MOLECULAR TRANSFORMATIONS OF STEROIDS BASED ON IONIC AND RADICAL REACTIONS OF HYPOIODITES

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MOLECULAR TRANSFORMATIONS OF STEROIDS BASED ON IONIC AND RADICAL REACTIONS OF HYPOIODITES

A DISSERTATION FOR
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HISANORI SENBOKU

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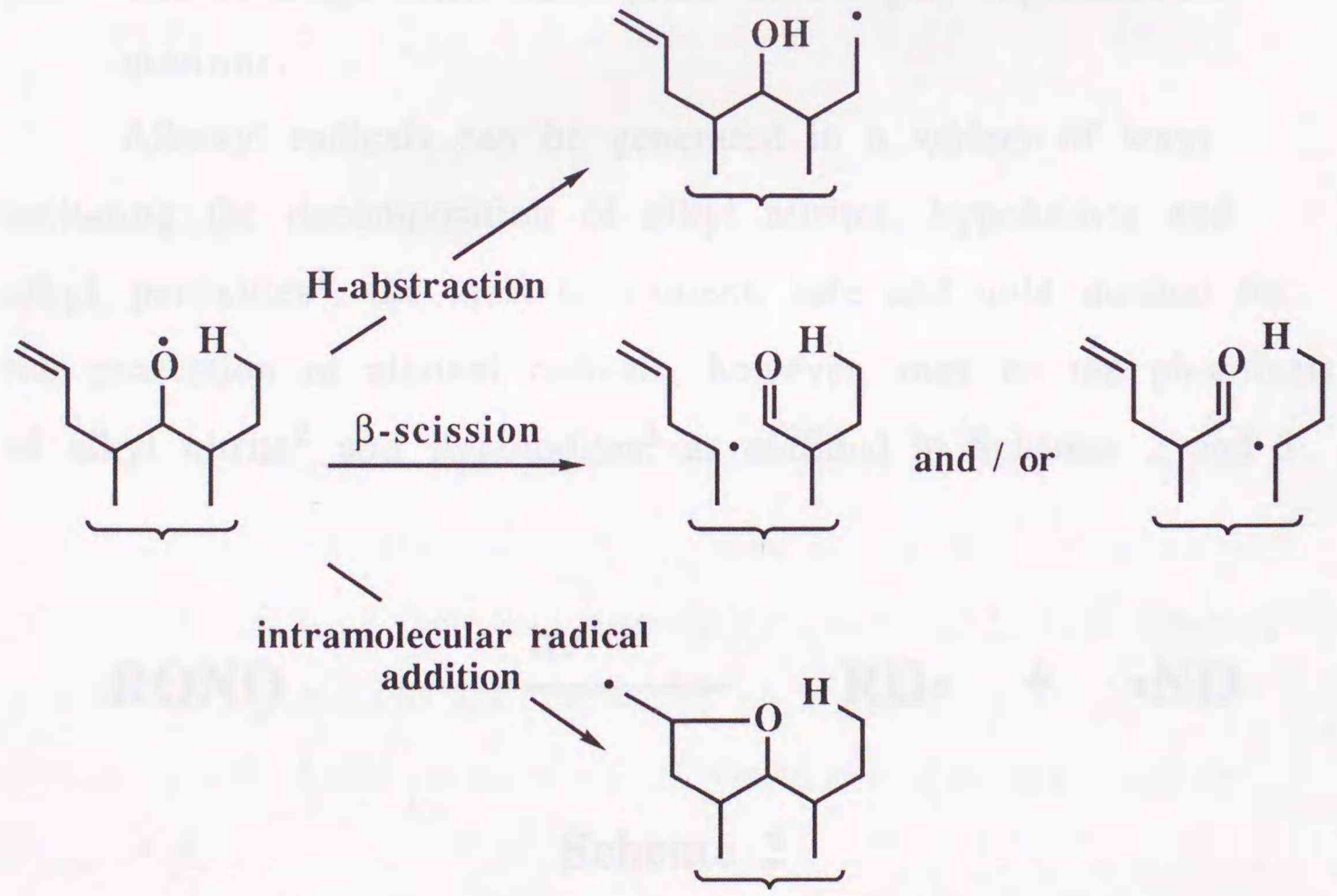
CHAPTER 1

INTRODUCTION

Utility of free radical reaction in organic synthesis has been amply demonstrated[1]. Of the radical reaction, alkoxyl radicals have been utilized most successfully in synthesis and numerous investigations have been carried out.

There are three important paths by which these alkoxyl radicals collapse to give stable species. The first one is the intramolecular hydrogen abstraction whenever a six-membered cyclic trandition state can be achieved[2]. The second is the elimination of an alkyl radical from an alkoxyl radical with the formation of a carbonyl group, which is usually refered as β-scission[3]. The last is the intramolecular addition reaction to form a cyclic ether when the alkoxyl radical is generated in a molecule bearing a proximate carbon-carbon double bond[4]. These three important processes are outlined in Scheme 1.



Scheme 1

Synthetic application of alkoxyl radicals has so far been centered on the intramolecular hydrogen abstraction. Barton[5], Breslow[6], as well as numerous other workers[2] thus have amply demonstrated the utility of the process in organic synthesis. There has been, however, only a few successful applications of the β-scission of alkoxyl radicals to organic synthesis[7], despite several synthetic advantage of process over the other ionic or thermal carbon-carbon bond cleavage such as retro aldol[8], retro Diels-Alder[9], Grob's fragmentation[10] etc. Advantage of the fragmentation of alkoxyl radicals when it is utilized in organic synthesis, are;

1) The reaction can usually be carried out under virtually neutral conditions at room temperature.
2) A carbonyl group is introduced with a C-C bond cleavage.
3) The cleavage often takes place in a highly regioselective manner.

Alkoxyl radicals can be generated in a variety of ways including the decomposition of alkyl nitrites, hypohalites and alkyl peroxides[1]. the most convenient, safe and mild method for the generation of alkoxyl radicals, however, may be the photolysis of alkyl nitrite[2] and hypoiodites[3] as outlined in Schemes 2 and 3.

$$\mathbf{RONO} \xrightarrow{h\nu} \mathbf{RO\cdot} + \mathbf{\cdot NO}$$

Scheme 2

$$ROX \xrightarrow{h\nu \text{ or } \Delta} RO\bullet + \bullet X$$

$$X = Cl, Br, I$$

Scheme 3

Hypoiodites have been used to generate alkoxyl radicals[3] for the intramolecular hydrogen abstraction. It is generally prepared *in situ* by the reaction of alcohol with lead(IV) tetraacetate - iodine[3] or mercury(II) oxide - iodine[11]. It has been accepted that the reaction of mercury(II) oxide with iodine generates iodine oxide[12] which is an active species for transforming alcohol into the corresponding hypoiodite according to the following equations.

$$HgO + 2I_2 \longrightarrow I_2O + HgI_2$$

$$ROH + I_2O \longrightarrow ROI + IOH$$

In this thesis, applications of β-scission of alkoxyl radicals generated by the photolysis of hypoiodites to the transformation of steroids into 18- and 19-norsteroids are described in Chapter 2 and 3. Intramolecular ionic addition of hypoiodites to carbon - carbon double bond to form cycic ethers are also described in Chapter 4.

All the hypoiodites used in this work were prepared *in situ* by the reaction of appropriate alcohol with each 2 equivalents of

mercury(II) oxide and iodine[11] in benzene at room temperature. The alkoxyl radicals were then generated by irradiating the hypoiodites in benzene.

Chapter 2 deals with a transformation of steroids into ring-A-aromatized steroids and 19-norsteroids involving a regioselective β-scission of alkoxyl radicals. Cholesterol was transformed into two marine natural products, 19-nor-5α-cholestan-3β-ol and 19-norcholest-4-en-3-one, and 19-norcholesta-1,3,5(10)-trien-3-ol. Transformations of 3β-hydroxyandrost-5-en-17-one into 19-nortestosterone, estrone, and the related estranes are also described.

Chapter 3 deals with synthesis of 18-norsteroids, deoxofukujusonorone and the related steroids, based on a regioselective β-scission of alkoxyl radicals as a key step. 3β-Hydroxypregn-5-en-20-one (pregnenolone) was transformed into 3β-hydroxy-18-norpregna-5,13-dien-20-one (12-deoxofukujusonorone) *via* 10 steps.

The author discusses an efficient formation of spirotetrahydrofuran ring by an intramolecular ionic cyclization of hypoiodites bearing carbon - carbon double bond at C_4 position in Chapter 4.

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CHAPTER 2

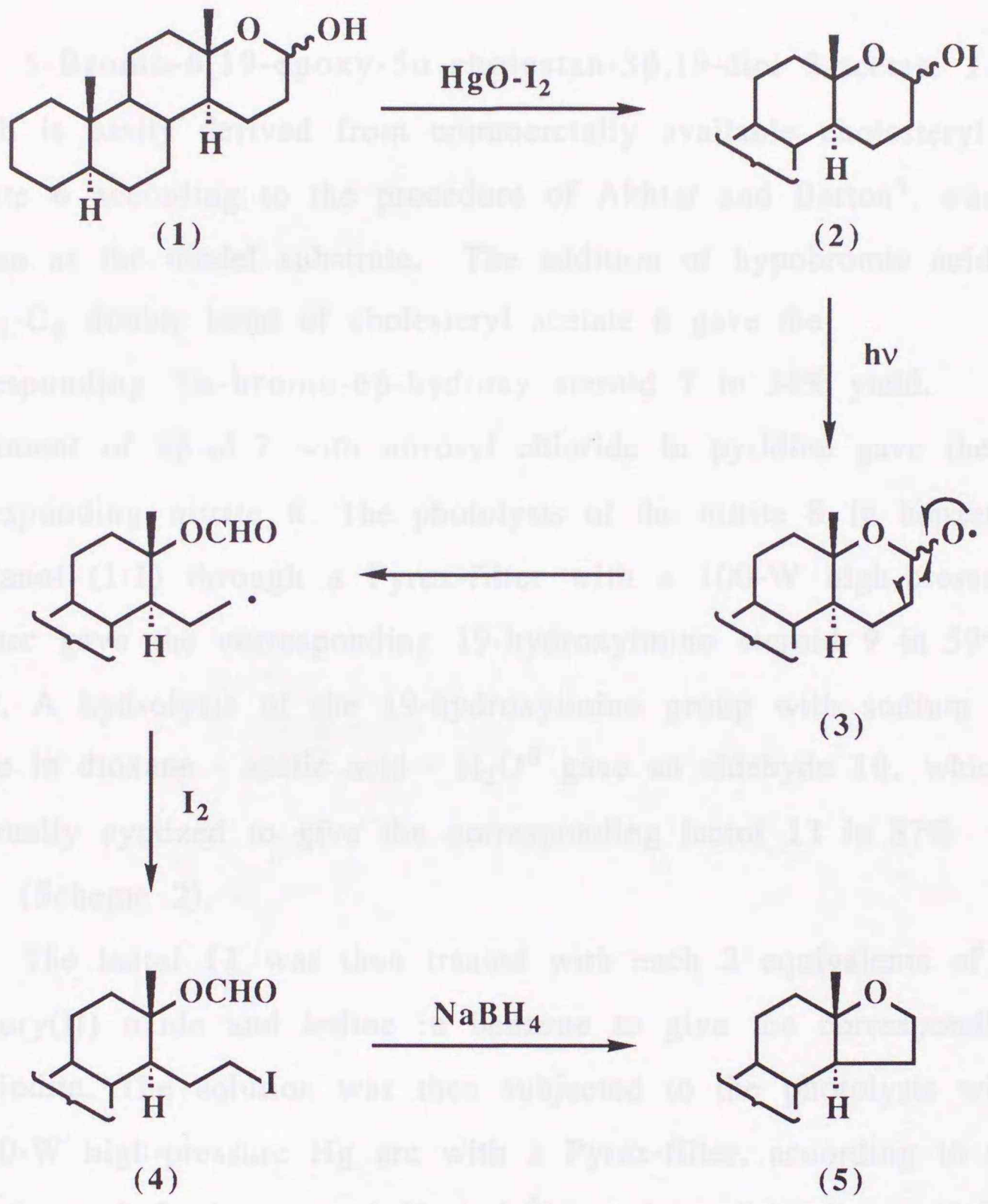
A NEW SYNTHESIS OF RING-A-AROMATIZED STEROIDS AND 19-NORSTEROIDS BASED ON A β-SCISSION OF ALKOXYL RADICALS GENERATED FROM HYPOIODITES

2-1 Introduction

19-Norsteroids occupy a significant position in steroids, since the group contains a number of compounds which have pronounced biological activities and are of importance as estrogens[1]. A variety of 19-norsteroids have also been isolated from marine creatures[2]. A number of methods for transformation of steroids into their 19-nor-derivatives have been reported[3]. Most of these involve an initial functionalization of the inactive 10β-methyl group of steroids, followed by the removal of the functionalized 10β-carbon based on the cleavage of their C_{10}-C_{19} bond.

On the other hand, several applications of a regioselective β-scission of alkoxyl radicals at C-C bond generated from the corresponding hypoiodites to synthetic problems have recently been reported by Suginome and colleagues[4]. For example, when steroidal hypoiodite **2** generated from the corresponding hemiacetal **1** with mercury(II) oxide and iodine in benzene was irradiated with a 100-W high-pressure Hg arc through a Pyrex-filter, a regioselective β-scission of the corresponding alkoxyl radical **3** occured at the C-C bond to give iodo-formate **4** in a 85% yield, which cyclized with sodium borohydride to give cyclic ethers **5**[4a] (Scheme 1).

In this chapter, a new transformation of steroids into ring-A-aromatized steroids and 19-norsteroids including some natural products will be described. The method is based on the removal of the 10β-methyl group by means of a regioselective β-scission of alkoxyl radicals generated from the corresponding hypoiodites as a key step.



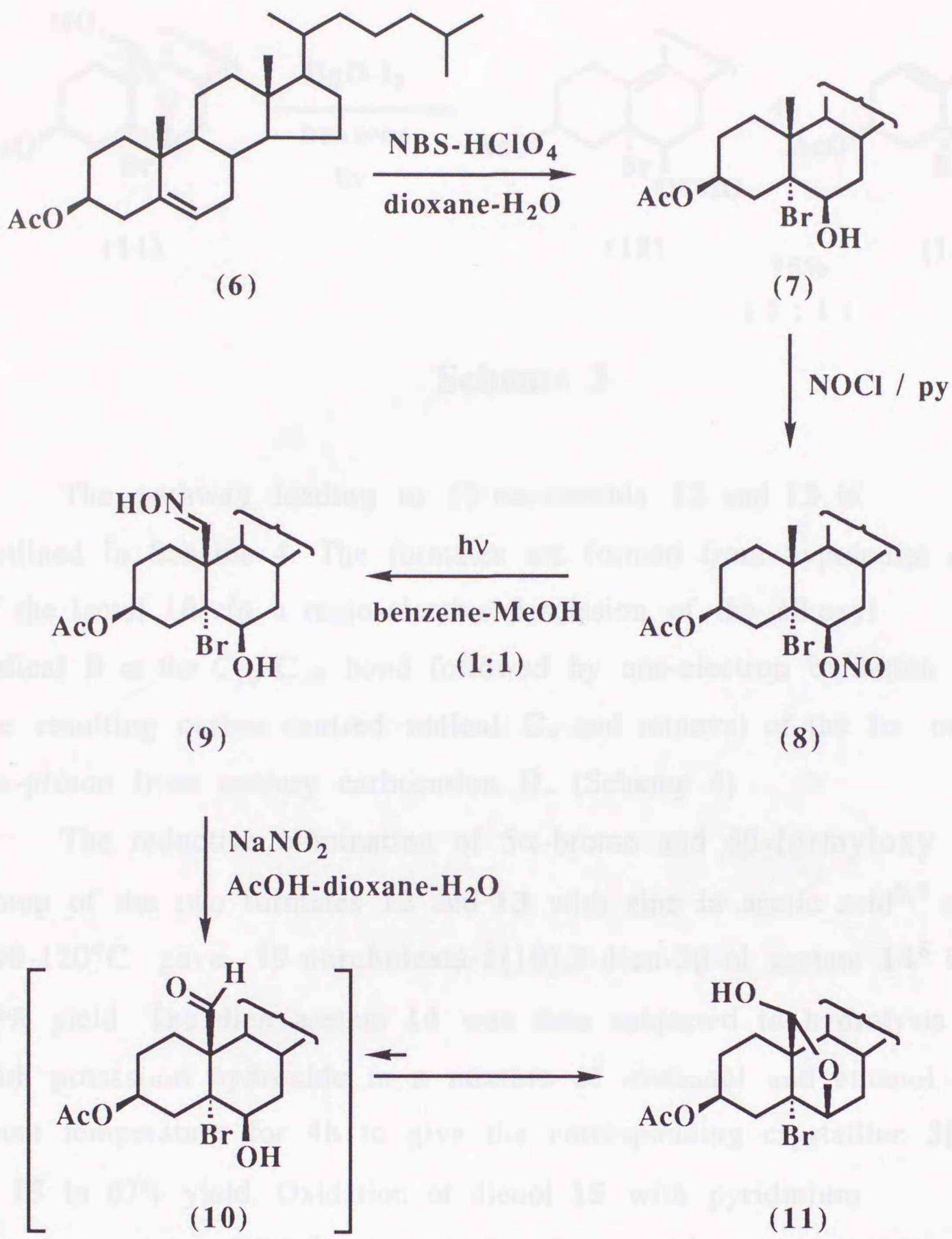
(1) (2) (3) (4) (5)

Scheme 1

2-2 A New Synthesis of Ring-A-aromatized Steroids based on a β-Scission of Alkoxyl Radicals generated from Hypoiodites

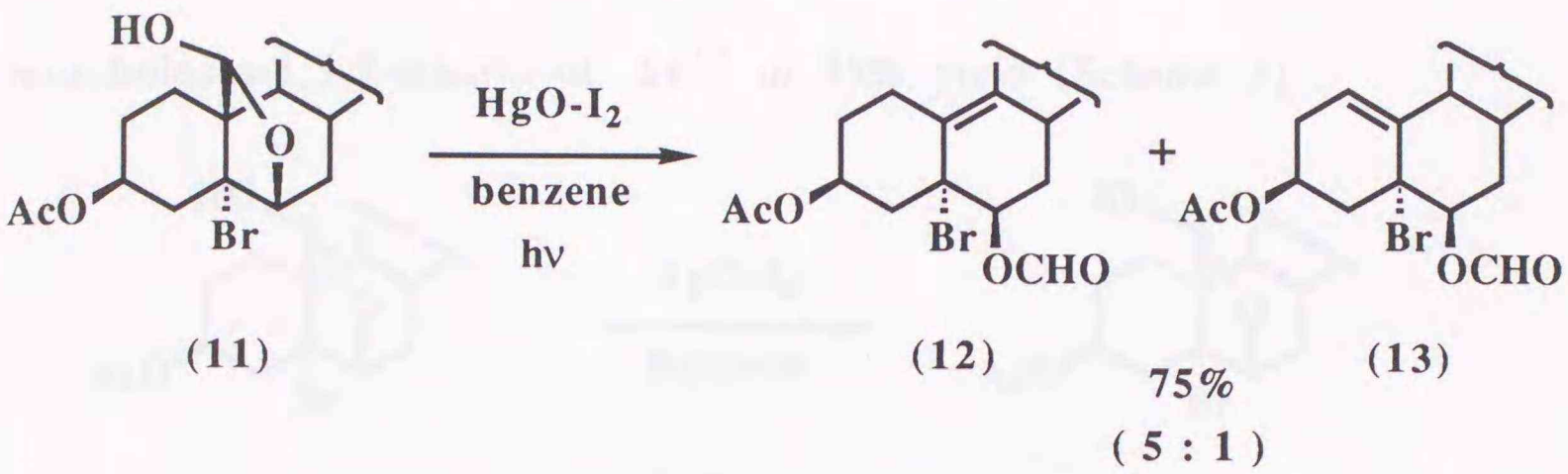
5-Bromo-6,19-epoxy-5α-cholestan-3β,19-diol 3-acetate **11**, which is easily derived from commercially available cholesteryl acetate **6** according to the procedure of Akhtar and Barton[5], was chosen as the model substrate. The addition of hypobromic acid to C_5-C_6 double bond of cholesteryl acetate **6** gave the corresponding 5α-bromo-6β-hydroxy steroid **7** in 34% yield. Treatment of 6β-ol **7** with nitrosyl chloride in pyridine gave the corresponding nitrite **8**. The photolysis of the nitrite **8** in benzene-methanol (1:1) through a Pyrex-filter with a 100-W high-pressure Hg arc gave the corresponding 19-hydroxyimino steroid **9** in 59% yield. A hydrolysis of the 19-hydroxyimino group with sodium nitrite in dioxane - acetic acid - H_2O[6] gave an aldehyde **10**, which eventually cyclized to give the corresponding lactol **11** in 87% yield (Scheme 2).

The lactol **11** was then treated with each 2 equivalents of mercury(II) oxide and iodine in benzene to give the corresponding hypoiodite. The solution was then subjected to the photolysis with a 100-W high-pressure Hg arc with a Pyrex-filter, according to the procedure of Suginome and Yamada[4a], to give a 5:1 mixture of 5-bromo-19-nor-5α-cholest-9-ene-3β,6β-diol 3-acetate 6-formate **12** and its 1(10)-ene isomer **13** (75%) *via* a regioselective β-scission of alkoxyl radicals at the C_{10}-C_{19} bond in 75% yield (Scheme 3).



