents and Results: 5% NaOH, reflux, 2 h, **120**: 63%; **121**: 30%; **122**: 1.1%; **123**: trace.

Scheme 27

showed that this reaction may be effected readily in 80% yield by simple dissolution of the ester **124** in a four-fold excess of acetic anhydride (*Scheme 28*).[162] The selective acylation of the ester **124** could be carried out in good yield in 90% formic acid.[166] The dimethyl ester of 3α-succinoxy-12β-hydroxy-11-ketocholanic acid **125c** was converted to the corresponding bromoketone **126c** in 50-70% yield with aid of phosphorus tribromide.[165] The inversion of C-12 configuration was not made on a suitable derivative with methyl 3α-acetoxy-12α-bromo-11-ketocholanate **126a**[18a] until 1967.[162] Conversion of monoformate **125b** to the corresponding bromoketone monoformate **12b** was never accomplished in yields greater than 48% despite much experimentation.[166] In a variant of the above procedure, Hershberg[161] converted 3α-acetoxy-12β-hydroxy-11-keto-24,24-diphenylcholene to the corresponding bromoketone in only 47% crude yield. In many experiments involving this procedure, a phosphorus-containing substance was isolated, the empirical formula of which corresponded to that of the 12-phosphite ester. Reduction of the bromoketones with Zn/HOAc led to the desired 11-ketone steroids (**127a** and **127c**).[165, 18a]

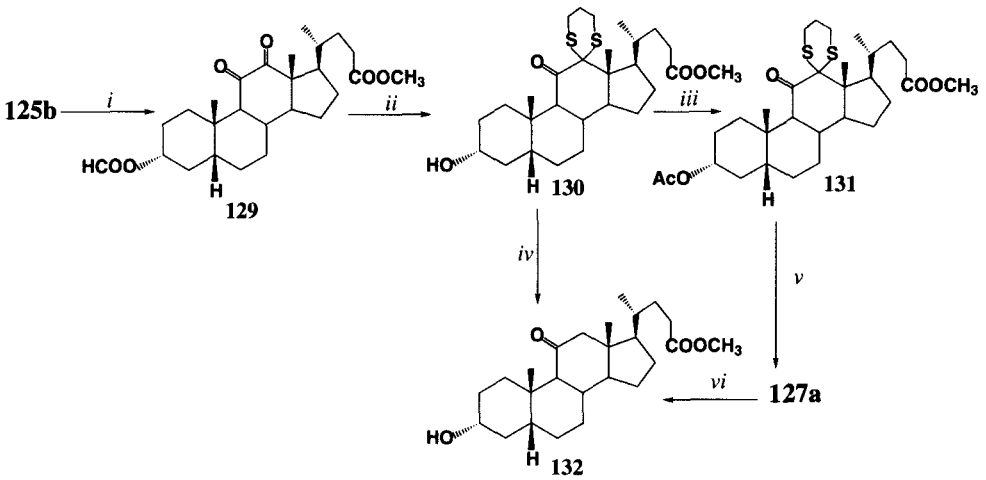


b) R=Ac; b) R=HCO; c) R=Su

Reagents and Results: (i) HCl, MeOH, rt., 2 h, **124**: 95%; (ii) Ac_2O, pyridine,45 min., **125a**: 80%; HCOOH, 65°, 3 h, **125b**: 92%; succinic anhydride, pyridine, rt.,overnight, **125c**: 91%; (iii) PBr_3, CH_2Cl_2, overnight, rt., **126a, b, c**: 70, 47, 50-60%; (iv) Zn, HOAc, reflux, 20 min.,**127a**: 88%; Zn, HOAc, reflux, 1 h, **127c**: 98%; (v) 5N NaOH, MeOH, reflux, 30 min., **128**: 94%.

Scheme 28

An alternative way of elimination 11β-OH in compound **125** was reported by Archer.[166] The pure ketol ester **125b** was first oxidized with chromic oxide to give the diketoformate **129** in 81% yield (*Scheme 29*). When the diketoformate **129** was treated with trimethylenedithiol in methanol