(6) (7) (9) (8) (10) (11)

Scheme 2



(11) (12) (13)

75%

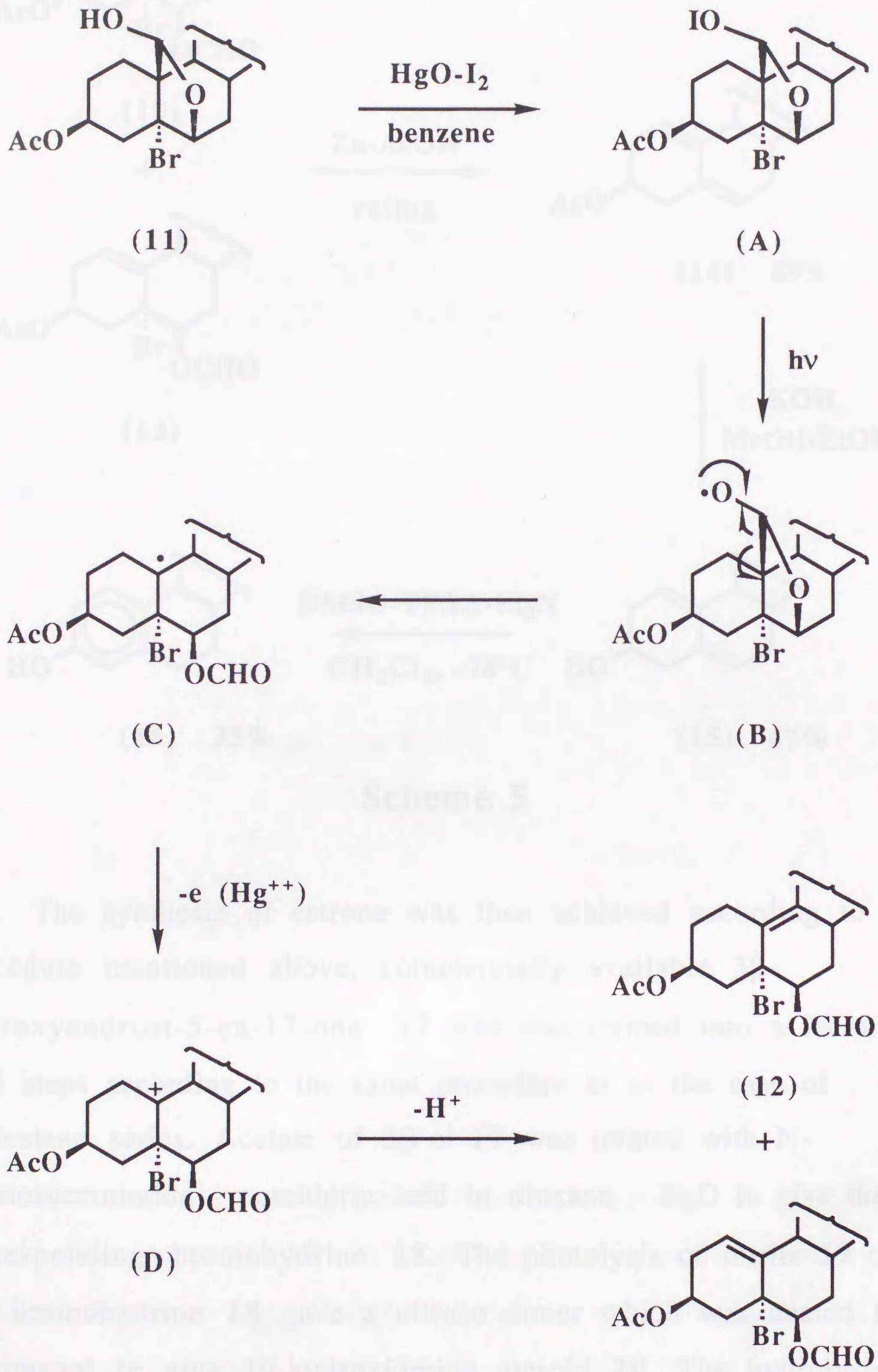
(5 : 1)

Scheme 3

The pathway leading to 19-norsteroids **12** and **13** is outlined in Scheme 4. The formates are formed from hypoiodite **A** of the lactol **10** *via* a regioselective β-scission of the alkoxyl radical **B** at the C_{10}-C_{19} bond followed by one-electron oxidation of the resulting carbon-centred radical **C**, and removal of the 1α- or 9α-proton from tertiary carbocation **D**. (Scheme 4)

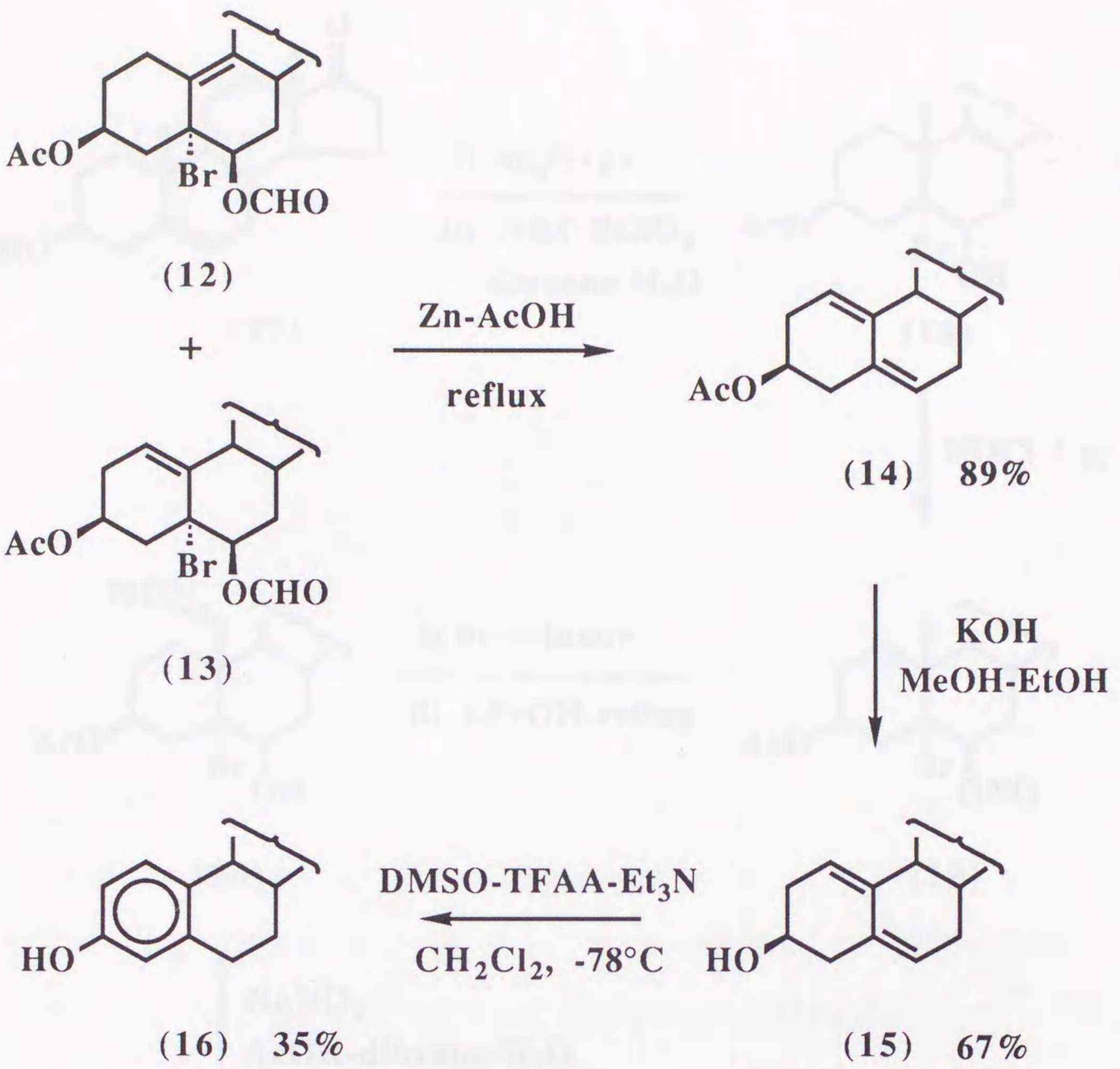
The reductive elimination of 5α-bromo and 6β-formyloxy group of the two formates **12** and **13** with zinc in acetic acid[6,7] at 100-120°C gave 19-norcholesta-1(10),5-dien-3β-ol acetate **14**[8] in 89% yield. The dien acetate **14** was then subjected to hydrolysis with potassium hydroxide in a mixture of methanol and ethanol at room temperature for 4h to give the corresponding crystalline 3β-ol **15** in 67% yield. Oxidation of dienol **15** with pyridinium chlorochromate (PCC)[9] in dichloromethane, with chromium(VI) trioxide - H_2SO_4 - acetone (Jones reagent), or with aluminium isopropoxide in acetone (Oppenauer oxidation) failed to aromatize their A-ring. Irradiation of the dienol pyruvate[10] also failed to give the ring-A-aromatized steroid. Oxidation of dienol **15** in dichloromethane with dimethyl sulphoxide - trifluoroacetic anhydride (TFAA) - triethyl amine at -78°C according to the procedure devised by Swern[11], however, successfully gave 19-

-norcholesta-1,3,5-trien-3-ol **16**[12] in 35% yield (Scheme 5).



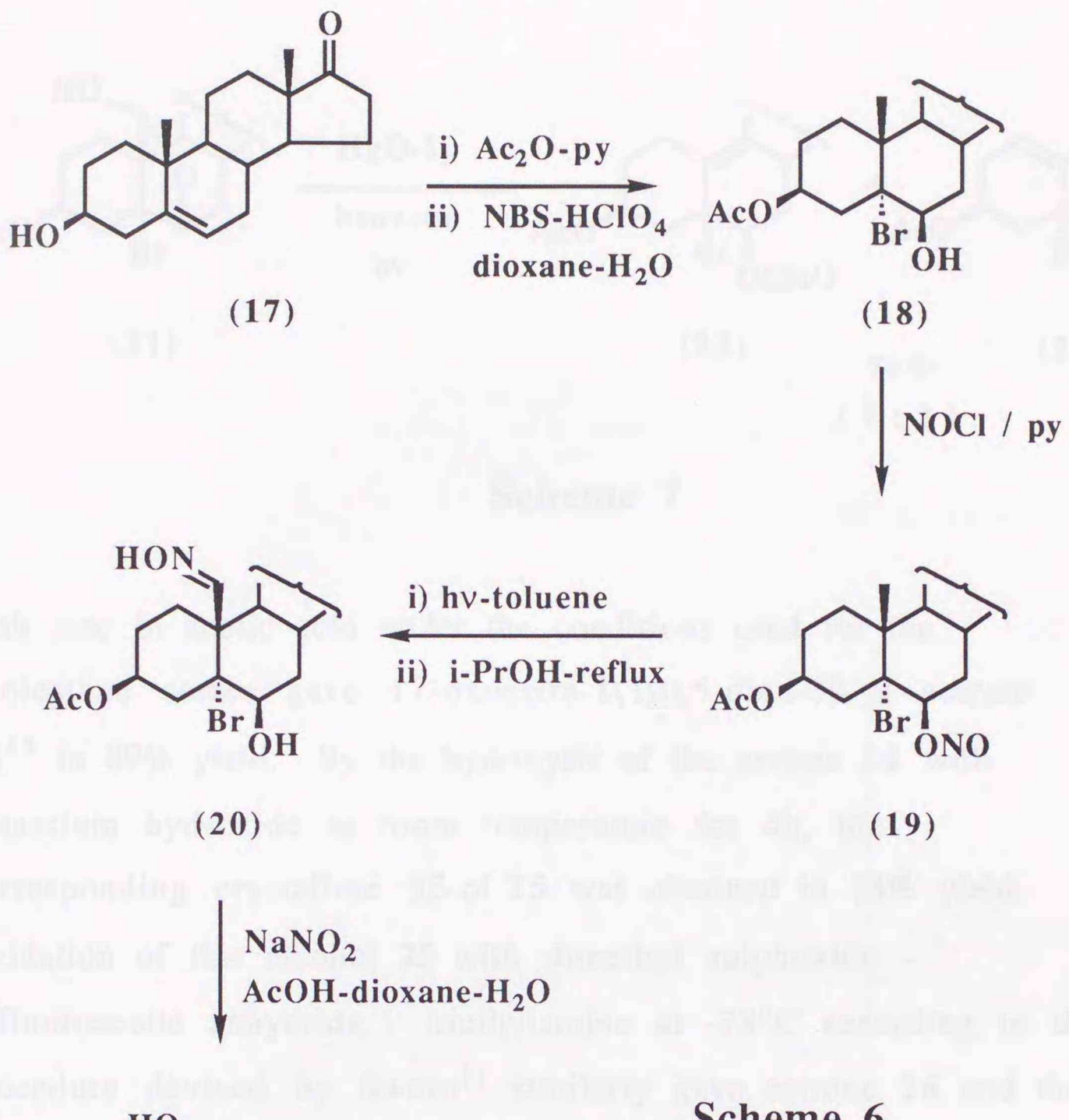
(11) (A) (B) (C) (D) (12) (13)

Scheme 4



Scheme 5

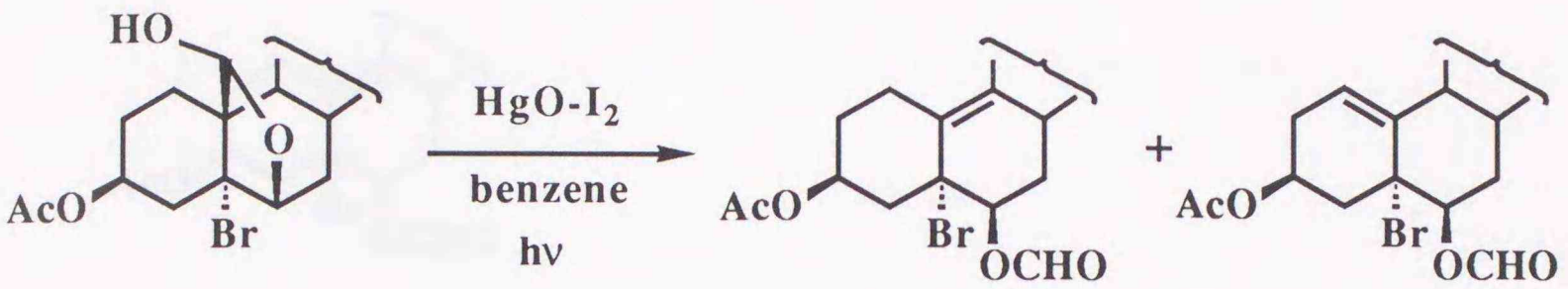
The synthesis of estrone was then achieved according to the procedure mentioned above; commercially available 3β-hydroxyandrost-5-en-17-one **17** was transformed into a lactol **21** in 6 steps according to the same procedure as in the case of cholestane series. Acetate of 3β-ol **17** was treated with N-bromosuccinimide - perchloric acid in dioxane - H_2O to give the corresponding bromohydrine **18**. The photolysis of nitrite **19** of the bromohydrine **18** gave a nitroso dimer which was heated in 2-propanol to give 19-hydroxyimino steroid **20**. The hydrolysis of the hydroxyimino group of oxime **20** with sodium nitrite in dioxane - acetic acid - H_2O gave lactol **21**[5] (Scheme 6).



(17) (18) (19) (20) (21)

Scheme 6

The lactol **21** was subjected to a regioselective β-scission through the photolysis of the corresponding hypoiodite under the same conditions as in cholestane series to give a 7:1 mixture of 5-bromo-17-oxo-5α-estr-9-ene-3β,6β-diol 3-acetate 6-formate **22** and its 1(10)-ene isomer **23** in 74% yield (Scheme 7). The reductive elimination of the mixture of the isomers **22** and **23**



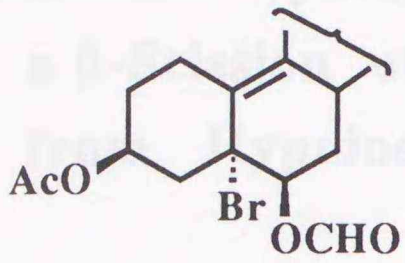
(21) (22) (23)

74%

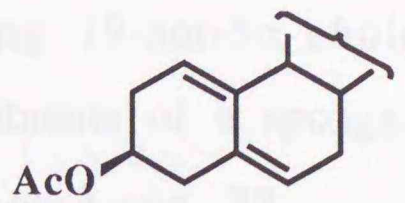
(7 : 1)

Scheme 7

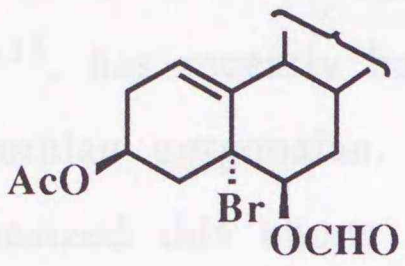
with zinc in acetic acid under the conditions used for the cholestane series gave 17-oxoestra-1(10),5-dien-3β-ol acetate **24**[13] in 89% yield. By the hydrolysis of the acetate **24** with potassium hydroxide at room temperature for 4h, the corresponding crystalline 3β-ol **25** was obtained in 78% yield. Oxidation of this alcohol **25** with dimethyl sulphoxide - trifluoroacetic anhydride - triethylamine at -78°C according to the procedure devised by Swern[11] similarly gave estrone **26** and the corresponding trifluoroacetate **27** in 40 and 20% yields, respectively (Scheme 8).



(22)

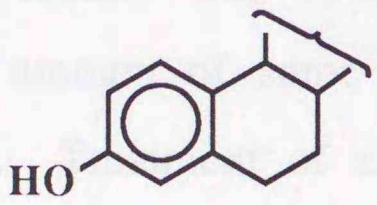
+ **Zn-AcOH**, **reflux** → 

(24) 89%

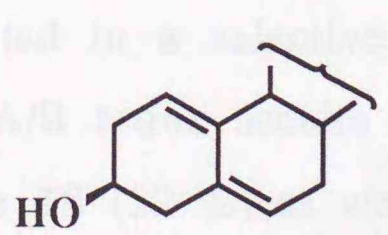


(23)

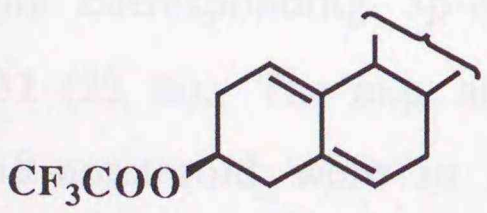
KOH
MeOH-EtOH



(26) 40%

+ **DMSO-TFAA-Et_3N**, **CH_2Cl_2, -78°C** ← 

(25) 78%

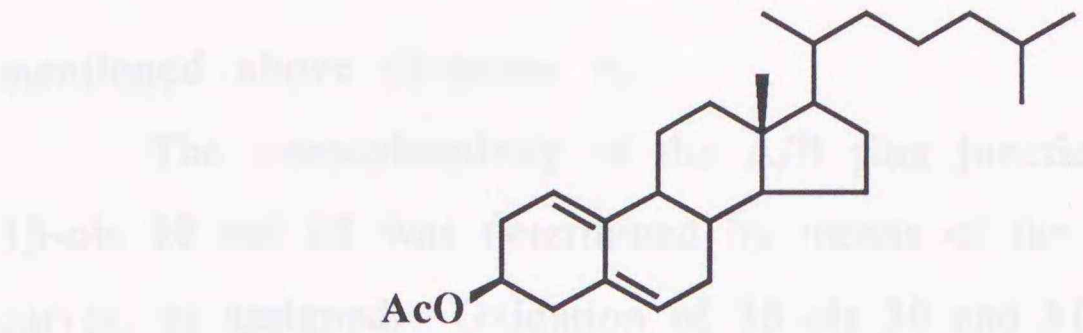


(27) 20%

Scheme 8

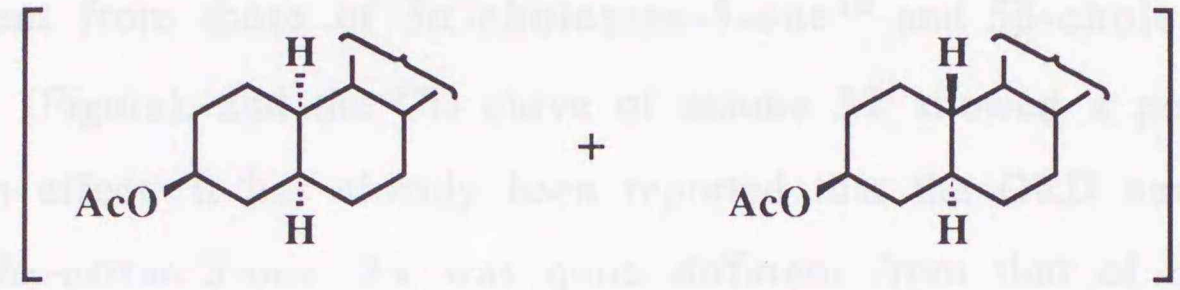
2 - 3 A New Synthesis of 19-Norsteroids based on a β-Scission of Alkoxyl Radicals generated from Hypoiodites

A number of 19-norsteroids including 19-nor-5α-cholestan-3β-ol **31** have been found to be the constituents of a sponge, *Axinella polypoides*[2a,2b]. 19-Norcholest-4-en-3-one **37**, synthesized from cholesterol *via* 7 steps by Tanabe et al. in 1967[15], has recently been isolated as a constituent of the Californian gorgonaian, *Muricea californica*, by Djerassi[2c] who synthesized this enone by Oppenauer oxidation of 19-norcholesterol[2c]. The dienol acetate **14** is an excellent starting material for the synthesis of these marine steroids. Thus, catalytic hydrogenation of dienol acetate **14** in glacial acetic acid with platinum as catalyst gave a mixture of 19-nor-5α,10α-cholestan-3β-yl acetate **28**, 19-nor-5α-cholestan-3β-yl acetate **29**, and a small amount of some 19-norsteroids devoid of the 3β-acetoxy group. Treatment of a mixture of acetates **28** and **29**, isolated by preparative TLC (PLC), with potassium hydroxide in ethanol and methanol at room temperature for 1h resulted in a selective hydrolysis of the 3β-acetoxy group of the A/B *trans* acetate **29** to give 19-nor-5α,10α-cholestan-3β-yl acetate **28** (52 %) as well as the corresponding 3β-ol **30** (3 %) and 19-nor-5α-cholestan-3β-ol **31** (22 %). The m.p. and mass and ^{1}H NMR spectral data of the 19-norsteroid were in agreement with those of 19-nor-5α-cholestan-3β-ol isolated from the sponge *Axinella polypoides*[2a,2b]. Acetate **28** was easily hydrolyzed under more severe condition (heated under reflux) to give the corresponding crystalline 3β-ol, identical with the alcohol **30** obtained by the mild hydrolysis as



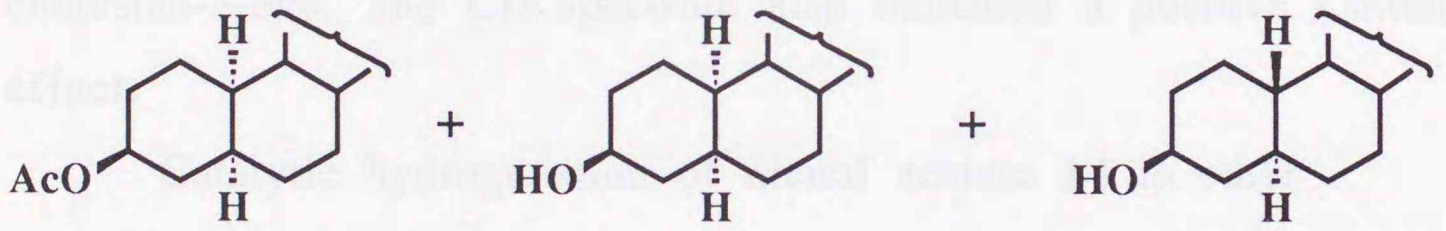
(14)

i) H_2-PtO_2-AcOH



(28) (29)

ii) KOH-MeOH-EtOH, r.t.



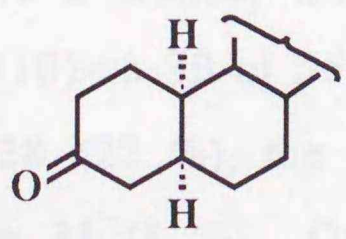
(28) 52% (30) 3% (31) 22%

19-norcholestanol

92%

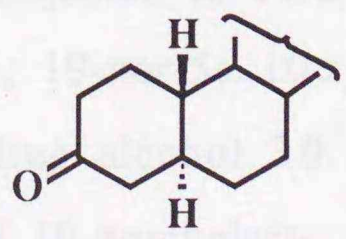
KOH-MeOH-EtOH, reflux

PCC



(32) 83%

PCC



(33) 85%

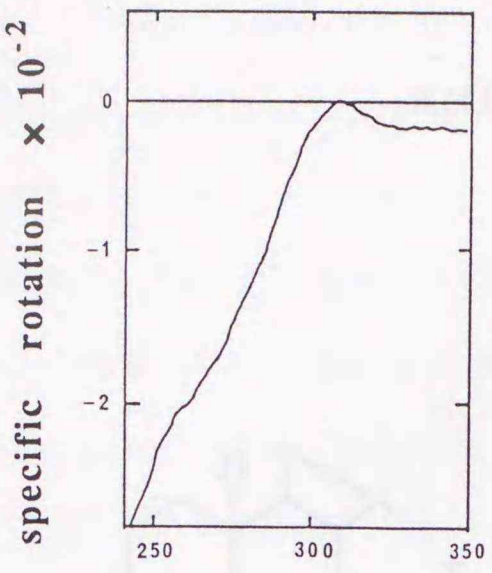
Scheme 9

mentioned above (Scheme 9).

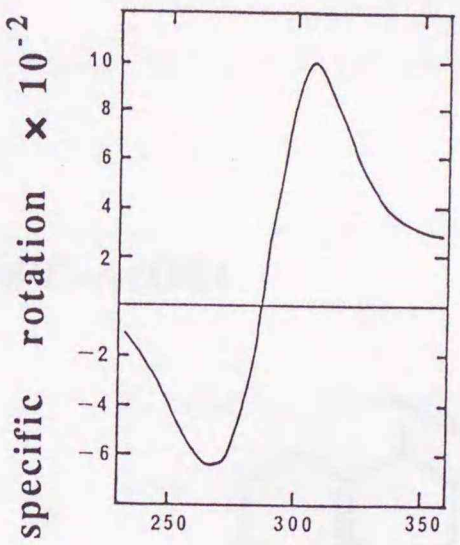
The stereochemistry of the A/B ring junctions of isomeric 3β-ols **30** and **31** was determined by means of the ORD and CD curves, as assigned. Oxidation of 3β-ols **30** and **31** with PCC, respectively, gave the corresponding 3-ones **32** and **33** in 83 and 85% yield. The ORD curves of ketone **32** and **33** in methanol is shown in Figure below. The ORD curve of ketone **32** was quite different from those of 5α-cholestan-3-one[16] and 5β-cholestan-3-one[17] (Figure), and the CD curve of ketone **32** showed a positive Cotton effect. It has already been reported that the ORD curve of 5α,10α-estran-3-one **34** was quite different from that of normal steroid ketones and didn't show a typical large Cotton effect[18]. On the other hand, the ORD curve of ketone **33** showed a positive Cotton effect, a result parallel with the reported ORD curve of 5α-cholestan-3-one. The CD spectrum also indicated a positive Cotton effect.

Catalytic hydrogenation of dienol acetate **14** in ethyl acetate with 10% Pd-C as catalyst, however, gave 19-norcholest-5(10)-en-3β-ol acetate **35** as the major product with accompanying formation of 19-nor-5α,10α-cholestan-3β-yl acetate **28**, and 19-nor-5α-cholestan-3β-yl acetate **29**. Treatment of this mixture with methanolic potassium hydroxide at room temperature for 24 h gave a product which was subjected to PLC to give 19-norcholest-5(10)-en-3β-ol **36**[15] (37 %), 19-nor-5α,10α-cholestan-3β-yl acetate **28** (22 %), the corresponding alcohol **30** (2 %), and its 10β-epimer **31** (8 %). Oxidation of 19-norcholest-5(10)-en -3β-ol **36** with PCC followed by the treatment with hydrochloric acid in methanol gave 19-norcholest-4-en-3-one **37** in 33% yield, which was identical with an authentic specimen[2c,15],

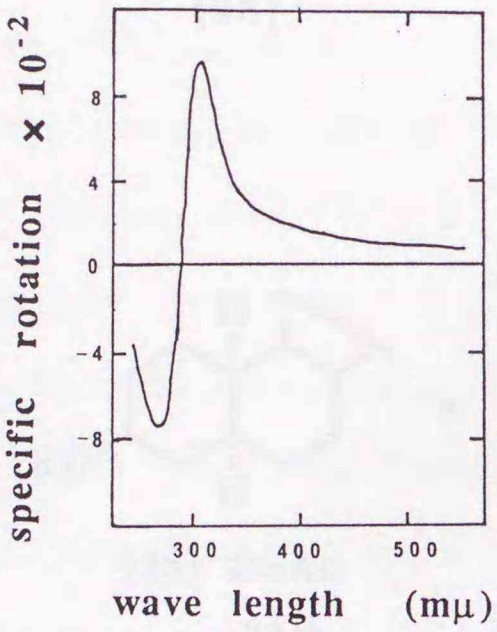
in every respect (Scheme 10).



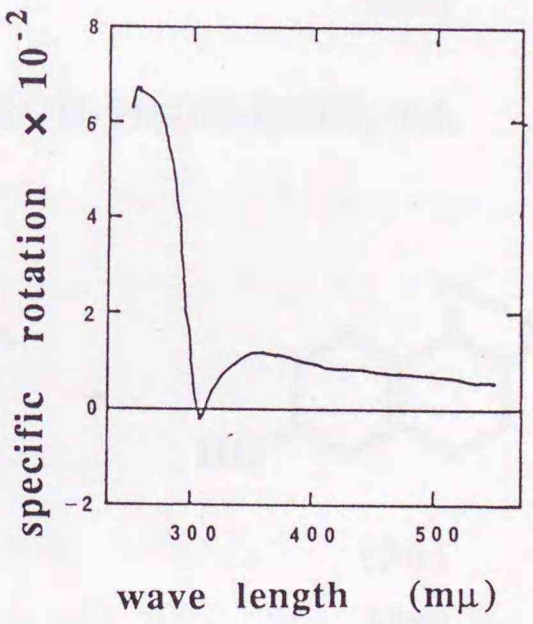
(32)



(33)

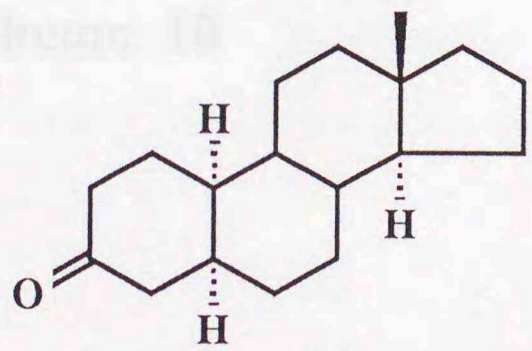


5α-cholestan-3-one

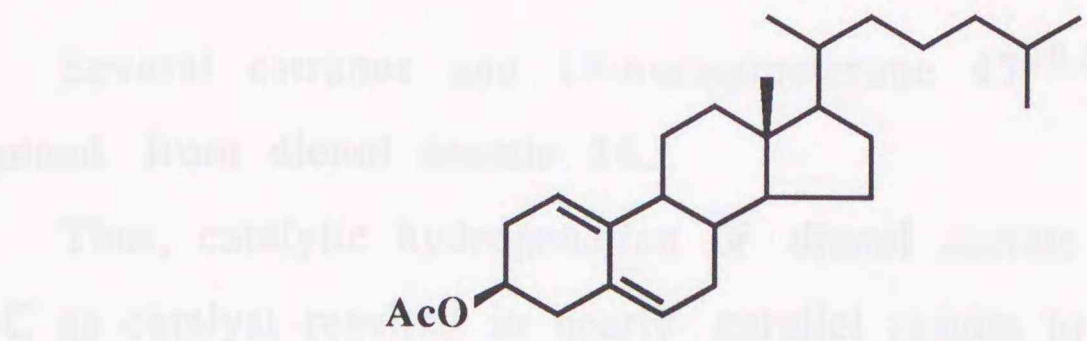


5β-cholestan-3-one

The ORD curves of 32, 33, 5α- and 5β-cholestan-3-one

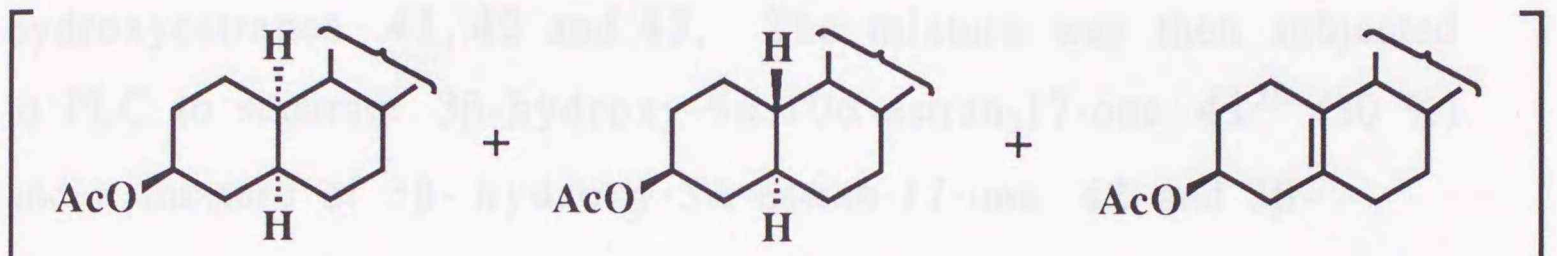


(34)



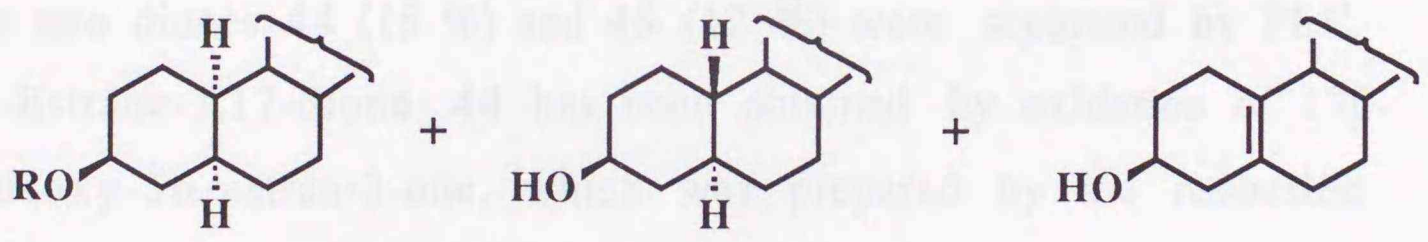
(14)

i) H_2-Pd/C-AcOEt



(28) (29) (35)

ii) KOH-MeOH-EtOH, r.t.



(28) R=Ac 22%

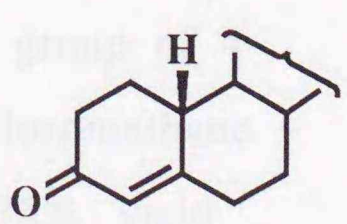
(30) R=H 2%

(31) 8%

(36) 37%

i) PCC

ii) H^+



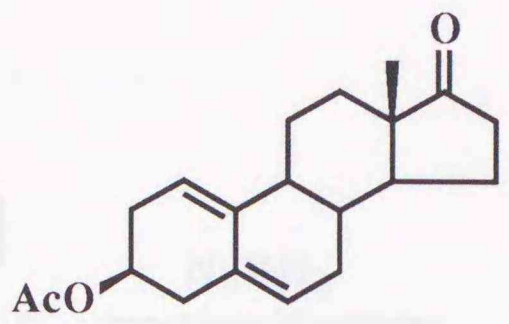
(37) 33%

19-norcholest-4-en-3-one

Scheme 10

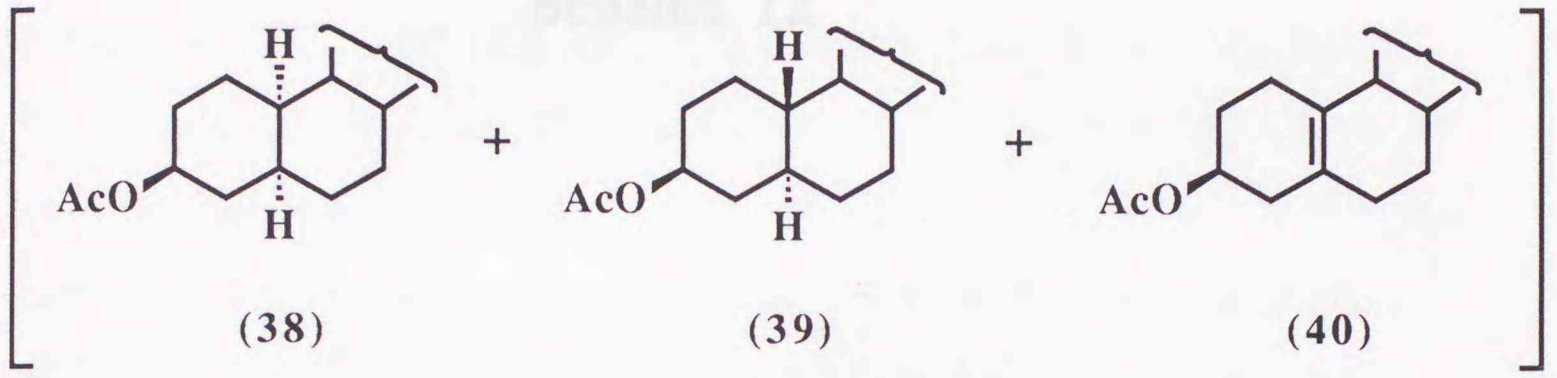
Several estranes and 19-nortestosterone **47**[19,23] can also be obtained from dienol acetate **24**.

Thus, catalytic hydrogenation of dienol acetate **24** with 10% Pd-C as catalyst resulted in nearly parallel results to those in the hydrogenation of dienol **14** and gave the 3β-hydroxyestrane acetates **38, 39**, and **40**. The mixture was subjected to hydrolysis with methanolic potassium hydroxide to give a mixture of 3β-hydroxyestranes **41, 42** and **43**. The mixture was then subjected to PLC to separate 3β-hydroxy-5α,10α-estran-17-one **41**[20] (30 %) and a mixture of 3β- hydroxy-5α-estran-17-one **42** and 3β-hydroxyestr-5(10)-en-17-one **43**. This mixture was then oxidized with PCC in dichloromethane followed by the treatment with hydrochloric acid in methanol to give a mixture of 5α-estrane-3,17-dione **44**[20,21] and estr-4-ene-3,17- dione **45**[15] (Scheme 11). The two diones **44** (15 %) and **45** (12 %) were separated by PLC. 5α-Estrane-3,17-dione **44** has been obtained by oxidation of 17β-hydroxy-5α-estran-3-one, which was prepared by the reduction of 19-nortestosterone with lithium and liquid ammonia[16]. A similar oxidation of 3β-ol **41** with PCC gave 5α,10α-estran-3,17-dione **46**[18,21]. The *cis* dione **46** has been synthesized by catalytic hydrogenation of estrone or estradiol over a ruthenium catalyst, followed by oxidation of the resulting 5α,10α-estrane-3β,17β-diol[18.21]. The selective reduction of the 17-carbonyl group of 4-en-3,17-dione **45** with sodium borohydride in dichloromethane - methanol at -78°C[22] gave 19-nortestosterone **47** in 75% yield (Scheme 12).



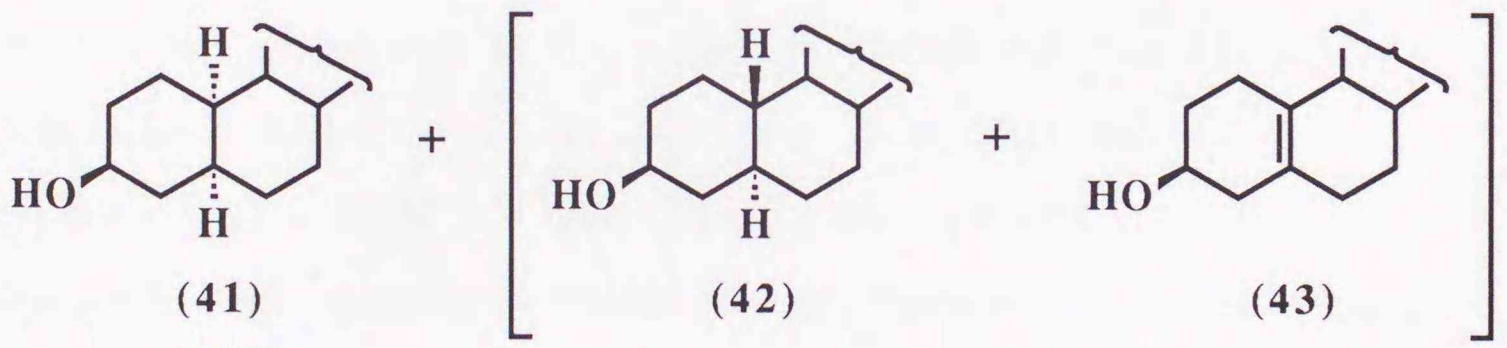
(24)

i) H_2-Pd/C-AcOEt



(38) (39) (40)

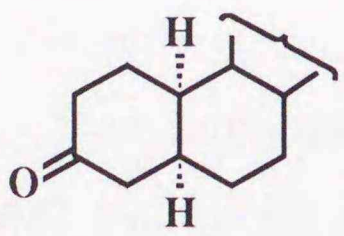
ii) KOH-MeOH, reflux



(41) 30%

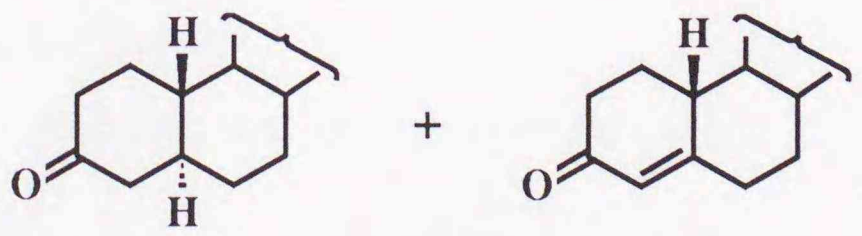
(42) (43)

PCC



(46) 92%

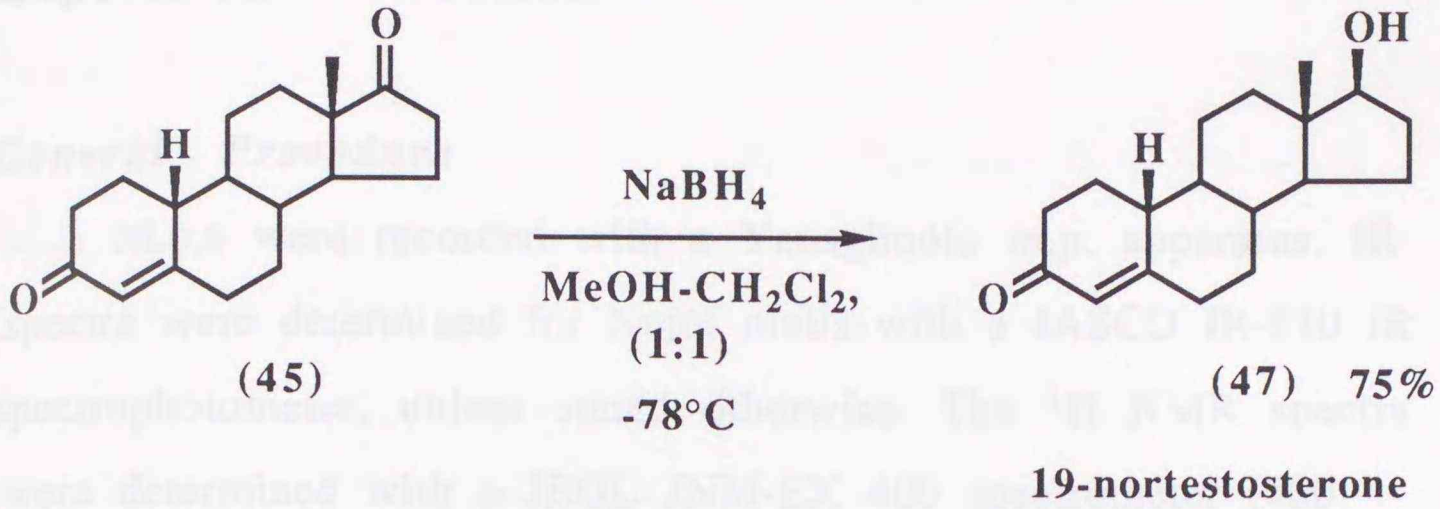
i) PCC
ii) H^+



(44) 15%

(45) 12%

Scheme 11



(45) (47) 75%

19-nortestosterone

Scheme 12

Experimental Section

General Procedure

M.p.s were recorded with a Yanagimoto m.p. apparatus. IR spectra were determined for Nujol mulls with a JASCO IR-810 IR spectrophotometer, unless stated otherwise. The ^1H NMR spectra were determined with a JEOL JNM-EX 400 spectrometer (400 MHz) or a JEOL JNM-EX 270 spectrometer (270 MHz) (Faculty of Pharmaceutical Sciences of this University) or with a Hitachi R-90 spectrometer (90 MHz) for solution in $CDCl_3$ with $SiMe_4$ as internal reference. The *J* values are in Hz. TLC was carried out on Merck Kieselgel 60-PF_{254}. The high- and low-resolution mass spectra were determined with a JEOL JMS-300 spectrometer (70eV) (Faculty of Pharmaceutical Sciences of this University). Elemental analysis were performed at the analytical Laboratory of Faculty of Pharmaceutical Sciences of this University. The ORD and CD were determined with a JASCO J-20A (Faculty of Agriculture of this University). Light petroleum refers to the fraction boiling in range 30-70°C. The photolysis was carried out in a Pyrex tube with a 100-W high-pressure Hg arc lamp.