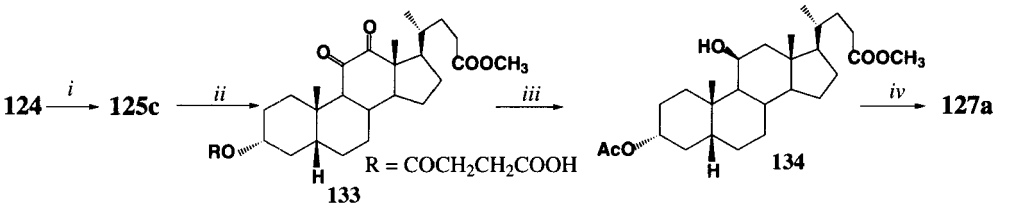


Reagents and Results: (i) CrO_3, HOAc, rt., 2 h, **129**: 81%; (ii) HCl, MeOH, trimethylene dithiol, rt., 2 h, **130**: 82%; (iii) Ac_2O, pyridine, rt., overnight, **131**: 88%; (iv) Raney nickel, MeOH, rt., 6 h, **132**: 84%; (v) Raney nickel, MeOH, rt., 6 h, **127a**: 95%; (vi) 5N KOH, reflux, 1 h, **132**: 93%.

Scheme 29

solution with hydrogen chloride gas as the condensing agent, the major product was the deformylated product **130**. On subsequent acetylation, diketoacetate **131** was obtained. The Raney nickel desulfuration of **131** was best carried out at room temperature for a peroid of several hours. In this way, the conversion to pure 3α-acetoxy-11-keto-cholanate **127a** and 3α-hydroxy-11-ketone-cholanate **132** was accomplished in 95% yield and 93% yield, respectively.

Under the conditions of the Wolff-Kishner reaction, the 12-keto group also could be reduced to the methylene group (*Scheme 30*).[167] The non-crystalline reaction product was converted into acetylated methyl ester **134**. The enolization could be anticipated. The chromic acid oxidation of ester **134** finally afforded **127a**.

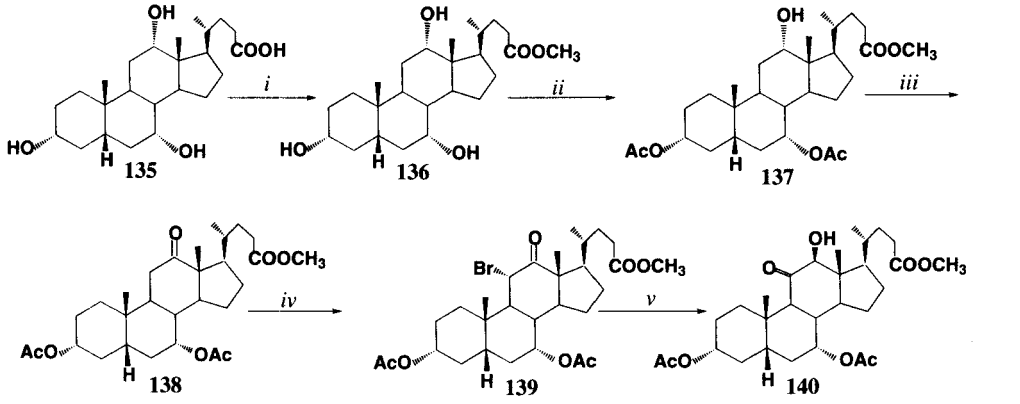


Reagents and Results: (i) succinic anhydride, pyridine, rt., 3 days, **125c**: 67%;
(ii) CrO_3, HOAc, rt., 1 h, **133**: 29%; (iii) hydrazine, EtOH, 200°, 6 h; diazomethane; Ac_2O, pyridine; **134**: 10%;
(iv) CrO_3, HOAc, rt., 17 h, **127a**: 91%.

Scheme 30

11-Oxocholic Acid Derivatives

The application of Marker and Lawson's method to cholic acid derivatives was first reported by Yanuka and Halperin.[168] Initially, cholic acid (**135**, *Scheme 31*) was methylated in methanol and acetyl chloride, then selectively acetylated at the 3α- and 7α- position[169, 170] to give the 3α,7α-diacetoxy-12α-hydroxy compound **137**.



Reagents and Results: (i) acetyl chloride, MeOH, rt., 2 h, **136**: 96%;
(ii) Ac_2O, pyridine, benzene, rt., 2 h, **137**: 86%; (iii) K_2CrO_4, AcOH, rt., 15 h, **138**: 94%;
(iv) BF_3, Br_2, rt., 5 days, **139**: 95-97%; (v) KOH; diazomethane; Ac_2O, pyridine, rt., 18 h, **140**: 41%.