5-Bromo-5α-cholestane-3β,6β-diol 3-acetate 7

This compound 7 was prepared according to a procedure reported by Akhtar and Barton[5].

δ (90 MHz) 0.68 (3H, s, 18-H), 1.32 (3H, s, 19-H), 2.02 (3H, s, CH_3COO-), 4.18 (1H, br.s, 6α-H), and 5.48 (1H, m, 3α-H);

IR 3426 (OH), 1704 (C=O), 1268, and 1032 cm^{-1}; m.p. 158-160°C (from hexane - CH_2Cl_2) (lit.[5] 172-174°C).

***5-Bromo-19-hydroxyimino-5α-cholestane-3β,6β-diol 3-acetate* 9**

This compound **9** was prepared according to a procedure reported by Akhtar and Barton[5].

δ (90 MHz) 0.59 (3H, s, 18-H), 2.01 (3H, s, CH_3COO-), 4.25 (1H. br.s, 6α-H), 5.48 (1H, m, 3α-H), and 7.47 (1H, s, 19-H);

IR 3486 (OH), 1720 (C=O), 1262, 1028, and 916 cm^{-1};

m.p. 172-174°C (from hexane) (lit.[5] 176-180°C).

***5-Bromo-6β,19-epoxy-5α-cholestane-3β,19-diol 3-acetate* 11**

This compound **11** was obtained by the hydrolysis of 5-bromo-19-hydoxyimino-5α-cholestane-3β,6β-diol 3-acetate **9** in a 87% yield according to a procedure reported by Jen and Wolff[6].

δ (270 MHz) 0.66 and 0.71 (each s, 18-H), 2.03 (3H, s, CH_3COO-), 2.70 (1H, dd, *J* 11.35 and 13.19, 4β-H), 4.14 and 4.24 (each 0.5H, each d, *J* 4.4, 6α-H), 5.29 (1H, m, 3α-H), 5.28 and 5.81 (each 0.5H, each d, *J* 4 and *J* 5, 19-H); IR 3380 (OH), 1738 (C=O), 1242, 1167, 1130, 1094, and 1035 cm^{-1} ; m/z 413 [$(M-OH-Br-CHO)^+$, 3.3%], 370 [$(M-Br-CHO-AcOH)^+$, 18.8], and 353 [$(M-OH-Br-CHO-AcOH)^+$, 100] ; Anal. Found. C, 64.54; H, 8.87; Br, 14.79. $C_{29}H_{47}BrO_4$ requires C, 64.55; H, 8.78; Br, 14.81; m.p. 159-162°C (from hexane - acetone).

***Photoreaction of Hypoiodites of Lactol* 11**

A solution of lactol **11** (250 mg, 0.46 mmol) in benzene (28 cm^3) containing mercury(II) oxide (201 mg, 0.93 mmol) and iodine (235 mg, 0.93 mmol) was flushed with nitrogen and then

irradiated with a Pyrex-filtered light generated by a 100-W high-pressure mercury arc lamp for 3h. The solution was filtered and the filtrate was washed successively with 5% aq. sodium thiosulphate, water and then brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was purified by PLC [silica gel; benzene - diethyl ether (10:1)] to give a mixture of 5-bromo-19-nor-5α-cholest-9-ene-3β,6β-diol 3-acetate 6-formate **12** and 5-bromo-19-nor-5α-cholest-1(10)-ene-3β,6β-diol 3-acetate 6-formate **13** (187 mg, 75 %).

δ (270 MHz) 0.72 (s, 18-H of 9-ene), 0.68 [s, 18-H of 1(10)-ene], 2.05 (3H, s, CH_3COO-), 5.06 (1H, m, 3α-H), 5.22 (br.s, 6α-H of 9-ene), 5.34 [br.s, 6α-H of 1(10)-ene], 5.71 [br.s, 1-H of 1(10)-ene], 8.11 (s, OCHO of 9-ene), and 8.17 [s, OCHO of 1(10)-ene]. The ratio of 9-ene **12** to 1(10)-ene **13** was 5 to 1 ; IR 1736 (AcO-),1720 (-OCHO), 1238, 1168, and 1033 cm^{-1}; m/z 412 [$(M-Br-OCHO)^+$, 1.4%], 352 [$(M-Br-OCHO-AcOH)^+$, 100], 197 (58), 144 (82) and 135 (60).

Reductive Elimination of Formate* 12 *and* 13 *with Zinc in Acetic Acid

The mixture of formate **12** and **13** (432 mg, 0.80 mmol) in glacial acetic acid (14.4 cm^3) containing zinc powder (864 mg, 13.2 mmol) was heated under reflux for 15 min. The solution was filtered and diethyl ether was added to the filtrate. The solution was washed successively with 5% aq. sodium hydrogencarbonate, water and brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was subjected to PLC (silica gel; benzene) to give the diene acetate **14** (296 mg, 89 %).

δ (270 MHz) 0.68 (3H, s, 18-H), 2.04 (3H, s, CH_3COO-), 5.00 (1H, m, 3α-H), 5.37 (1H, br.s, 1-H), and 5.48 (1H, br.d, *J* 5.1, 6-H); IR 1734 (AcO-), 1674 (C=C), 1248, and 1033 cm^{-1}; m/z 412 (M^+, 0.3%), 352 [$(M-AcOH)^+$,100], 197 (70), and 135 (77). (Found: M^+, 412.3408. $C_{28}H_{44}O_2$ requires *M* 412.3394); m.p. 72-74°C (from MeOH) (lit.[8] 74-75°C; lit.[13] 74-76°C)

***Hydrolysis of the Diene Acetate* 14**

To a solution of the diene acetate **14** (510 mg, 1.2 mmol) in ethanol (8 cm^3) was added a solution of sodium hydroxide (296 mg) in methanol (13 cm^3). The solution was stirred for 4h at room temperature. The solvent was evaporated off to give a product, which was dissolved in diethyl ether. The solution was washed successively with 2N hydrochloric acid, water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product, which was subjected to PLC (silica gel). The plates were developed three times with benzene - diethyl ether (10:1) to give dienol **15** (306 mg, 67 %).

δ (270 MHz) 0.68 (3H, s, 18-H), 4.05 (1H, m, 3α-H), 5.35 (1H, br.s, 1-H), and 5.55 (1H, br.d, *J* 5.13, 6-H); IR 3198 (-OH), 1658 (C=C), and 1056 cm^{-1}; m/z 370 (M^+, 100%), 352 [$(M-H_2O)^+$, 9.8], 257 (24), 239 (19) and 197 (26). (Found: M^+, 370.3264. $C_{26}H_{42}O$ requires *M* 370.3236); m.p. 69.5-71.5°C (from MeOH)

Synthesis of **19-*Norcholesta*-1,3,5-*trien*-3-*ol* 16**

A solution of DMSO (0.024 cm^3) in dichloromethane (0.135 cm^3) was stirred at -78°C (solid CO_2 - MeOH) for 15 min. To this solution was added TFAA (0.037 cm^3). After the mixture had been stirred for 30 min, a solution of dienol **15** (50 mg, 0.14 mmol) in dichloromethane (0.5 cm^3) was added dropwise to the mixture at -65°C; the mixture was then stirred for 1.5h and triethylamine (0.068 cm^3) was then added. The solution was stirred for 1h at -65°C, and the solution was allowed to warm to room temperature. Water was added to the reaction mixture, and the solution was extracted with dichloromethane. The extract was washed with water and brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was then subjected to PLC [silica gel; benzene - diethyl ether (10:1)] to give 19-norcholesta-1,3,5-trien-3-ol **16** [14.5 mg, 35 % based on converted 3-ol **15**] and recovered starting material **15** (8.1 mg). The trienol showed m.p. 114-116°C (from MeOH) (lit.[12] 113-115°C).

δ (90 MHz) 0.70 (3H, s, 18-H), 2.78 (2H, br.s, 6-H), 6.55 (1H, s, 4-H), 6.65 (1H, d, *J* 2.6, 2-H), and 7.14 (1H, d, *J* 7.91, 1-H); IR 3566, 3282 (OH), 1611, 1508, 1367, 1241, 1159 and 867 cm^{-1}; m/z 369 [$(M+H)^+$, 30%], 368 (M^+, 100), 213 (72), and 160 (54).

5-*Bromo*-5α-*androstane*-3β,6β-*diol*-17-*one* 3-*acetate* 18

This compound **18** was prepared according to a procedure reported by Akhtar and Barton[5].

δ (90MHz) 0.89 (3H, s, 18-H), 1.35 (3H, s, 19-H), 2.03 (3H, s, CH_3COO-), 4,24 (1H, br.s, 6α-H), and 5.47 (1H, m, 3α-H); IR 3504

(OH), 1736, 1728 (C=O), and 1244 cm^{-1}; m.p. 169-171°C (from hexane - acetone) (lit.[5] 171-172°C).

5-*Bromo*-19-*oximino*-5α-*androstane*-3β,6β-*diol*-17-*one* 3-*acetate* 20

This compound **20** was prepared according to a procedure reported by Akhtar and Barton.[5]

δ (90 MHz) 0.81 (3H, s, 18-H), 2.02 (3H, s, CH_3COO-), 4.29 (1H. br.s, 6α-H), 5.46 (1H, m, 3α-H), and 7.70 (1H, s, 19-H); IR 3424 (OH), 1731, 1708 (C=O), and 1251 cm^{-1}; m.p. 165-166°C (from hexane - acetone) (lit.[5] 178-180°C).

5-*Bromo*-6β,19-*epoxy*-5α-*androstane*-3β,19-*diol*-17-*one* 3-*acetate* 21

This lactol **21** was obtained by the hydrolysis of hydroxyimino group of **20** according to a procedure reported by Jen and Wolff[6].

δ (270 MHz) 0.88 and 0.93 (each s, 18-H), 2.03 (3H, s, CH_3COO-), 2.77 (1H, dd, *J* 11.4 and 13.2, 4β-H), 4.20 and 4.30 (each 0.5H, each d, *J* 4.5, 6α-H), 5.27 (1H, m, 3α-H), 5.29 and 5.85 (each 0.5H, each d, *J* 4 and *J* 5, 19-H); IR 3460 (OH), 1747, 1708 (C=O), and 1275 cm^{-1}; m.p.163-165°C (from hexane - acetone) (lit.[5] 178-180°C).

***Photoreaction of Hypoiodites of Lactol* 21**

A solution of lactol **21** (280 mg, 0.63 mmol) in benzene (32 cm^3) containing mercury(II) oxide (275 mg, 1.27 mmol) and iodine (322 mg,1.27 mmol) was flushed with nitrogen and then irradiated with Pyrex-filtered light generated by a 100-W high-pressure mercury arc for 3h. The solution was worked up as in the case of the photolysis of the hypoiodite of cholestane lactol **11**. The product was purified by PLC [silica gel; benzene-diethyl ether (4:1)] to give a 7:1 mixture of 5-bromo-5α-estr-9-ene-3β,6β–diol-17-one 3-acetate 6-formate **22** and 5-bromo-5α-estr-1(10)-ene-3β,6β-diol-17-one 3-acetate 6-formate **23** (208 mg, 74 %).

δ (270 MHz) 0.91 (s, 18-H of 9-ene), 0.93 [s, 18-H of 1(10)-ene], 2.05 (3H, S, CH_3COO-), 5.09 (1H, m, 3α-H), 5.27 (br.s, 6α-H of 9-ene), 5.38 [br.s, 6α-H of 1(10)-ene], 5.79 [br.s, 1-H of 1(10)-ene], 8.13 (s, OCHO of 9-ene) and 8.17 [s, OCHO of 1(10)-ene]; IR 1739 (AcO-), 1720 (-OCHO), 1369, 1241, and 1164 cm^{-1}; m/z 440(M^+, 0.19%), 438 (M^+, 0.19), 254 [$(M-Br-OCHO-AcOH)^+$, 100], 197 (58), and 104 (44).

Reductive Elimination of Formate* 22 *and* 23 *with Zinc in Acetic Acid

The mixture of formate **22** and **23** (157 mg, 0.36 mmol) in glacial acetic acid (6.4 cm^3) containing zinc powder (321 mg, 4.91 mmol) was heated under reflux for 30 min. The solution was then worked up as in the case of the formate **12** and **13**. The product was subjected to PLC [silica gel; benzene - diethyl ether (4:1)] to give the diene acetate **24** (100 mg, 89 %).

δ (270 MHz) 0.89 (3H, s, 18-H), 2.05 (3H, s, CH_3COO-), 5.01 (1H, m, 3α-H), 5.42 (1H, br.s, 1-H), and 5.51 (1H, br.d, *J* 5.86 , 6-H); IR 1743 (AcO-), 1728 (C=O), 1692 (C=C), and 1242 cm^{-1}; m/z 314 (M^+, 2.4%), 270 (15.4), 254 [$(M-AcOH)^+$, 100], 197 (70), and 104 (75); Anal. Found. C, 76.29; H, 8.87. $C_{28}H_{44}O_2$ requires C, 76.40; H, 8.33; m.p. 86-92°C (from MeOH) [lit.[13] 115°C (from benzene - diethyl ether)]

***Hydrolysis of the Diene Acetate* 24**

To a solution of the diene acetate **24** (100 mg, 0.32 mol) in ethanol (2 cm^3) was added a solution of potassium hydroxide (18 mg) in methanol (3 cm^3). The solution was stirred for 4h at room temperature. The solution was then worked up as in the case of the cholestane series. The product was subjected to PLC [(silica gel); benzene - diethyl ether (1:1)] to give 3β-ol **25** (68 mg, 78 %). The analytical sample was obtained by recrystallization from hexane - acetone, m.p. 134.5-135.5°C; δ (270 MHz) 0.89 (3H, s, 18-H), 3.9-4.2 (1H, m, 3α-H), 5.41 (1H, br.s, 1-H), and 5.58 (1H, br.d, *J* 5.5, 6-H); IR 3498 (OH), 1733 (C=O), 1220, 1076 and 1061 cm^{-1}; m/z 272 (M^+, 100%), 254 [$(M-H_2O)^+$, 19], 197 (22), and 129 (20); (Found: M^+, 272.1786. $C_{18}H_{24}O_2$ requires *M*, 272.1777)

***Synthesis of Estrone* 26**

A mixture of DMSO (0.024 cm^3) and dichloromethane (0.135 cm^3) was stirred at -78°C for 30 min. To this solution was added TFAA (0.037 ml). After the mixture had been stirred for 30 min, a solution of dienol **25** (20 mg, 0.0074 mmol) in dichloromethane

(0.5 cm^3) was added dropwise over 5 min to the mixture. After the solution has been stirred for 100 mim, triethylamine (0.068 cm^3) was then added, and the solution was stirred for another 30 min at -78°C. The temperature of the stirred solution was then raised to room temperature and then water was added. The solution was extracted with dichloromethane. The combined organic layers were washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was subjected to PLC [silica gel; benzene-diethyl ether (2:1)] to give three fractions in order of mobility on TLC plate.

The most mobile fraction (5.3 mg, 20 %) was 17-oxo-estra-1(10),5-dien-3β-ol trifluoroacetate **27**, m.p. 108-111°C (from MeOH). δ (270 MHz) 0.90 (3H, s, 18-H), 5.19-5.27 (1H, m, 3α-H), 5.41 (1H, br.s, 1-H), and 5.58 (1H, br.d, *J* 5.7, 6-H); IR 1781, 1739 (C=O), 1220, and 1173 cm^{-1}; m/z 368 (M^+, 26%), 254 [(M-$CF_3COOH)^+$, 100), and 104 (83). (Found: M^+, 368.1588. $C_{20}H_{23}O_3F_3$ requires *M*, 368.1599).

The next mobile fraction (5.9 mg, 30 %) was estrone **26**, which was identical with an authentic specimen in every respect. An analytical sample was obtained by recrystallization from MeOH, m.p. 250-252°C; δ (90 MHz) 0.91 (3H, s, 18-H), 2.7-3.0 (2H, br.m, 6-H), 6.58 (1H, s, 4-H), 6.67 (1H, d, *J* 2.9, 2-H), and 7.15 (1H, d, *J* 8.1, 1-H); IR 3340 (OH), 1720 (C=O), 1621, 1585, 1499, 1289, 1250, 1056, 820, and 789 cm^{-1}; m/z 270 (M^+, 100%), 185 (37), and 146 (30).

The polar fraction (4.8 mg, 24 %) was the starting dienol **25**. The yield of estrone based on the converted dienol was 40%.

Catalytic Hydrogenation of **19-*Norcholesta*-1(10),5-*dien*-3β-*ol Acetate* 14 *with Platinum Oxide***

The diene acetate **14** (217 mg, 0.53 mmol) in a stirred mixture of acetic acid (4 cm^3) and diethyl ether (4 cm^3) containing platinum(IV) oxide (20 mg) was hydrogenated under hydrogen at room temperature. After hydrogenation was complete, the catalyst was removed by filtration. The solution was washed successively with 5% aq. sodium hydrogencarbonate, water, and brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was subjected to PLC (silica gel; benzene) to give two fractions, A (16 mg, 8 %) and B (184 mg), in order of the mobility.

Fraction A was an oily mixture of the stereoisomers of 19-norcholestane (Found. M^+, 358.3620. $C_{26}H_{46}$ requires, *M* 368.3599); δ (270 MHz) 0.64 and 0.66 (each 3H, each s, 18-H); IR (neat) 2922, 2860, 1365, 1448, 1380, and 1363cm^{-1}; m/z 358 (M^+, 94), 343 [$(M-CH_3)^+$, 4.5] and 203 (100).

Fraction B was a mixture of products, which was dissolved in ethanol (5 cm^3) containing potassium hydroxide (20 mg) and methanol (5 cm^3). The solution was stirred for 1h at room temperature and the solvent was evaporated on a rotary evaporater. The residue was dissolved in diethyl ether and the solution was washed successively with dil. hydrochloric acid, water, and brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent left a residue, which was subjected to PLC [silica gel; hexane - ethyl acetate (3:1)] to give three fractions.

The most mobile fraction (113 mg, 52 %) was 19-nor-5α,10α-cholestan-3β-ol acetate **28**, which was recrystallized from methanol, m.p. 106-107.5°C; δ (270 MHz) 0.66 (3H, s, 18-H), 2.03

(3H, s, CH_3COO-), 5.01 (1H, t, *J ca.* 3, 3α-H); IR 1737, 1728 (C=O), 1238, 1058, and 956 cm^{-1}; m/z 417 [$(M+H)^+$, 2.3%], 416 (M^+, 6.5), 356 [$(M-AcOH)^+$, 87], 202 (100), and 201 (97); Anal. Found. C, 80.58; H, 11.57. $C_{28}H_{48}O_2$ requires C, 80.71; H, 11.61.

The next mobile fraction (6 mg, 3 %) was 19-nor-5α,10α-cholestan-3β-ol **30**, which was recrystallized from methanol to yield a specimen for analysis, m.p.136-138°C; δ (270 MHz) 0.65 (3H, s, 18-H), 4.08 (1H, t, *J ca.*3, 3α-H); IR 3310, 3240 (OH), 1027, and 956 cm^{-1}; m/z 375 [$(M+H)^+$, 13%], 374 (M^+, 43), 356 [$(M-H_2O)^+$,26], 216 (36) and 201 (100); Anal. Found. C, 83.19; H, 12.49. $C_{26}H_{46}O$ requires C, 83.35; H, 12.38.

The most polar fraction (42 mg, 22 %) was 19-nor-5α-cholestan-3β-ol **31**, which was recrystallized from methanol to yield an analytical sample, m.p. 107.5-109°C (lit.[2b] 107-108°C); δ (270 MHz) 0.66 (3H, s, 18-H), 3.46-3.67 (1H, m, 3α-H); IR 3372 (OH), 1171, 1058, and 1036 cm^{-1}; m/z 375 [$(M+H)^+$, 14%], 374 (M^+, 45), 356 [$(M-H_2O)^+$, 45], 220 (51) and 201 (100); Found. M^+ 374.3538. $C_{26}H_{46}O$ requires *M* 374.3548.

***Hydrolysis of* 19-*Nor*-5α,10α-*cholestan*-3β-*ol Acetate* 28**

To a solution of 19-nor-5α,10α-cholestan-3β-ol acetate **28** (57 mg, 0.14 mmol) in ethanol (4 cm^3) was added a solution of potassium hydroxide (25 mg) in methanol (4 cm^3). After the solution had been heated under reflux for 2h, additional potassium hydroxide (70 mg) in methanol (7 cm^3) was added and heated under reflux for a further 8.5h. Evaporation of the solvent gave a residue, which was dissolved in diethyl ether and the solution was washed successively with dil. hydrochloric acid,

water, and brine. After the dryness over anhydrous sodium sulphate, the solvent was evaporated to give a product, which was subjected to PLC [silica gel; hexane - ethyl acetate (3:1)] to yield the alcohol, 19-nor-5α,10α-cholestan-3β-ol **30** (47 mg) in 92% yield, which was identical with an authentic specimen obtained above.

Oxidation of* 19-*Nor*-5α,10α-*cholestan*-3β-*ol* 30 *with PCC

A solution of PCC (27 mg) in dichloromethane (2 cm^3) was added to a solution of 19-nor-5α,10α-cholestan-3β-ol **29** (47 mg, 0.13 mmol) in dichloromethane (4 cm^3). After the solution was stirred for 5h at room temperature, treated with diethyl ether, and filtrated. The filtrate was washed successively with water and brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product, which was recrystallized from methanol to yield the pure ketone **32** (22 mg, 47 %), m.p. 123-125.5°C. The solvent was evaporated from the mother liquor and the residue was subjected to PLC [silica gel; benzene - diethyl ether (10:1)] to yield a further crop (17 mg) of the ketone (total yield 83 %).

δ (270 MHz) 0.64 (3H, s, 18-H), 2.59 (1H, dd, *J* 6.2 and *J* 13.9, 4β-H); IR 1720 (C=O), 1332, 1293, 1245, and 1172 cm^{-1}; m/z 372 (M^+, 100%), 218 (66), 217 (75), and 108 (68); Anal. Found. C, 83.64; H,12.02, $C_{26}H_{44}O$ requires C, 83.80; H, 11.90.

Oxidation of **19-*Nor*-5α-*cholestan*-3β-*ol* 31** ***with PCC***

A solution of PCC (18 mg) in dichloromethane (2 cm^3) was added to a solution of 19-nor-5α-cholestan-3β-ol **31** (32 mg, 0.086 mmol) in dichloromethane (3 cm^3). The solution was stirred for 48h at room temperature, and work up as in the oxidation of the 5α,10α-isomer to give the 3-one **33** (27 mg, 85 %), which was recrystallized from methanol, m.p. 74-75°C; δ (270 MHz) 0.69 (3H, s, 18-H) ; IR 1719 (C=O), 1263, 1200, 1173, 1084, and 956cm^{-1}; m/z 372 (M^+, 50%), 357 [$(M-CH_3)^+$, 2], 217 (100), and 162 (27). Found. M^+, 372.3378. $C_{26}H_{44}O$ requires *M*, 372.3391; $[\alpha]_{250}$ -356.4°, $[\alpha]_{267}$ -613.6° (min), $[\alpha]_{275}$ +524.9°, $[\alpha]_{300}$ +823.5°, $[\alpha]_{306}$ +951.6° (max), $[\alpha]_{325}$ +542.3°, $[\alpha]_{350}$ +298.6° (23°C, c 0.104, MeOH); CD ε +1.270 (c 0.104, MeOH).

Catalytic Hydrogenation of* 19-*Norcholesta*-1(10),5-*dien*-3β-*ol Acetate* 14 *over Pd-C

The diene acetate **14** (135 mg, 0.33 mmol) was dissolved in ethyl acetate (13 cm^3) containing 10% Pd-C catalyst (30 mg) and hydrogenated in the stirred solution under hydrogen at room temperature. After hydrogenation was complete (TLC), the catalyst and the solvent were removed. The residue was dissolved in ethanol (3 cm^3) containing potassium hydroxide (20 mg). The solution was stirred for 24h at room temperature. After the solvent was evaporated, diethyl ether was added to the residue. The solution was washed successively with dil. hydrochloric acid, water, and brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a mixture of product, which was

subjected to PLC [silica gel; benzene - diethyl ether (3:1)] to give four fractions A, B, C, and D in order of mobility.

Fraction A (30 mg, 22 %) was 19-nor-5α,10α-cholestan-3β-ol acetate **28**, identical with the authentic specimen obtained above. Fraction B (2 mg, 2 %) was 19-nor-5α,10α-cholestan-3β-ol **30**, identical with an authentic specimen.

Fraction C (47 mg, 37 %) was 19-nor-cholest-5(10)-en-3β-ol **36**. An analytical sample, m.p. 106.5-108°C (lit.[15] 108-109°C) was obtained by recrystallization from methanol. δ (270 MHz) 0.68 (3H, s, 18-H), 4.0-4.1 (1H, br.m, 3α-H); IR 3276 (OH), 1336, 1252, 1053 and 962 cm^{-1}; m/z 372 (M^+, 100%), 354 [$(M-H_2O)^+$, 85], 339 (20), 259 (30) and 215 (61).

Fraction D (37 mg) was a mixture, which was subjected to PLC [silica gel; benzene - diethyl ether (2:1)] to give 19-nor-5α-cholestan-3β-ol **31** (10 mg, 8 %), identical with an authentic sample.

***Synthesis of* 19-*Norcholest*-4-*en*-3-*one* 37**

A solution of PCC (40 mg) in dichloromethane (5 cm^3) was added to a solution of 19-norcholest-5(10)-en-3β-ol **36** (70 mg, 0.19 mmol) in dichloromethane (5 cm^3). After the solution had been stirred for 14h at room temperature, additional PCC (20 mg) in dichloromethane (2 cm^3) was added and the solution was stirred for a further 2h. After diethyl ether had been added, the solution was filtered. The filtrate was washed successively with water and brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a product, which was dissolved in methanol (15 cm^3). After the addition of conc. hydrochloric acid

(0.2 cm^3), the solution was stirred for 1.5h at room temperature. The solvent was then removed and the residue was dissolved in diethyl ether. The solution was washed successively with water, and saturated brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was subjected to PLC [silica gel; benzene - diethyl ether (3:1)] to give oily 19-norcholest-4-en-3-one **37** (23 mg, 30 %) (lit.[2c,15] oil) ^1H NMR δ (90 MHz) 0.72 (3H, s, 18-H), and 5.82 (1H, s, 4-H); IR 1683, 1615 (C=C-C=O), 1259, and 1205 cm^{-1}; m/z 371 [$(M+H)^+$, 30%], 372 (M^+, 100), 355 $(M-CH_3)^+$, 6], 352 (5), 215 (61), and 110 (51).

Catalytic Hydrogenation of* 17-*Oxoestra*-1(10),5-*dien*-3β-*ol Acetate* 24 *over Pd-C

A solution of the diene acetate **24** (308 mg, 0.75 mmol) in ethyl acetate (30 cm^3) containing 10% Pd-C catalyst (65 mg) was stirred under hydrogen at room temperature. After the hydrogenation was complete (TLC), the catalyst and the solvent were removed to give a mixture of products, which was dissolved in methanol containing potassium hydroxide (5 %). The solution was heated under reflux for 1.5h and the solvent was evaporated off. The residue was dissolved in diethyl ether, and the solution was washed successively with dil. hydrochloric acid, water, and brine. It was then dried over anhydrous sodium sulphate and the evaporation of the solvent gave crude products, which were then subjected to PLC [silica gel; benzene - diethyl ether (2:3)] to yield two fractions.

The more mobile fraction (82 mg, 30 %) was 3β-hydroxy-5α,10α-estran-17-one **41** which, after recrystallization from

light petroleum - acetone, melted at 154-155°C (lit. 152-154°C). δ (270 MHz) 0.86 (3H, s, 18-H), 2.44 (1H, dd, *J* 8.4 and *J* 10.3, 16-H), and 4.10 (1H, t, *J ca.* 3, 3α-H); IR 3550, 3486(OH), 1726 (C=O), 1202, 1109, 1050, 961, and 922 cm^{-1}; m/z 276 (M^+, 100%), 258 [$(M-H_2O)^+$, 40], 202 (38), 108 (51), and 67 (63).

The less mobile fraction (132 mg) was a mixture of 3β-hydroxy-5α-estran-17-one **42** and 3β-hydroxyestr-5(10)-en-17-one **43**. This fraction was dissolved in dichloromethane (5 cm^3) and a solution of PCC (103 mg) in dichloromethane (5 cm^3) was added. After the solution had been stirred for 16h, additional PCC (60 mg) in dichloromethane (3 cm^3) was added and the solution was stirred for a further 3h, and was then worked up as in the oxidation of 19-norcholest-5(10)-en-3β-ol. The product was subjected to PLC [silica gel; benzene - diethyl ether (2:3)] to give two fractions.

The more mobile fraction (41 mg, 15 %) was 5α-estrane-3,17-dione **44**, which was recrystallized from aq. methanol, m.p. 72-74°C (lit.[20] 73-75°C); δ (90 MHz) 0.90 (3H, s, 18-H); IR 1737, 1720 (C=O), 1187, 1097, 1051, and 996 cm^{-1}; m/z 274 (M^+, 100%), 256 (24), and 230 (49).

The less mobile fraction (31 mg, 12 %) was estr-4-en-3,17-dione **45**, which was recrystallized from methanol. m.p. 163-165°C (lit.[15] 163-167°C); δ (90 MHz) 0.94 (3H, s, 18-H), and 5.85 (1H, s, 4-H); IR 1744 (C=O), 1674, 1621 (C=C-C=O), 1251, and 1044 cm^{-1}; m/z 272 (M^+, 100%), 244 (23), 228 (28), 110 (55), and 41 (56).

5α,10α-*Estrane*-3,17-*dione* 46

A solution of PCC (94 mg) in dichloromethane (5 cm^3) was added to a solution of 3β-hydroxy-5α,10α-estran-17-one **41** (120 mg, 0.438 mmol) in dichloromethane (5 cm^3). After the solution was stirred for 18h, it was treated with diethyl ether, and filtered; the filtrate was washed successively with water and saturated brine, and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a residue, which was recrystallized from methanol to yield the dione **46** (78 mg, 65 %), m.p. 159-162°C (lit.[18] 163-165°C) (lit.[21] 164°C). A further crop (32 mg, total yield 92%) of the dione was obtained from the mother liquor by PLC [silica gel; benzene - diethyl ether (2:3)]; δ (90 MHz) 0.86 (3H, s, 18-H); IR 1748, 1722 (C=O), 1200, 1153, and 1000cm^{-1}

***Synthesis of* 19-*Nortestosterone* 47**
by Reduction with Sodium Borohydride

Sodium borohydride (30 mg) was added to a solution of estr-4-en-3,17-dione **45** (29 mg, 0.107 mmol) in 1:1 dichloromethane-methanol (7.2 cm^3) at -78°C (solid CO_2-MeOH). The solution was stirred for 6h and then warmed up to room temperature. Dichloromethane was added to the solution, which was then washed successively with 1N sodium hydroxide, and water; it was then dried over anhydrous sodium sulphate. Evaporation of the solvent gave crude 19-nortestosterone **47**, which was pulified by PLC [silica gel; benzene - diethyl ether (1:2)] and then recrystallization from light petroleum - acetone to give pure material, m.p. 112-113°C (lit.[19] 122-123°C) (lit.[23] 114-115°C); δ (90 MHz) 0.81 (3H, s, 18-H), 3.75 (1H, t, *J* 7.9, 17α-H),

and 5.82 (1H, br.s, 4-H); IR 3368 (OH), 1656, 1620 (C=C-C=O), 1263, 1203, and 1056 cm^{-1}; m/z 275 [$(M+H)^+$, 28%], 274 (M^+, 100), 256 [$(M-H_2O)^+$, 19], and 110 (90).

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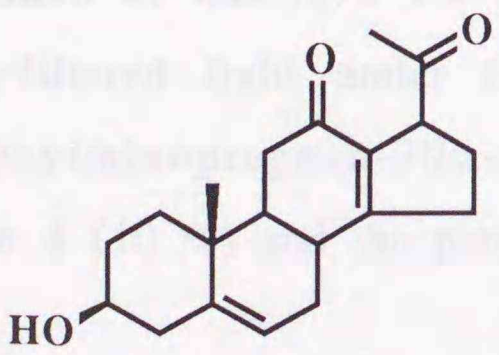
CHAPTER 3

A NEW SYNTHESIS OF 18-NORSTEROIDS BASED ON A β-SCISSION OF ALKOXYL RADICALS GENERATED FROM HYPOIODITES

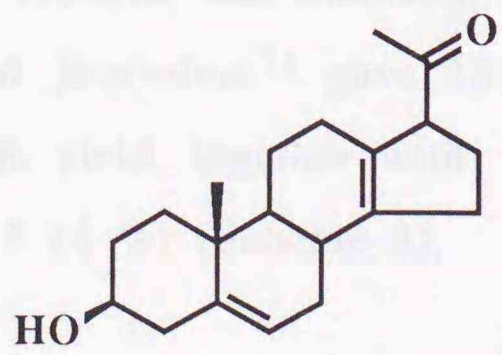
3-1 Introduction

In the previous chapter, new transformations of steroids into ring-A-aromatized steroids and 19-norsteroids based on a β-scission of alkoxyl radicals generated from hypoiodites were described. In this chapter, new synthesis of 18-norsteroids based on a β-scission of alkoxyl radicals generated by the photolysis of the corresponding hypoiodites is described.

Compared with the synthesis of 19-norsteroids[1], a few methods for the synthesis of 18-norsteroids have been reported. These methods include a total synthesis[2], decarboxylation of 18-oxygenated steroids prepared by hypoiodite reaction[3], and cleavage and regeneration of the D-ring[4] under rather strong conditions. A new transformation of steroids into 18-norsteroids under mild conditions involves a regioselective β-scission of the alkoxyl radicals as well as 19-norsteroids generated from 18-hydroxy-18,20α-epoxysteroids. The author has chosen fukujusonorone[5] **1**, the first 18-norsteroid isolated from *Adonis amurensis* Regel et Radd, as the target molecule in the present study, and have achieved a transformation of commercially available 3β-hydroxypregn-5-en-20-one (pregnenolone) into 12-deoxofukujusonorone **2** in 10 steps, as described below.



(1) fukujusonorone



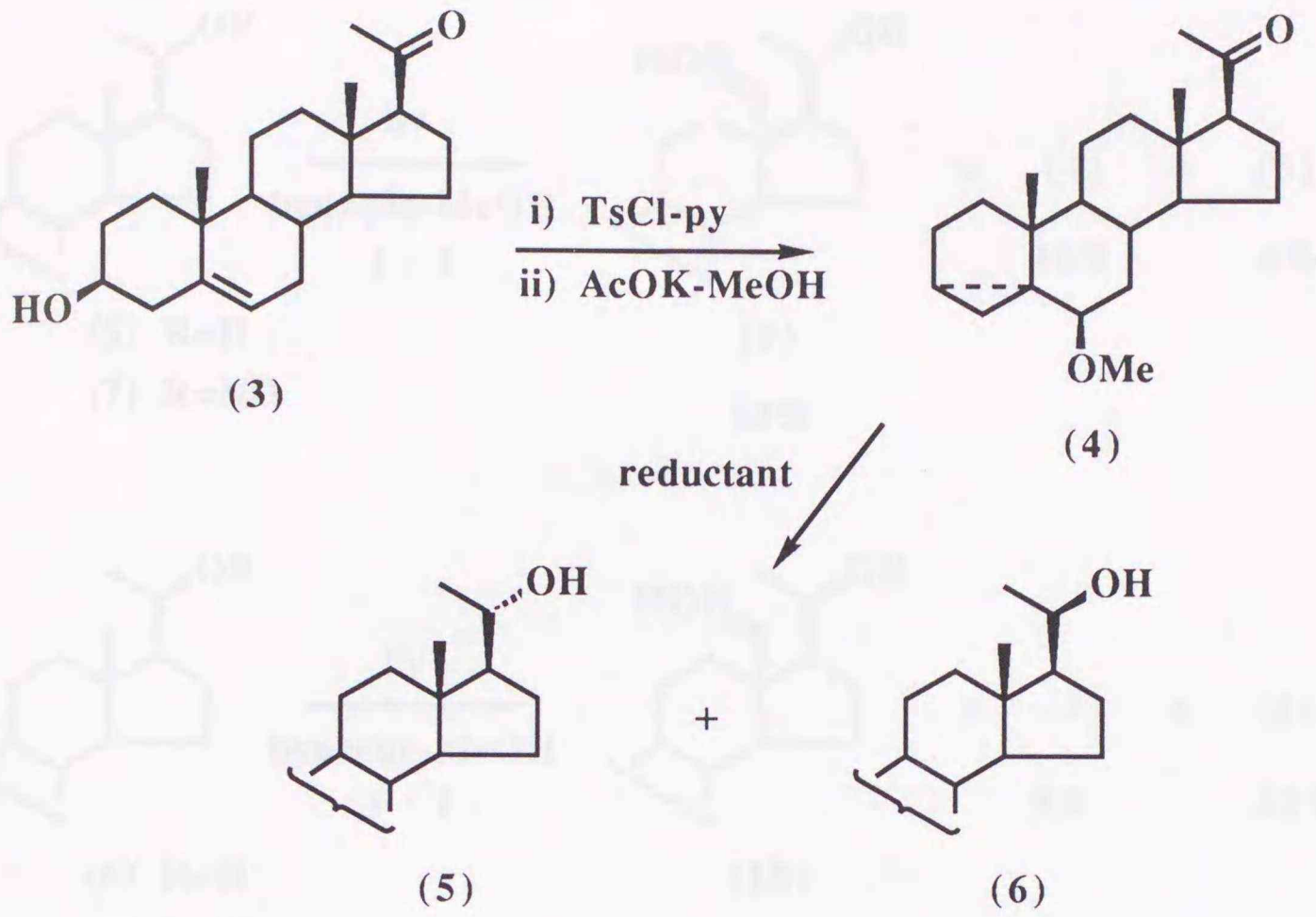
(2)

3-2 A New Synthesis of 18-Norsteroids based on a β-Scission of Alkoxyl Radicals generated from Hypoiodites

The functional groups of the A and B-rings of 3β-hydroxypregn-5-en-20-one **3** (pregnenolone), the starting steroid selected for the transformation into fukujusonorone **1**, were protected by the standard method[6]. Thus, the conversion of pregnenolone **3** into its tosylate, followed by a treatment with methanol containing potassium acetate under reflux, gave 6β-methoxy-3α,5-cyclo-5α-pregnan-20-one **4**[7].

A reduction of the carbonyl group of the masked pregnenolone **4** with sodium and ethanol[8] gave the corresponding 20α-ol **5**[7] as the major product (58 %) with an accompanying formation of the 20β-isomer **6**[7] (29 %) while a reduction of 20-ketone **4** with sodium borohydride in ethanol gave the 20β-ol **6** as the major product (79 %) as well as the 20α-isomer **5** (13 %). The predominant formation of the 20β-isomer over its 20α-epimer in the reduction of steroidal 20-ketone with complex hydride has been well documented[9,10].

The 20α-ol **5** was transformed into the corresponding nitrite **7** with nitrosyl chloride in pyridine by the standard method[11]. Irradiation of this in a 1:1 mixture of benzene and methanol with Pyrex-filtered light under the standard procedure[11] gave 18-hydroxyiminopregnan-20α-ol **8** in 63% yield, together with ketone **4** (10 %) and the parent 20α-ol **5** (4 %) (Scheme 2).



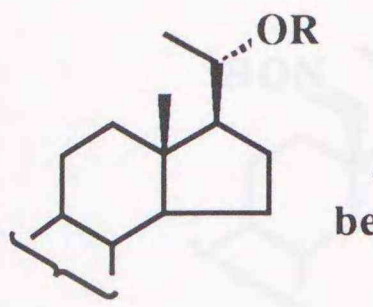
(3) (4) (5) (6)

Na-EtOH-reflux	**58%**	**29%**
$NaBH_4$-EtOH-r.t.	**13%**	**79%**

Scheme 1

Although similar photoreaction of the 20β-ol nitrite **9** gave ketone **4** (9 %) and the parent 20β-ol **6** (21 %), the corresponding 18-hydroxyimino 20β-ol **10** was obtained in only 12% yield.