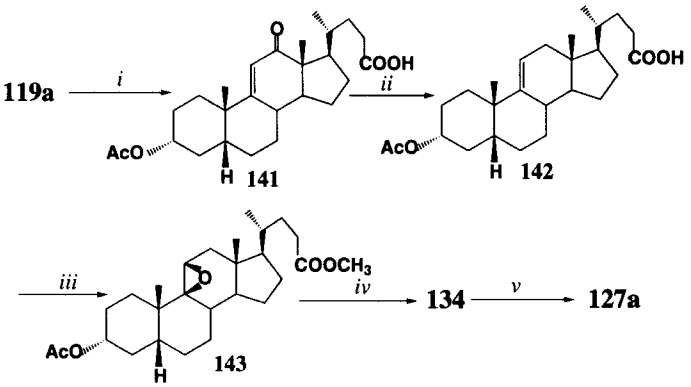
Scheme 31

Oxidation of this product with potassium chromate[169, 170] afforded methyl 3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **138**. Jones' oxidation can also give satisfactory results.[171] Exposure of **138** to the action of bromine at 70° in the presence of hydrobromic acid as a catalyst produced a complex mixture, with a low yield of bromo ketone **139**.[168] To improve the reaction HBr was substituted by BF_3, a strong Lewis acid, known to be very effective as a catalyst in bromination reactions.[172] The desired 11α-bromo ketone **139** was obtained in a high yield of 95-97%. Only minor amounts of the 11β-bromo epimer could be detected. Conversion of this bromoketone **139** to the tautomerized ketol followed by treatment with diazomethane and acetic anhydride gave **140**.[173]

2. Epoxidation

11-Oxo-deoxycholic Acid Derivatives

A mixture of 3α-hydroxycholenic acids with double bonds at the C_9-C_{11} and C_{11}-C_{12} positions could be synthesized from deoxycholic acid.[174-176] The introduction of C_9-C_{11} double bond could be accomplished directly by dehalogenation of **119a** with sodium ethylate (*Scheme 32*).[174]



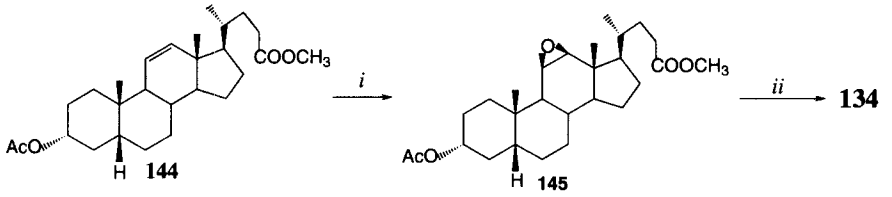
Reagents and Results: (i) sodium ethoxide, EtOH, reflux, 2 h, **141**: 77%; (ii) carbazide hydrochloride, sodium ethoxide, 180°, 15 h, **142**; (iii) HCl, MeOH; $KMnO_4$, HOAc, 0°, 2 h, **143**: 30%; (iv) H_2, PtO_2, HOAc, rt., 16 h, **134**: 93%; (v) CrO_3, HOAc, rt., 1 h, **127a**.

Scheme 32

Treatment of the acid with semicarbazide acetate gave a semicarbazone which was reduced by heating with sodium ethoxide in a sealed tube for fifteen hours at 180°. The application of perbenzoic acid to the C_9-C_{11} double bond was shown by Chakravorty and Wallis[174] to yield an oxide mixed with some starting materials. The action of stronger oxidizing agent such as potassium permanganate, lead tetrapropionate, osmium tetroxide, hydrogen peroxide, and perbenzoic acid under a variety of conditions was investigated by Hick and co-workers.[177] The oxidation of methyl 3α-acetoxy-$\Delta^{9,11}$-cholenate with potassium permanganate resulted in formation of two isomeric oxides. The β-oxide was identified with an oxide prepared by the action of perbenzoic acid and the other oxide was not completely characterized. In the same reaction, Constantin and Sarett[178] found that the other "oxide" was inert to chromic acid and to perbenzoic acid and it was finally was identified as methyl $\Delta^{9,11}$-3α-

acetoxy-12-ketocholenate rather than an epimeric oxide. The β-oxide readily underwent hydrogenolysis with platinum in acidic solution. Finally, oxidation of **134** with chromium trioxide in acetic acid gave methyl 3α-acetoxy-11-ketocholanate **127a**.[178]

Methyl 3α-acetoxy-11β,12β-oxidocholanate **145** was also prepared by potassium permanganate oxidation.[177, 179] The action of hydrogen fluoride on this "β-oxide" followed by zinc reduction gave **134** (*Scheme 33*).