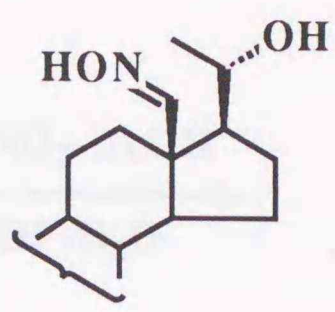
The predominant formation of 18-hydroxyimino steroids in the photoreaction of steroidal 20α-nitrite, rather than in the photoreaction of the 20β-epimer, has repeatedly been reported,[12,13] and the results explained in terms of the smaller steric interaction between 12β-hydrogen and the 20-Me group in the 20α-isomer in the transition state as shown in the Figure[13].



hν

benzene-MeOH

1 : 1



+ (4) + (5)

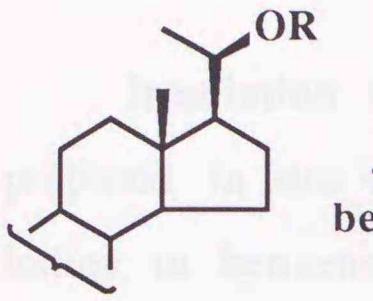
10% 4%

(5) R=H

(7) R=NO

(8)

63%



hν

benzene-MeOH

1 : 1

+ (4) + (6)

9% 12%

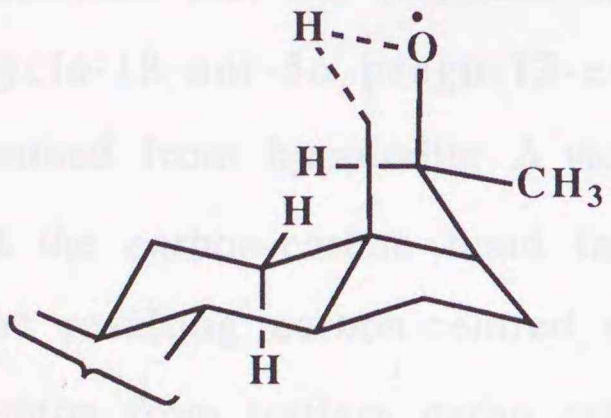
(6) R=H

(9) R=NO

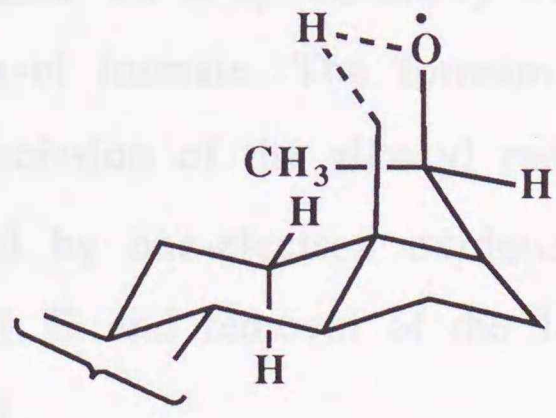
(10)

12%

Scheme 2



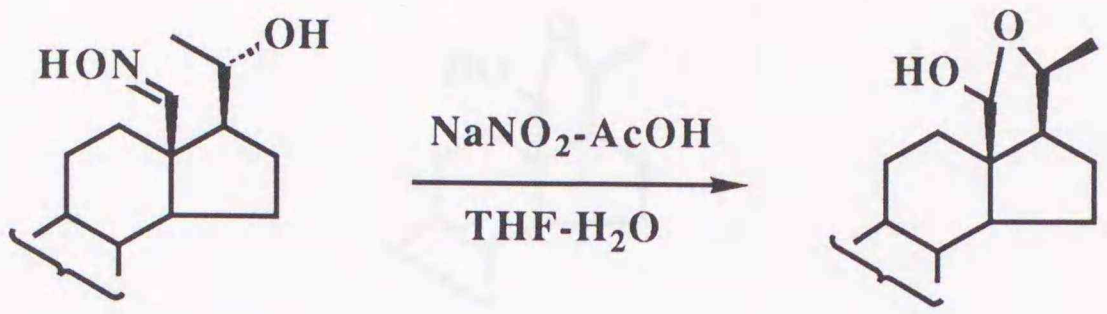
20α-isomer



20β-isomer

Figure

The 18-hydroxyiminopregnan-20α-ol **8** was then subjected to deoximation with sodium nitrite and acetic acid[14] in THF to give a crystalline lactol **11** in 75% yield (Scheme 3).

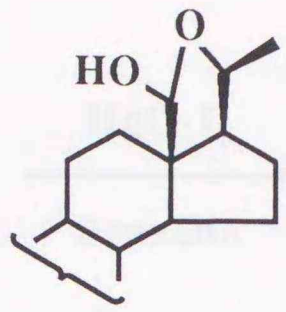


(8) (11)

75%

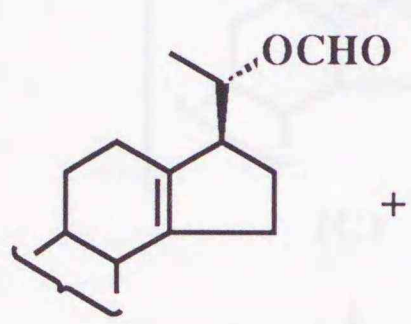
Scheme 3

Irradiation of the hypoiodite (**A** in Scheme 5) of lactol **11**, prepared *in situ* with each 2 equivalents of mercury(II) oxide and iodine in benzene by the standard method described in Chapter 2 gave a mixture of isomeric 18-norpregnen-20α-ol formates (**12**, **13**, and **14**) as outlined in Scheme 4. The formate **12**, obtained in 48% yield, was readily isolated by PLC. High-resolution mass spectrometry indicated that the molecular formula is $C_{22}H_{32}O_3$. The anticipated reaction pathway (outlined in Scheme 5) together with the IR, ^1H NMR and mass spectral results (see Experimental) indicated that the structure of formate **12** is 6β-methoxy-3α,5-cyclo-18-nor-5α-pregn-13-en-20α-ol formate. The formate **12** is formed from hypoiodite **A** *via* a β-scission of the alkoxyl radical **B** at the carbon-carbon bond followed by one-electron oxidation of the resulting carbon-centred radical **C** and removal of the 14α-proton from tertiary carbo cation **D**.



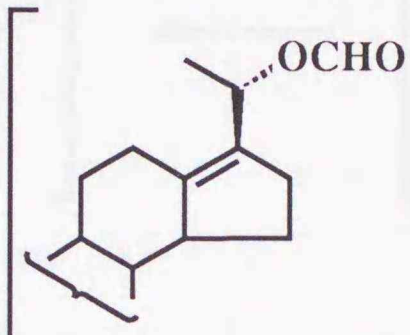
(11)

i) $HgO\text{-}I_2$-benzene
ii) hν



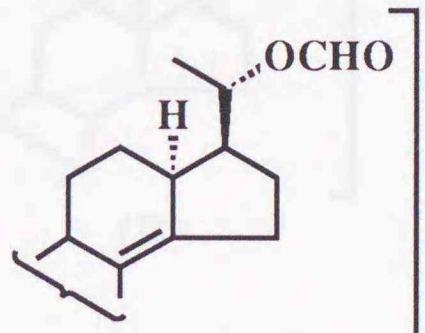
(12) 48%

+



(13)

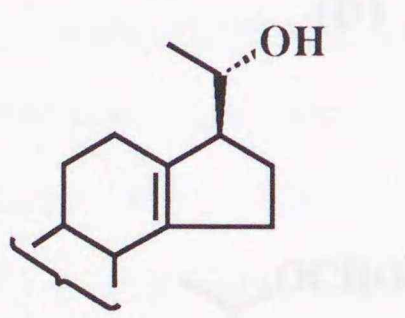
+



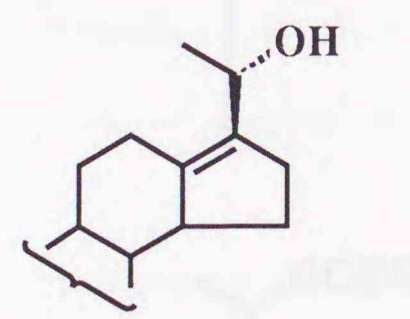
(14)

KOH-MeOH

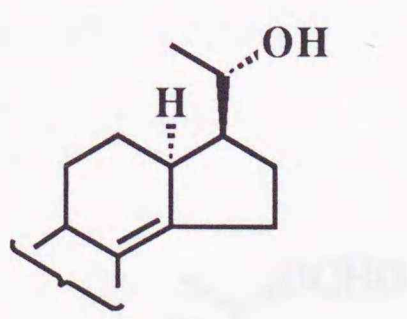
KOH-MeOH



(18)
85%

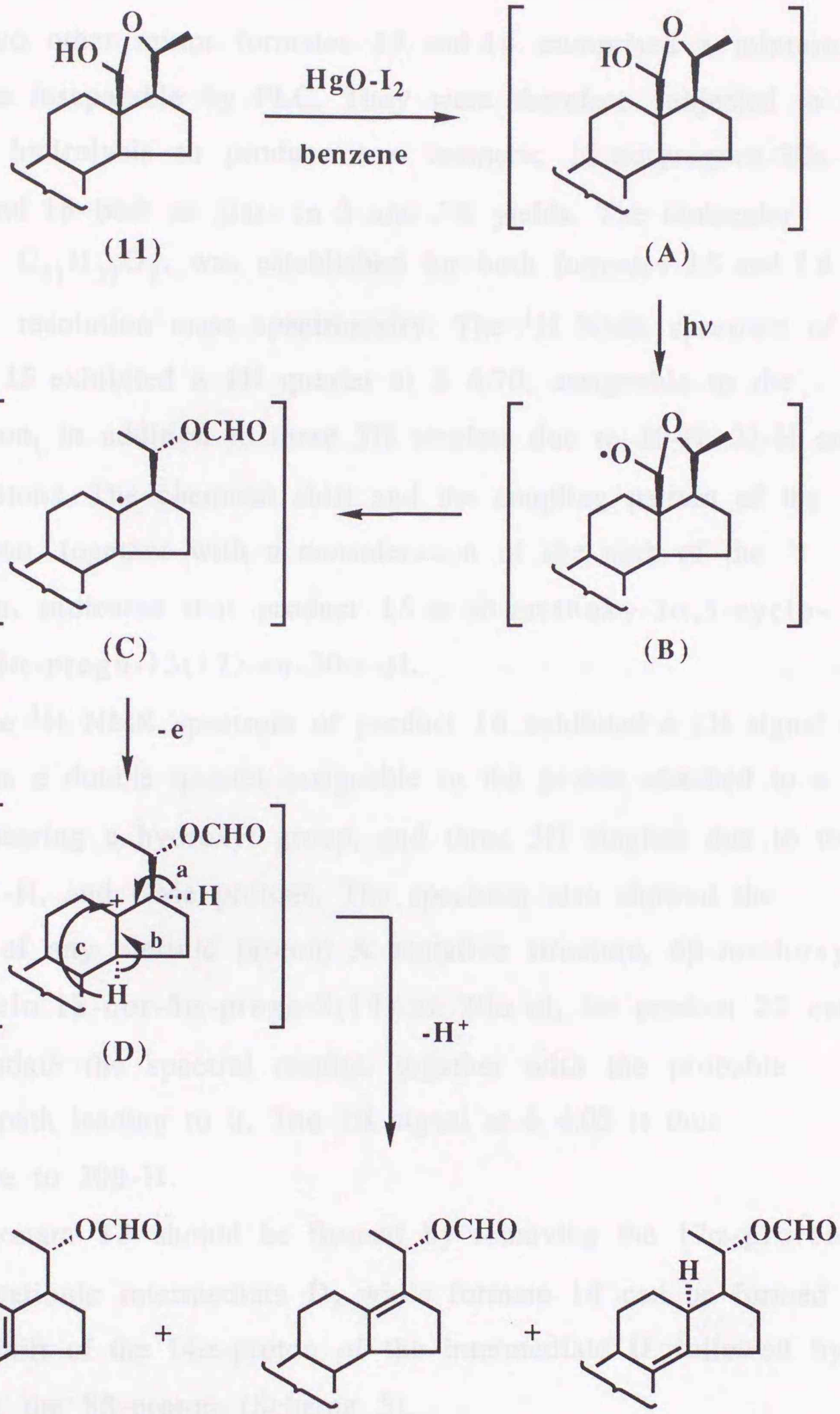


(15)
3%



(16)
5%

Scheme 4


HO
O
HgO-I2
benzene
IO
O
(11)
(A)
hν
OCHO
O
•O
(C)
(B)
-e
OCHO
a
H
+
c
b
H
(D)
-H+
OCHO
OCHO
H
OCHO
+
+
(12)
(13)
(14)

Scheme 5

Two other minor formates **13** and **14** comprised a mixture, and were inseparable by PLC. They were therefore subjected to alkaline hydrolysis to produce two isomeric 18-norpregnen-20α-ols **15** and **16** both as glass in 3 and 5% yields. The molecular formula, $C_{21}H_{32}O_2$, was established for both formates **15** and **16** by high- resolution mass spectrometry. The ^1H NMR spectrum of product **15** exhibited a 1H quartet at δ 4.70, assignable to the 20β-proton, in addition to three 3H singlets due to 19-H, 21-H and OMe protons. The chemical shift and the coupling pattern of the 20β-proton, together with a consideration of the path of the formation, indicated that product **15** is 6β-methoxy-3α,5-cyclo-18-nor-5α-pregn-13(17)-en-20α-ol.

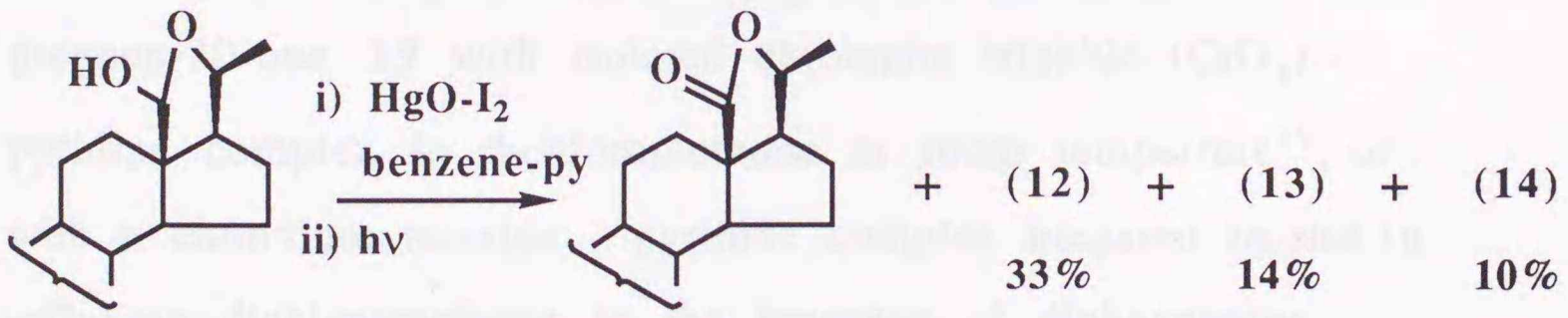
The ^1H NMR spectrum of product **16** exhibited a 1H signal at δ 4.05 as a double quartet assignable to the proton attached to a carbon bearing a hydroxyl group, and three 3H singlets due to the 19-H, 21-H, and OMe protons. The spectrum also showed the absence of any olefinic proton. A tentative structure, 6β-methoxy-3α,5-cyclo-18-nor-5α-pregn-8(14)-en-20α-ol, for product **22** can accommodate the spectral results, together with the probable reaction path leading to it. The 1H signal at δ 4.05 is thus assignable to 20β-H.

Formate **13** should be formed by removing the 17α-proton from a cationic intermediate **D**, while formate **14** can be formed *via* 1,2-shift of the 14α-proton of the intermediate **D** followed by removing the 8β-proton (Scheme 5).

Both the products and their yields in this β-scission of the hypoiodite of lactol **9** when pyridine was added to the solvent were then examined. Thus the photoreacion of the hypoiodite of lactol **9** in benzene containing a small amount of pyridine (2.5

equivalents of the substrate steroid) under otherwise the above-mentioned similar conditions gave a new product **17** in 25% yield, together with formates **12** (33 %), **13** (14 % after the hydrolysis to 20β-ol **15**) and **14** (10% after the hydrolysis to 20α-ol, **16**) (Scheme 6). The mass spectrometry and combustion analysis indicated that it had the molecular formula $C_{22}H_{32}O_3$. The IR spectrum exhibited a band assignable to the γ-lactone group. The ^1H NMR spectrum exhibited a 1H double quartet at δ 4.66 with *J* 4.8 and 6.6 Hz, in addition to signals attributable to 19-H, 21-H, and OMe. These results indicate that the new product **17** is 6β-methoxy-18,20α-epoxy-3α,5-cyclo-5α-pregnan-18-one.

This experiment thus indicated that the addition of pyridine lowered the yield of formate **12**, which seemed to be a straightforward precursor leading to fukujusonorone, to led even more byproducts.



(11) **(17)**

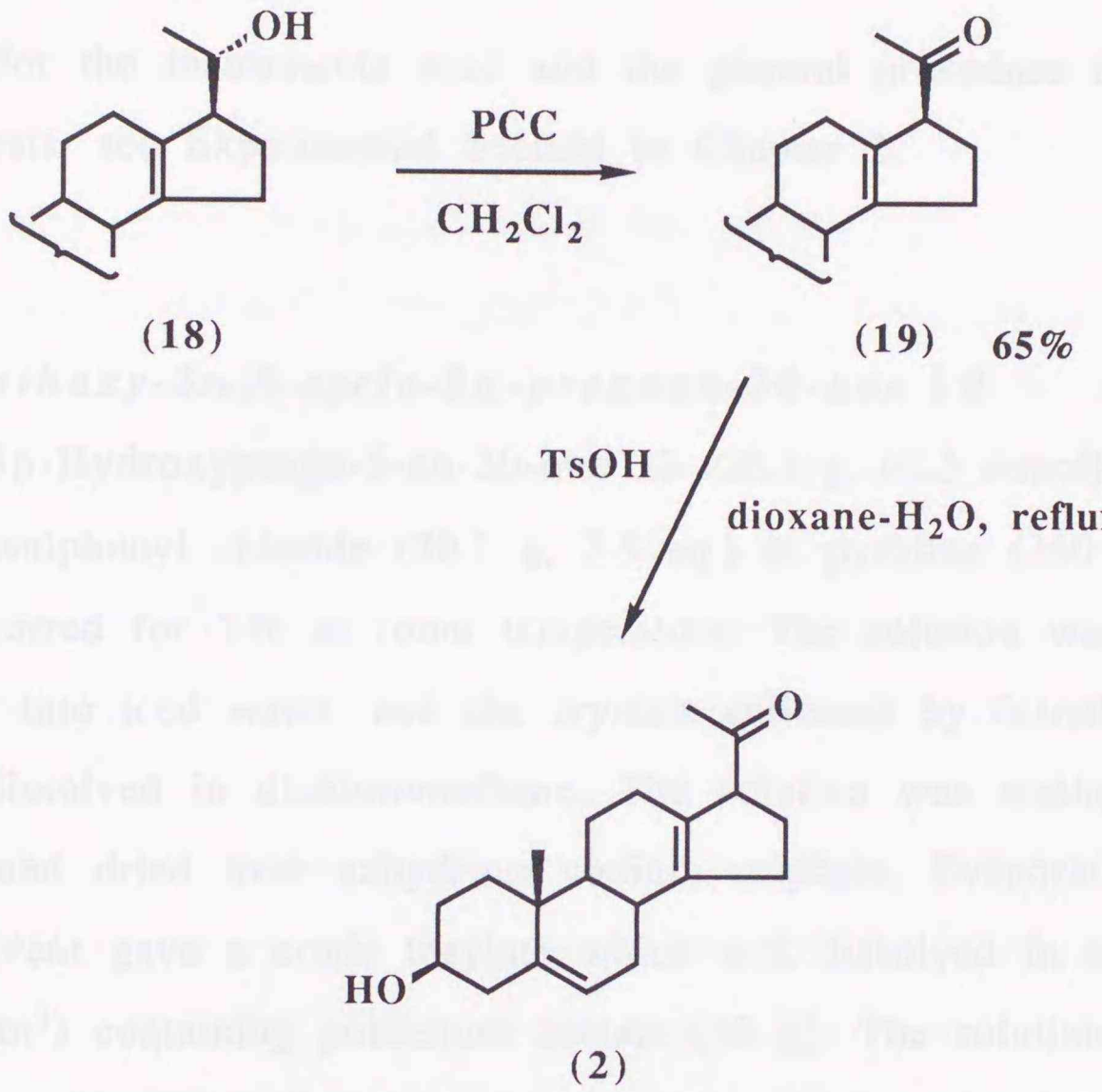
25%

Scheme 6

The hydrolysis of formate **12** with potassium hydroxide in methanol gave the corresponding 20α-ol **18** as a glass in 85% yield. The spectral results were in full agreement with the assigned structure. The oxidation of the 20α-ol with pyridinium chlorochromate (PCC) in dichloromethane at room temperaure gave crystalline 6β-methoxy-3α,5-cyclo-18-nor-5α-pregn-13-en-20-one **19** in 65% yield.

All attempts to oxidize the allylic 12-methylene group of pregnen-20-one **19** to a carbonyl group under various published procedures have been unsuccessful; the oxidation of pregnene **19** with *t*-butyl chromate in carbon tetrachloride containing acetic acid and acetic anhydride at 60~65°C[15], or with *t*-butyl hydroperoxide in the presence of chromium hexacarbonyl [$Cr(CO)_6$] in refluxing acetonitrile[16], or with pyridinium dichromate (PDC) at 100°C[17], or with excess sodium periodate and a catalytic amount of ruthenium trichloride and cetyltrimethylammonium bromide as the phase - transfer catalyst[18], resulted in the formation of a complex mixture of products: the oxidation of pregnen-20-one **19** with isolated chromium trioxide (CrO_3) - pyridine complex in dichloromethane at room temperture[19], or with a chromium trioxide - pyridine complex prepared *in situ* in refluxing dichloromethane in the presence of diphosphorus pentaoxide[20], or with *t*-butyl hydroperoxide and selenium dioxide in dichloromethane at 25°C[21], gave no oxidized product, and the starting material was recovered unchanged.

Finally, the treatment of masked 18-nor-5α-pregnen-20-one **19** with *p*-toluenesulphonic acid in dioxane by a standard method gave 12-deoxofukujusonorone, 3β-hydroxy-18-norpregna-5,13-dien-20-one **2** in 85% yield (Scheme 7).



(18) (19) 65%

(2)

Scheme 7

The foregoing transformation of normal steroids into 18-norsteroids involving the selective β-scission of alkoxyl radicals generated from lactols under almost neutral conditions is an additional example that selective radical fragmentation is as useful as is ionic fragmentations in organic synthesis.

Experimental Section

General Procedure

For the instruments used and the general procedure of the photolysis, see Experimental Section in Chapter 2.

6β-*Methoxy*-3α,5-*cyclo*-5α-*pregnan*-20-*one* **10**

3β-Hydroxypregn-5-en-20-one **3** (20.1 g, 63.5 mmol) and *p*-toluenesulphonyl chloride (30.1 g, 2.5 eq.) in pyridine (260 cm^3) were stirred for 24h at room temperature. The solution was then poured into iced water, and the crystals collected by filtration were dissolved in dichloromethane. The solution was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude tosylate which was dissolved in methanol (600 cm^3) containing potassium acetate (35 g). The solution was heated under reflux for 1h and the solvent was removed by evaporation. To the residue was added water; the reaction mixture was then extracted with diethyl ether. The ether layer was worked up in the usual way.

The product was recrystallized from methanol to give cyclosteroid **4** (16.8g, 80 %), m.p. 128~129°C. (Found. C, 79.70; H, 10.43. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.37); IR 1705 (C=O) and 1097 cm^{-1}; δ (90 MHz) 0.67 (3H, s, 18-H), 1.03 (3H, s, 19-H), 2.11 (3H, s, 21-H), 2.76 (1H, t, *J ca.* 3, 6α-H), 3.32 (3H, s, OMe); *m/z* 330 (M^+, 26), 315 [$(M\text{-}Me)^+$, 37], 298 [$(M\text{-}MeOH)^+$, 50], 275 (73), and 43 (100 %).

***6β-Methoxy-3α,5-cyclo-5α-pregnan-20α- and 20β-ols* 5 *and* 6 *by Reduction of Cyclosteroid* 4**

(a) With Sodium and Ethanol

To cyclosteroid **4** (3.53 g, 10.7 mmol) in refluxing ethanol (350 cm^3) was added sodium (17.85 g, 776.1 mmol). The solution was heated under reflux until all of the sodium was consumed. To this solution was added additional ethanol (50 cm^3) and sodium (10.15g, 441 mmol); the solution was heated under reflux until all of the added sodium had reacted. Evaporation of the solvent gave a product which was dissolved in diethyl ether. The ether solution was worked up in the usual way. The product was subjected to PLC [silica gel; benzene - diethyl ether (3:1)] to give two 20-ols, **5** and **6**.

The more mobile alcohol was 20β-ol **6** (1.04 g, 29 %), m.p. 72~73.5°C (from acetone) (lit. a glass). IR 3322 (OH) and 1101 cm^{-1}; δ (90 MHz) 0.81 (3H, s, 18-H), 1.03 (3H, s, 19-H), 1.13 (3H, d, *J* 6.2 , 21-H), 2.77 (1H, *J ca.* 3Hz, 6β-H), 3.22 (3H, s, OMe), and 3.71 (1H, m, 20α-H). The less mobile alcohol was 20α-ol **5** (2.05 g, 58 %), m.p. 99~102°C (from acetone) (lit. a glass). IR 3500 (OH), and 1093 cm^{-1}; δ (90 MHz) 0.72 (3H, s, 18-H), 1.02 (3H, s, 19-H), 1.22 (3H, d, *J* 6.2 Hz, 21-H), 2.77 (1H, t, *J ca.* 3, 6α-H), 3.32 (3H, s, OMe), and 3.71 (1H, m, 20β-H).

(b) With Sodium Borohydride

To cyclosteroid **4** (102 mg, 0.309 mol) in ethanol (20 ml) was added sodium borohydride (13 mg, 0.344 mmol). The solution was stirred at room temperature for 90h. Evaporation of the solvent gave a product which was dissolved in diethyl ether. The solution was worked up in the usual way. The product was

subjected to PLC [silica gel; benzene - diethyl ether (3:1)] to give a more mobile 20β-ol **5** (81 mg, 79 %) and a less mobile 20α-ol **6** (13 mg, 13 %).

18-*Hydroxyimino*-6β-*methoxy*-3α,5-*cyclo*-5α-*pregnan*-20α-*ol* 8 *by the Photolysis of Cyclosteroid*-20α-*ol Nitrite* 7

To a solution of 20α-ol **5** (258 mg, 0.777 mmol) in pyridine was added dropwise nitrosyl chloride in pyridine. The solution was stirred for 3 m at room temperature. The solution was then poured into water-ice, and the crystals collected by filtration were dissolved in diethyl ether. The solution was worked up in the usual way. Evaporation of the solvent gave nitrite **7**, which was dissolved in benzene (20 cm^3) and methanol (20 cm^3). The solution was irradiated with Pyrex-filtered light for 1h at room temperature. After the solvent was removed, the product was subjected to PLC [silica gel; hexane - ethyl acetate (1:1)] to give three products (**4**, **5**, and **8**) in order of their mobility on the TLC plate.

The most mobile product (26 mg, 10 %) was the parent ketone **4**. The next mobile product (11 mg, 4 %) was 20α-ol **5**. The most polar product **8** (178 mg, 63 %) was 18-hydroxyiminopregnan-20α-ol, m.p. 155~156°C (from hexane - dichloromethane). (Found. C, 73.13; H, 9.81; N, 3.78. $C_{22}H_{35}NO_3$ requires C, 73.09; H, 9.76; N, 3.87). IR 3330 and 3200 (OH), 1099, and 930 cm^{-1}; δ (270 MHz), 1.00 (3H, s, 19-H), 1.20 (3H, d, *J* 2.57 , 6β-H), 3.32 (3H, s, OMe), 4.03 (1H, m, 20β-H), and 7.56 (1H, s, -

CH=NOH); *m/z* 363 [$(M+H_2)$,$^+$ 1.4], 361 (M^+, 1.8), 344 [$(M-OH)^+$, 100], 329 [$(M-MeOH)^+$, 59], and 312 [$(M-OH-MeOH)^+$, 52 %].

***The Photoreaction of Cyclosteroid-20β-ol Nitrite* 10**

To a solution of 20β-ol **12** (240 mg, 0.723 mmol) in pyridine (3 cm^3) was added dropwise nitrosyl chloride in pyridine. The solution was stirred for 10 m at room temperature. The solution was then worked up as in the case of nitrite **7** to give nitrite **10**, which was dissolved in dry benzene (18 cm^3) and methanol (18 cm^3). The photolysis was carried out using a procedure similar to that for nitrite **7**, to give three products: **4** (21 mg, 9 %), **6** (50 mg, 21 %) and 18-hydroxyiminopregnan-20β-ol **11** (31 mg, 12 %), (Found: M^+ 361.2624. $C_{22}H_{35}NO_3$ requires *M*, 361.2617); IR 3310 (OH) cm^{-1}; δ (270 MHz) 0.95 (3H, s, 19-H), 1.14 (3H, d, *J* 6, 21-H) 2.80 (1H, t, *J* 3, 6α-H), 3.34 (3H, s, 6β-OMe), 3.60 (1H, m, 20α-H) 7.52 (1H, s, CH=NOH); *m/z* 361(M^+, 5.9), 344 [$(M-OH)^+$, 100], 329[$(M-OH-Me)^+$, 312 (56), and 306 (66).

6β-*Methoxy*-18,20α-*epoxy*-3α,5-*cyclo*-5α-*pregnan*-18-*ols* 11 *by Hydrolysis of Oxime* 8 *with Sodium Nitrite - Acetic Acid*

To a solution of 18-Hydroxyiminopregnan-20α-ol **8** (566 mg, 1.57 mmol) in THF (16 cm^3) and acetic acid (0.6 cm^3) was added sodium nitrite (1.88 g, 27.25 mmol) in water (10 cm^3). The solution was stirred for 22h at room temperature and poured into water-ice. The crystals collected by filtration were dissolved in diethyl ether. The solution was worked up in the usual way.

Removing the solvent gave a product which was purified by PLC [silica gel; hexane - ethyl acetate (2:1)] to give lactol **11** (408 mg, 75 %), m.p. 148~150°C (from acetone). (Found. C, 76.12; H, 9.94. $C_{22}H_{34}O_2$ requires C, 76.26; H, 9.89). IR 3392 (OH), 1108, 1092, 1060, and 1024 cm^{-1}; δ (270 MHz) 1.00 and 1.02 (each s, 19-H), 1.21 (d, *J* 6.23, 21-H), 2.81 (t, *J* 2.93, 6β-H), 3.34 (s, OMe), 4.3~4.5 (m, 20β-H), 5.10 and 5.15 (each d, *J* 5.23, and 3.29, 18-H). *m/z* 348 [$(M+H_2)^+$, 0.3], 347 [$(M+H)^+$, 1.7], 346 (M^+, 6.3), 331 [$(M-Me)^+$, 33.1], 314 [$(M-MeOH)^+$, 65.8], 291 (62.6), 268 (80.4), and 147 (100 %).

β-Scission of Alkoxyl Radical generated from the Photolysis of Hypoiodite of Lactol 11

(a) In Benzene

To lactol (287 mg, 0.829 mmol) in benzene (40 cm^3) were added mercury(II) oxide (359 mg, 1.66 mmol) and iodine (421 mg, 1.66 mmol). The solution was flushed with nitrogen and irradiated with a Pyrex-filtered light for 7h at room temperature. The solution was filtered, and the organic layer of the filtrate was washed with a 5% sodium thiosulphate solution, water, and brine successively, and dried over anhydrous sodium sulphate.

Removing the solvent gave a product which was subjected to PLC [silica gel; hexane - ethyl acetate (3:1)], resulting in two fractions, (A and B). The more mobile fraction (A) was a mixture of the products. The less mobile fraction (B) was 6β-methoxy-3α,5-cyclo-18-nor-5α-pregn-13-en-20α-ol formate **12** as a glass (138 mg, 48 %). (Found: M^+, 344.2357. $C_{22}H_{32}O_3$ requires *M*, 344.2352). IR (neat) 1719 (C=O), 1193, and 1096 cm^{-1}; δ (270 MHz) 1.02 (3H, s,

19-H), 1.33 (3H, d, *J* 6.2 , 21-H), 2.78 (1H, t, *J* 2.6 , 6α-H), 3.32 (3H, s, OMe), 5.28 (1H, m, 20β-H), and 8.04 (1H, s, OCHO). *m/z* 344 (M^+, 22), 307 (40), 298 [$(M-HCOOH)^+$, 10], 284 (18), 266 (14), 248 (16), and 216 (100%).

Fraction A (37 mg) was hydrolyzed with potassium hydroxide (5 %) in methanol (5 cm^3) while stirring at room temperature for 1h. After the solvent was evaporated, the residue was dissolved in diethyl ether. The solution was washed with dilute hydrochloric acid, water, and brine, successively, and dried over anhydrous sodium sulphate. The product was again subjected to PLC [silica gel; hexane - ethyl acetate (2:1)] to give two fractions (A_1 an A_2). The less mobile fraction (A_2) was 6β-methoxy-3α,5-cyclo-5α-pregn-13(17)-en-20α-ol **15** (7 mg, 3 %) as a glass. (Found: M^+, 316.2415. $C_{21}H_{32}O_2$ requires *M*, 316.2402); (neat) 3390 (OH) and 1090 cm^{-1}; δ (270 MHz) 0.96 (3H, s, 19-H), 1.24 (3H, d, *J* 6.6, 21-H), 2.79 (1H, t, *J ca.* 3, 6α-H), 3.31 (3H, s, 6β-OMe) and 4.70 (1H, q, *J* 6.6 , 20β-H).

The more mobile fraction was an isomeric 20α-ol **22** as a glass (12 mg, 5 %), tentatively assigned as 8(14)-ene. (Found: M^+, 316.2421. $C_{21}H_{32}O_2$ requires *M*, 316.2402). IR 3412 (OH) and 1096 cm^{-1}; δ (270 MHz) 1.01 (3H, s, 19-H), 1.16 (3H, d, *J ca.* 3, 6α-H), 3.34 (3H, s, 6β-OMe), and 4.05 (1H, dq, *J* 6.2 and 2.2, 20β-H). *m/z* 316 (M^+, 0.25), 298 [$(M-H_2O)^+$, 1.02], 284 [$(M-MeOH)^+$, 20], 266 [$(M-H_2O-MeOH)^+$, 8] and 239 (100 %).

(b) In Benzene Containing Pyridine

To a solution of lactol **11** (102 mg, 0.295 mmol) in benzene (16 cm^3) and pyridine (0.06 cm^3, 0.743 mmol, 2.52 equiv.), were added mercury(II) oxide (135 mg, 0.623 mmol) and iodine (160

mg, 0.630 mmol). The solution was flushed with nitrogen and irradiated with a Pyrex-filtered light for 4h at room temperature. The solution was worked up in the same way, as mentioned above. The product was subjected to PLC [silica gel; hexane - ethyl acetate (3:1)], giving three fractions (A, B, and C).

Fraction A (27 mg) was a mixture of the products. Fraction B (25 mg, 25 %) was lactone **17**, m.p. 164~165°C (from acetone). (Found: C, 76.73; H, 9.35. $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36). IR 1753 (C=O), 1269, 1171, 1123, and 1086 cm^{-1}; δ (270MHz) 1.09 (3H, s, 19-H), 1.36 (3H, d, *J* 6.6, 21-H), 2.78 (1H, t, *J* 2.9, 6α-H), 3.31 (3H, s, OMe), and 4.66 (1H, dq, *J* 4.8 and 6.6, 20β-H). *m/z* 344 (M^+, 39), 329 [$(M-Me)^+$, 55], 312 [$(M-MeOH)^+$, 82], 289 (100), 105 (38), and 91 (47 %). Fraction C was formate **12** (33 mg, 33 %).

Fraction A was subjected to hydrolysis; to a solution of fraction A (33 mg) in methanol (3.2 cm^3) was added potassium carbonate (20 mg, 0.15 mmol) in water (1cm^3). The solution was stirred for 1 and a half hours at room temperature. After the solvent was evaporated, the product was extracted with diethyl ether. The ether solution was worked up in the usual way to give a mixture of products. The mixture was subjected to PLC [silica gel; hexane - ethyl acetate (3:1)], resulting in two products. The more mobile product (13 mg, 14 %) was identified as being compound **15**. The less mobile product (9 mg, 10 %) was identical with product **16**.

6β-*Methoxy*-3α,5-*cyclo*-5α-*pregn*-13-*en*-20α-*ol* **18** *by Hydrolysis of* 18-*Norpregn*-13-*en*-20α-*ol Formate* **12**

Formate **12** (138 mg, 0.401 mmol) was dissolved in methanol containing 5% potassium hydroxide. The solution was stirred for 2h at room temperature. After removing the solvent, the residue was dissolved in diethyl ether. The solution was then washed with a dilute hydrochloric acid, water, and brine, successively, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude 20α-ol **18**, which was subjected to PLC [silica gel; hexane - ethyl acetate (2:1)] to give pure 20α-ol **18** (108 mg, 85 %) as a glass. (Found: M^+, 316.2402): IR (neat) 3376 (OH), and 1098 cm^{-1}; δ (270 MHz) 1.03 (3H, s, 19-H), 1.14 (3H, d, *J* 6.6, 21-H), 2.79 (1H, t, *J ca.* 3, 6α-H), 3.32 (3H, s, OMe), and 4.28 (1H, dq, *J* 6.6 and 1.47, 20β-H); *m/z* 316 (M^+, 30), 284 [$(M-MeOH)^+$, 22], 279 (31), and 216 (100 %).

6β-*Methoxy*-3α,5-*cyclo*-5α-*pregn*-13-*en*-20-*one* **19** *by Oxidation of* 18-*Norpregn*-13-*en*-20α-*ol* **18**

To a solution of 20α-ol **24** (218 mg, 0.690 mmol) in dichloromethane (5 cm^3) was added PCC (148 mg, 0.688 mmol) in dichloromethane (8 cm^3). The solution was stirred for 17h at room temperature. After the addition of diethyl ether to the solution, the mixture was filtered. The filtrate was worked up in the usual way to give a crude ketone **19** (141 mg, 65 %), m.p. 105~106°C (from acetone - water). (Found: M^+, 314.2260. $C_{21}H_{30}O_2$ requires *M*, 314.2246). IR 1690 (C=O), and 1099 cm^{-1}; δ (270 MHz) 1.04 (3H, s, 19-H), 2.17 (3H, s, 21-H), 2.65 (1H, t, *J* 9.9 , 17α-H), 2.76 (1H, t, *J* 2.6 , 6α-H), 3.12 (1H, d, *J* 1.1), and 3.29 (3H, s, OMe). *m/z*

314 (M^+, 30), 300 (13), 282 [(M-MeOH)$^+$, 14], 277 (37), and 43 (100 %).

3β-*Hydroxy*-18-*norpregna*-5,13-*dien*-20-*one* 2 (*12-Deoxofukujusonorone*)

To a solution of the masked 18-norsteroid **19** (68 mg, 0.22 mmol) in dioxane (4 cm^3), was added *p*-toluenesulphonic acid (8 mg, 0.042 mmol) in water (3 cm^3). The solution was heated at 80°C for 1h, and then poured into water-ice (10 cm^3). The mixture was extracted with diethyl ether three times. The combined extracts were worked up in the usual way to give a crude 12-deoxofukujusonorone. It was purified by PLC [silica gel; hexane - ethyl acetate (1:1)] to give a pure 12-deoxofukujusonorone **2**, (55 mg, 85%), m.p. 130~131°C. (from hexane - dichloromethane). (Found: M^+, 300.2073. $C_{20}H_{28}O_2$ requires *M*, 300.2089). IR (KBr) 3300 (OH), 1682 (C=O), 1182, 1054, and 843 cm^{-1}; δ (270 MHz) 1.02 (3H, s, 19-H), 2.17 (3H, s, 21-H), 2.64 (1H, t, *J ca.* 10, 17α-H), 3.46~3.58 (1H, m, 3α-H), and 5.34 (1H, d, *J* 5, 6-H); *m/z* 300 (M^+, 57), 285 [(M-Me)$^+$, 21], 257 [(M-CH_3CO)$^+$, 31], 239 [(M-MeCO-H_2O)$^+$, 40], 84 (88), and 43 (100 %).

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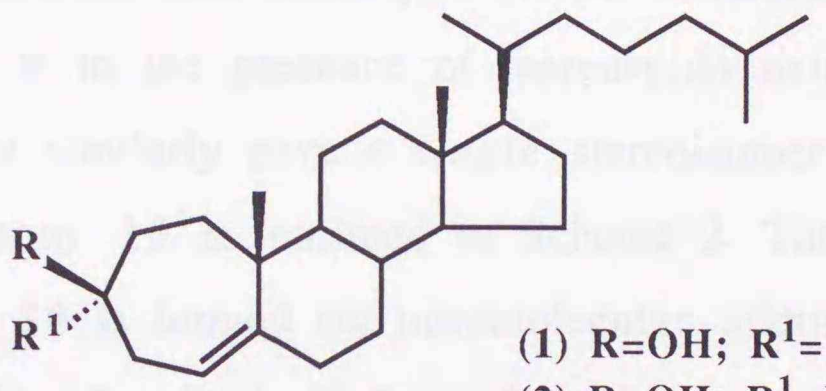
CHAPTER 4

AN EFFICIENT FORMATION OF SPIROTETRAHYDROFURAN RINGS BY IONIC CYCLIZATION OF UNSATURATED ALCOHOL *VIA* HYPOIODITES

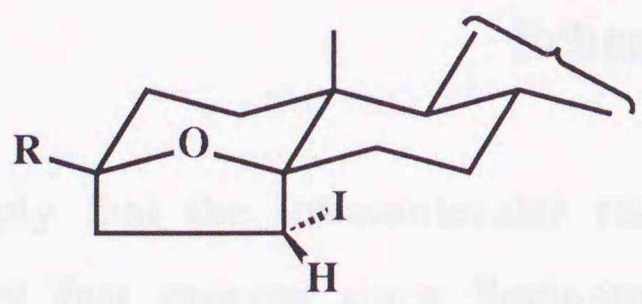
4-1 Introduction

It has been reported that an intramolecular addition of the alkoxyl species takes place in preference to β-scission which leads to secosteroids in some cases[1,2]. For example, the photoinduced reactions of the hypoiodites of cyclic homoallyl alcohols **1-4** such as *A*-homocholest-4a-en-3-ols[1] prepared *in situ* with mercury(II) oxide and iodine in benzene gave cyclic ethers **5–8**, almost exclusively (as outlined in Scheme 1).



(1) R=OH; R^1=H
(2) R=OH; R^1=Me
(3) R=H; R^1=OH
(4) R=Me; R^1=OH

i) HgO-I_2-benzene
ii) hν



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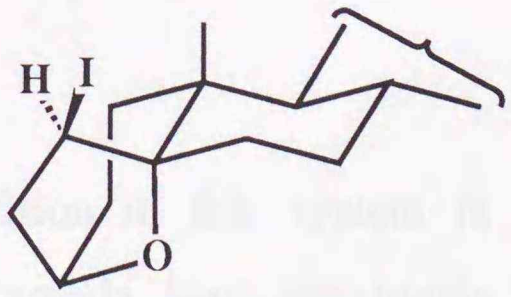


(5) R=H
(7) R=Me

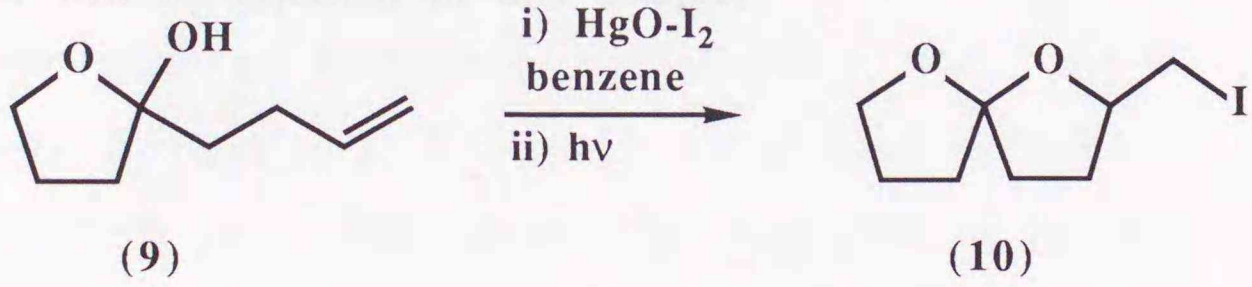
(6) R=H
(8) R=Me

Scheme 1

The exclusive formation of tetrahydrofuran derivatives was also reported in the photolysis of hypoiodites generated from *B*-homocholest-5-en-7a-ols[3], and simple six-membered cyclic alcohols, *viz.* cyclohex-3-enols[4].