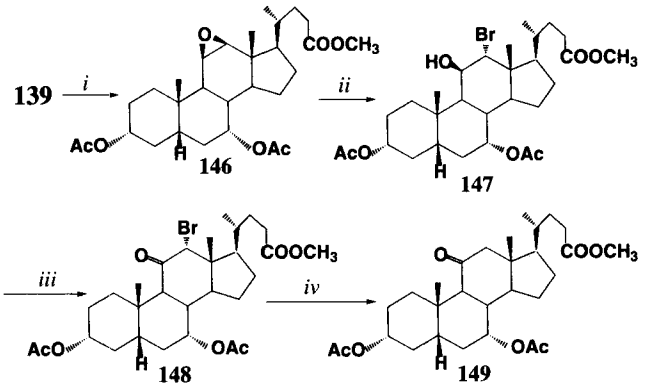


Reagents and Results: (i) $KMnO_4$, HOAc, rt., 2 min., **145**: 61%; (ii) HF, -80°, 3 min.; Zn, HOAc, **134**

Scheme 33

11-Oxocholic Acid Derivatives.

The procedure for the preparation of the 3α,7α-diacetoxy-11-oxo-steroid **149** using methyl 3α,7α-diacetoxy-11α-bromo-12-oxo-5β-cholan-24-oate **139** as a starting material was adapted from that used[180] for the preparation of 7-deoxy-C_{11}-oxygenated-steroids (*Scheme 34*).[181] The borohydride reduction of **139** in ethanol[180] or methanol[182] under conditions similar to those utilized for 7-deoxy-steroids yielded a complex mixture. When pyridine was used as a solvent for borohydride reduction

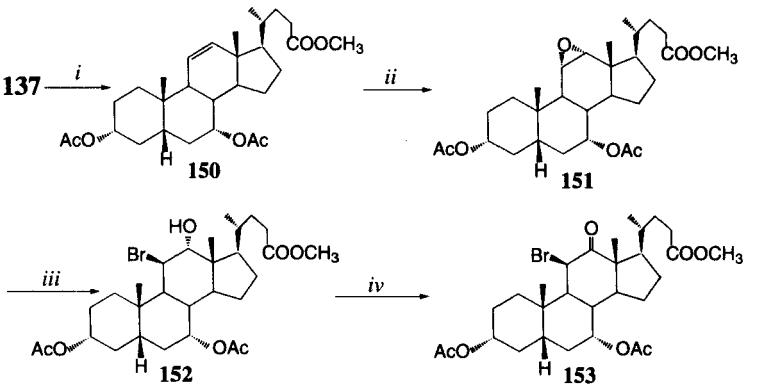


Reagents and Results: (i) $NaBH_4$, NaOAc, pyridine, rt., 4 days, **146**: 32%;
(ii) 48% HBr, HOAc, rt., 25 min., **147**: 48%; (iii) CrO_3, AcOH, rt., 2.5 h, **148**: 94%;
(iv) Zn, HOAc, reflux, 2 h, **149**: 92%.

Scheme 34

for 2 h, bromoketone **139** was not reduced. However, when the reaction time was prolonged and sodium acetate added, the epoxide **146** was formed directly. The epoxide was cleaved by hydrogen bromide followed by chromic acid oxidation to give ketone **148** which was reduced to **149**. During the

synthesis of 11β-bromo ketone **153**, Yanuka and Halperin[168] applied perbenzoic acid to the C_{11}-C_{12} double bond and obtained an α-oxide **151** (*Scheme 35*).



Reagents and Results: (i) $POCl_3$, pyridine, 37°, 24 h, **150**; (ii) PhCOOOH, $CHCl_3$, **137-151**: 18%; (iii) 48% HBr, acetone, **152**; (iv) CrO_3, HOAc, **153**: 80%.

Scheme 35

IV. CONCLUSION

11-Oxo steroids and their derivatives are very important intermediates in the synthesis of bioactive steroids such as cortisone, hydrocortisone, alphaxalone, desogestrel, 3-oxo desogestrel, mifepristone. The synthesis of 11-oxo steroids can be accomplished by the oxidation of 11-hydroxy steroids which can be obtained by microbiological transformation or partial synthesis. Epoxidation of $\Delta^{9(11)}$ steroids followed by hydrolysis can also produce 11-oxo steroids. Jones' oxidation on $\Delta^{9(11)}$ steroids can produce 9β-hydroxy-11-oxo derivatives. Hydrolysis of 11α-bromoketone can give 11-oxygenated steroids.

Acknowledgement.- The author wishes to thank Prof. J. R. Dias of this Department and referees for their numerous suggestions.

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(***Received February 18, 1997; in revised form May 6, 1997***)