The formation of these tetrahydrofurane derivatives was interpreted by Suginome and colleagues as arising *via* an intramolecular addition of the alkoxyl radicals.

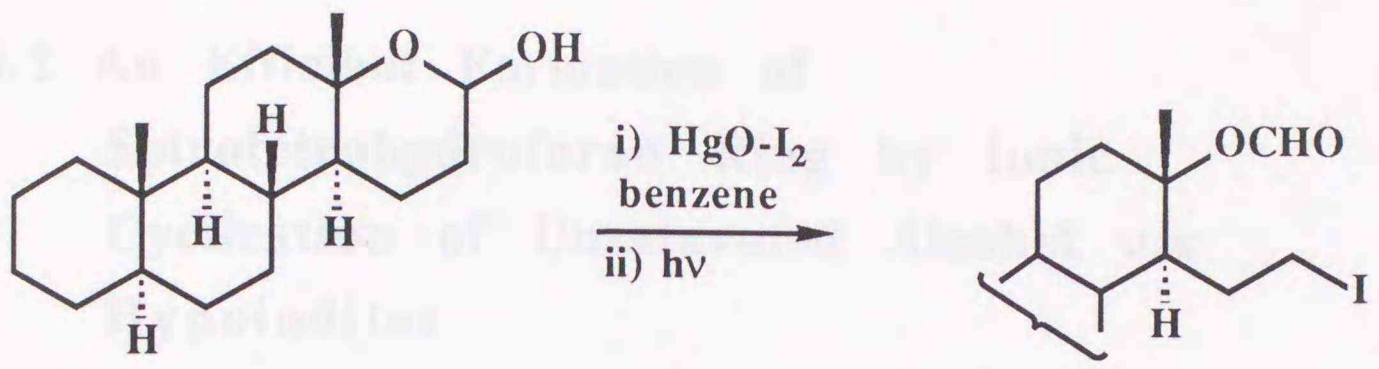
In connection with these studies on the intramolecular addition *vs.* β-scission of alkoxyl species, American investigators[5] have recently reported that photolysis of an unsaturated alcohol (4-en-1-ol type) **9** in the presence of mercury(II) oxide and iodine in benzene similarly gave a *single* stereoisomer of spirotetrahydrofuran **10** as outlined in Scheme 2. They claimed that cyclic ether **10** is formed *via* intramolecular addition of the corresponding alkoxyl radical. If their claim is correct, it would



(9) **(10)**

Scheme 2

imply that the intramolecular radical addition in this system is a very fast process since Suginome and Yamada have previously found that photolysis of the hypoiodites of similar lactols such as **11** in benzene resulted in a readly β-scission to give iodo-formate **12** as outlined in Scheme 3[6].



(11) (12)

Scheme 3

The author, therefore, decided to confirm whether the formation of spirotetrahydrofurans in preference to the β-scission is general in alkoxyl radicals by using a model system where the β-scission of alkoxyl radicals is assumed to be especially facile.

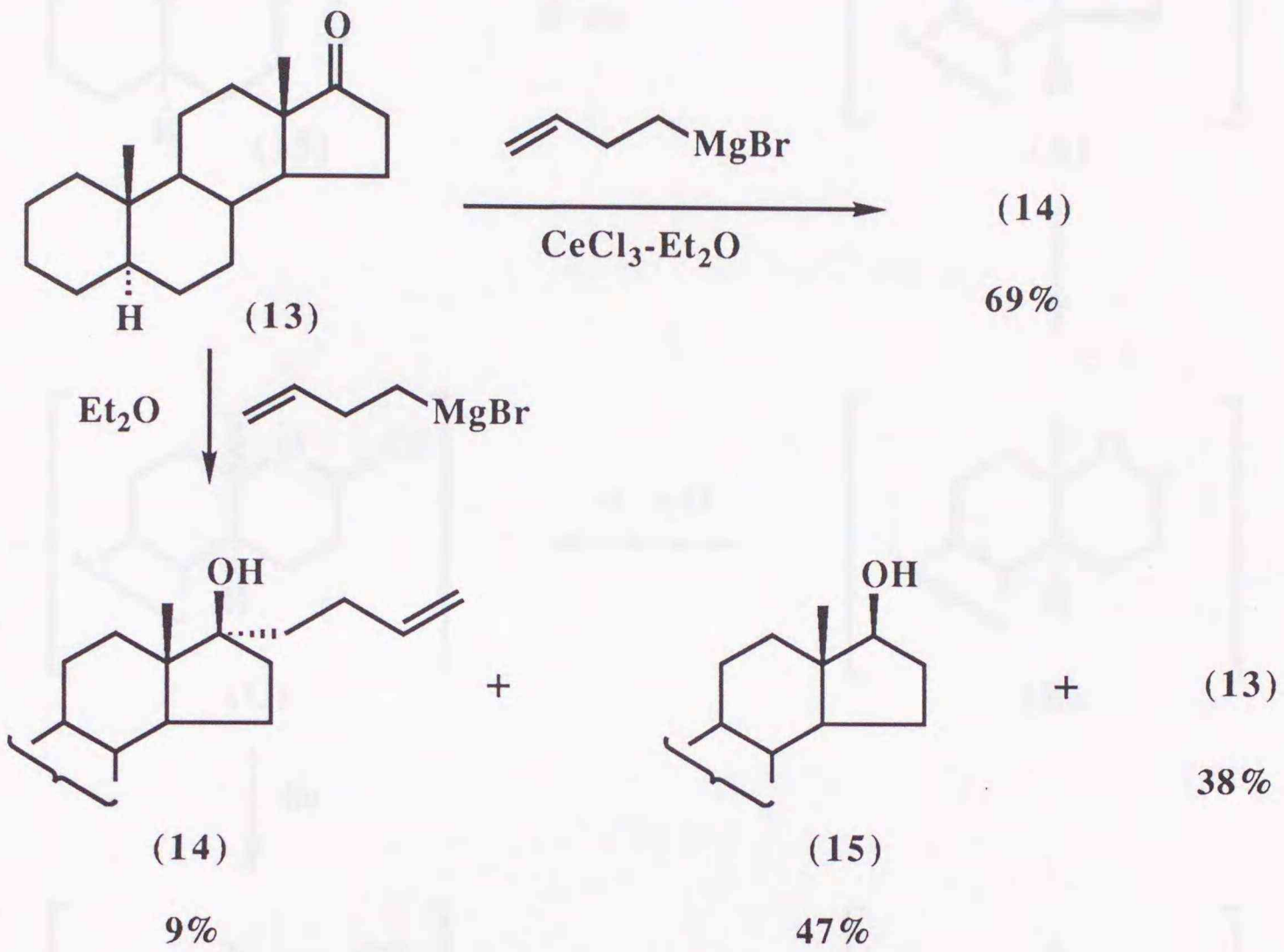
It was found that spirotetrahydrofuran derivatives are in fact formed from the model olefinic alcohol (4-en-1-ol type) hypoiodite under the standard photolysis conditions but also in the dark. They are formed *via* an ionic process and not *via* an intramolecular addition of the alkoxyl radical as was claimed[5]. The results will be reported in this Chapter.

4-2 An Efficient Formation of Spirotetrahydrofuran Ring by Ionic Cyclization of Unsaturated Alcohol *via* Hypoiodites

The author has chosen 17α-(3-butenyl)-5α-androstan-17β-ol **14** for examining the intramolecular addition *vs.* β-scission since the photoinduced reaction of the hypoiodite of the parent 5α-androstan-17β-ol **15** has been known to result readily in β-scission. Thus, Suginome and colleagues have reported that irradiation of the hypoiodite of 5α-androstan-17β-ol **15** in the presence of mercury(II) oxide and iodine in benzene resulted in an exclusive β-cleavage of the corresponding alkoxyl radical to give a carbon centred radical **A** which gave an iodo-formate **16** through intermediates **B**, **C**, **D**, and **E** (as outlined in Scheme 5)[7].

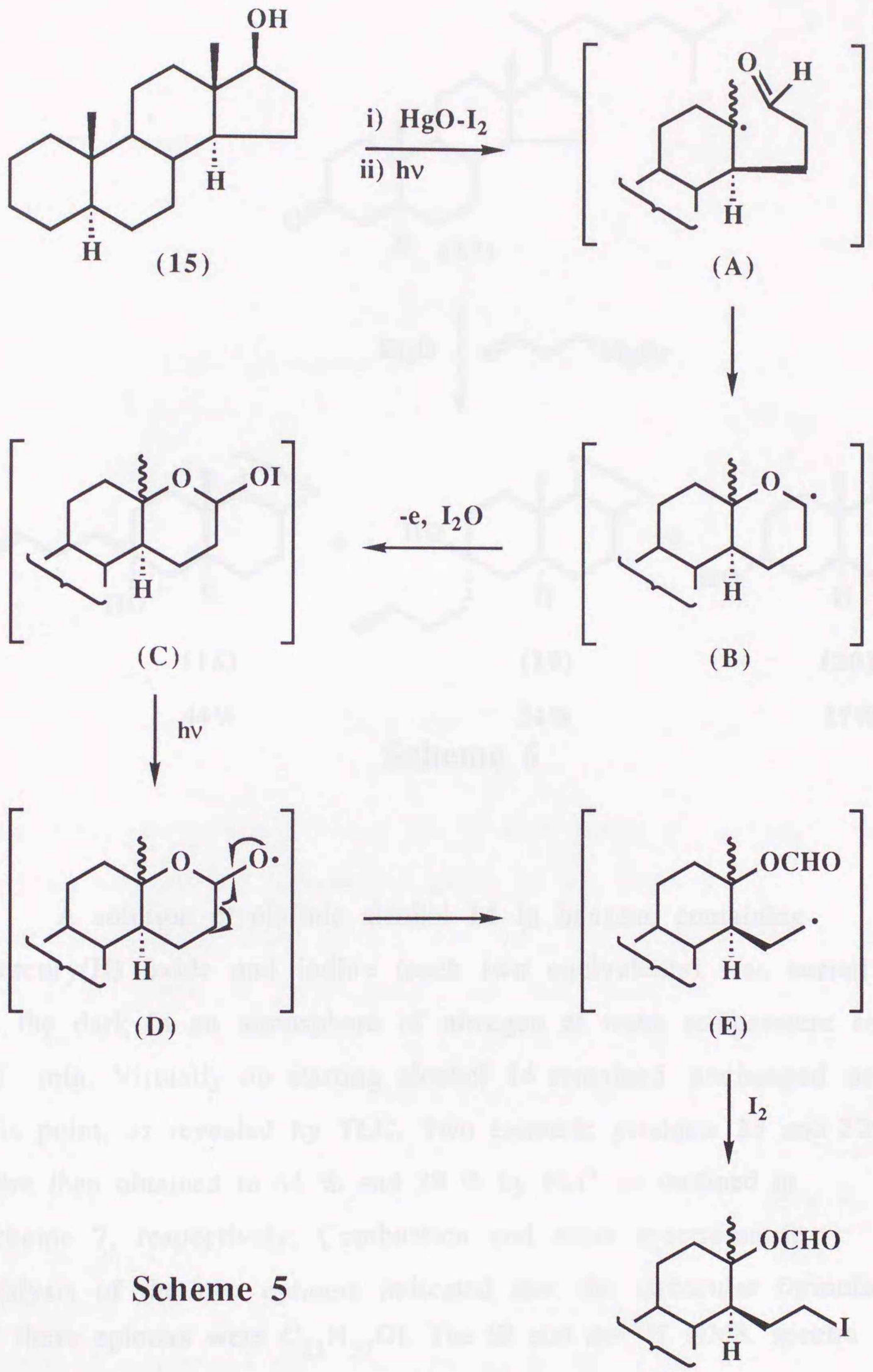
The reaction of 5α-androstan-17-one **13** with 3-butenylmagnesium bromide in diethyl ether gave 17α-(3-butenyl)-5α-androstan-17β-ol **14** and 5α-androstan-17β-ol **15** in 9% and 47% yields, respectively. The poor yield of olefinic alcohol **14** in this Grignard reaction was improved to 69% without the formation of byproduct **15** by executing the reaction in the presence of cerium trichloride[8]. The assigned stereochemistry is based solely on a consideration of the reaction stereochemistry.

3β- And 3α-(3-butenyl)-5α-cholestan-3-ols **18** and **19** were similarly prepared by the reaction of 5α-cholestan-3-one **17** with 3-butenylmagnesium bromide in 44 and 22% yields although these olefinic alcohols **18** and **19** are not proper models for study of β-scission *vs.* addition since the alkoxyl radical generated from the parent alcohol **20** is known to be unsusceptible to β-scission[7].

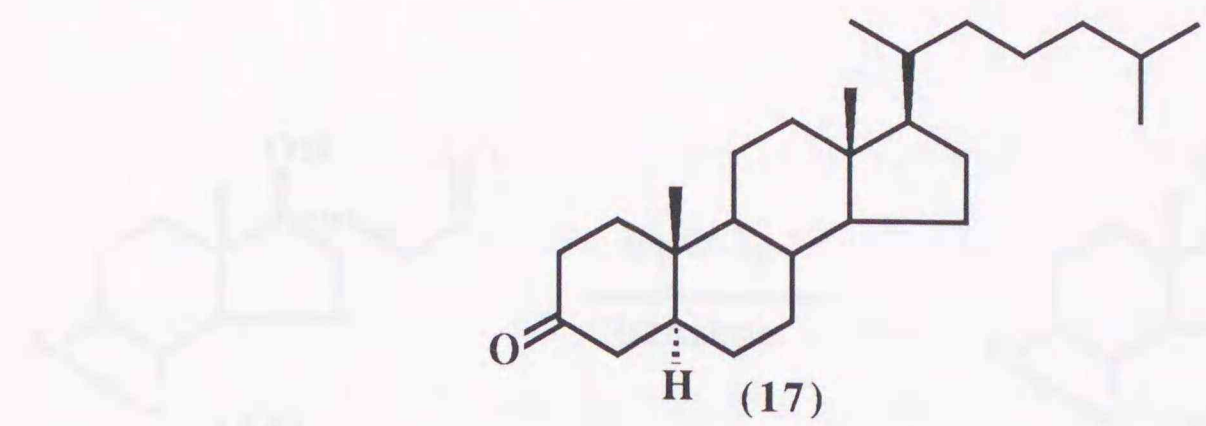


Scheme 4

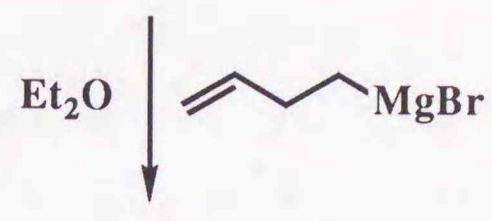
It was unable to assign the configurations of the butenyl groups of olefinic alcohols **18** and **19** by spectroscopy. The stereochemistry at C-3 of the epimeric alcohols **18** and **19**, however, was assignable on the basis of their polarity difference. Thus, a more mobile epimer **18** on TLC plate should have an axial hydroxyl group (as outlined in Scheme 6)[9].

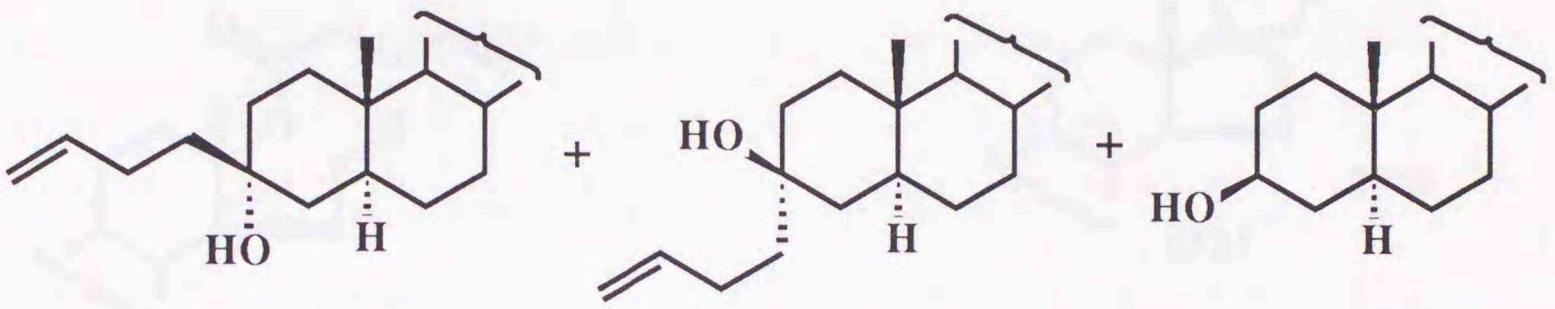

OH
H
H
(15)
i) HgO-I2
ii) hν
O
H
H
(A)
O
OI
H
(C)
-e, I2O
O
H
(B)
hν
O
O•
H
(D)
OCHO
H
(E)
I2
OCHO
I
H
(16)

Scheme 5



(17)



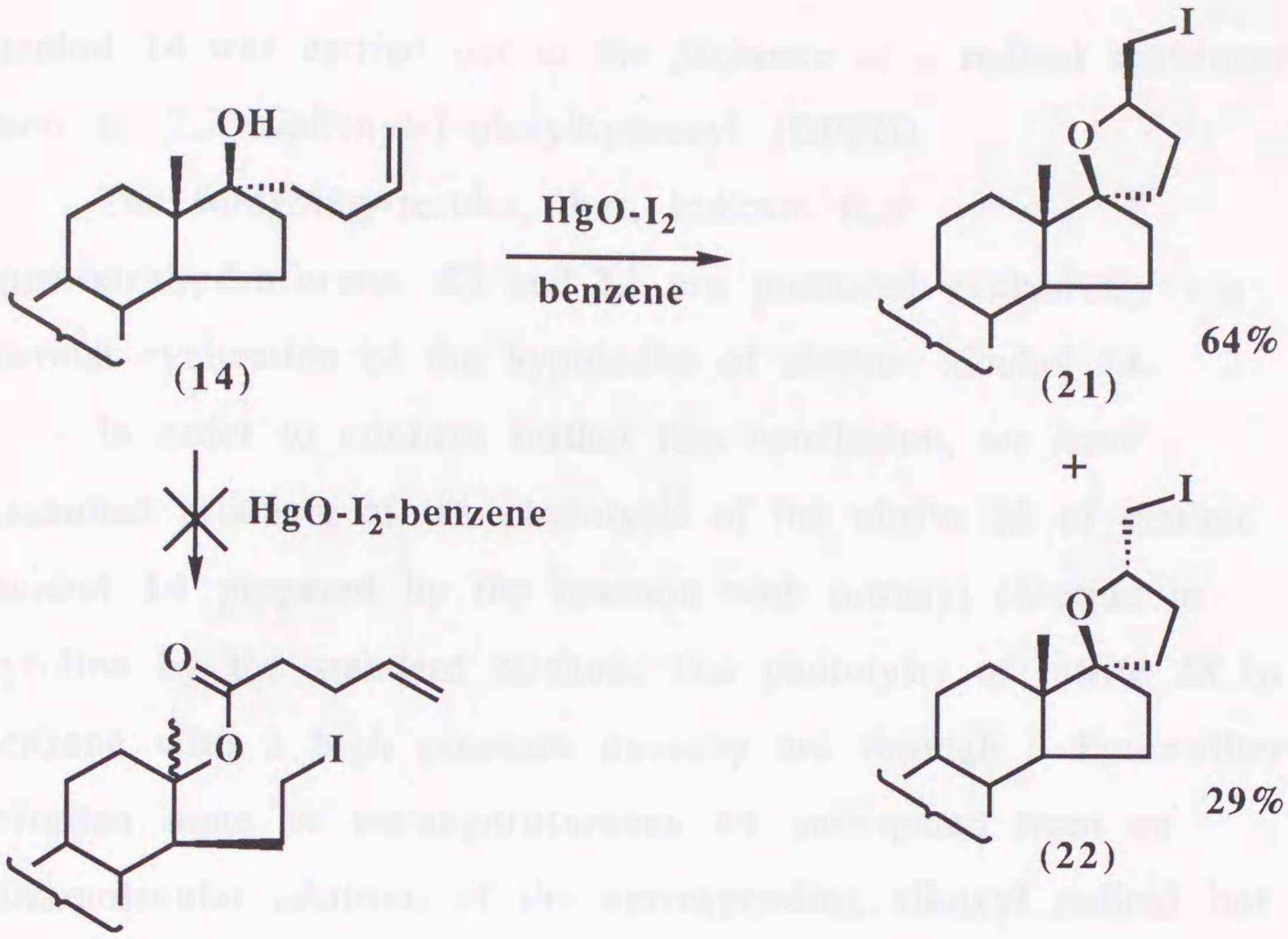


(18) (19) (20)

44% 24% 17%

Scheme 6

A solution of olefinic alcohol **14** in benzene containing mercury(II) oxide and iodine (each two equivalents) was stirred in the dark in an atmosphere of nitrogen at room temperature for 15 min. Virtually no starting alcohol **14** remained unchanged at this point, as revealed by TLC. Two isomeric products **21** and **22** were then obtained in 64 % and 29 % by PLC, as outlined in Scheme 7, respectively. Combustion and mass spectrometric analysis of the two epimers indicated that the molecular formula of these epimers were $C_{23}H_{37}OI$. The IR and the ^1H NMR spectra (see Experimental) in conjunction with the pathways of the formation of the product indicated that the epimers were



Scheme 7

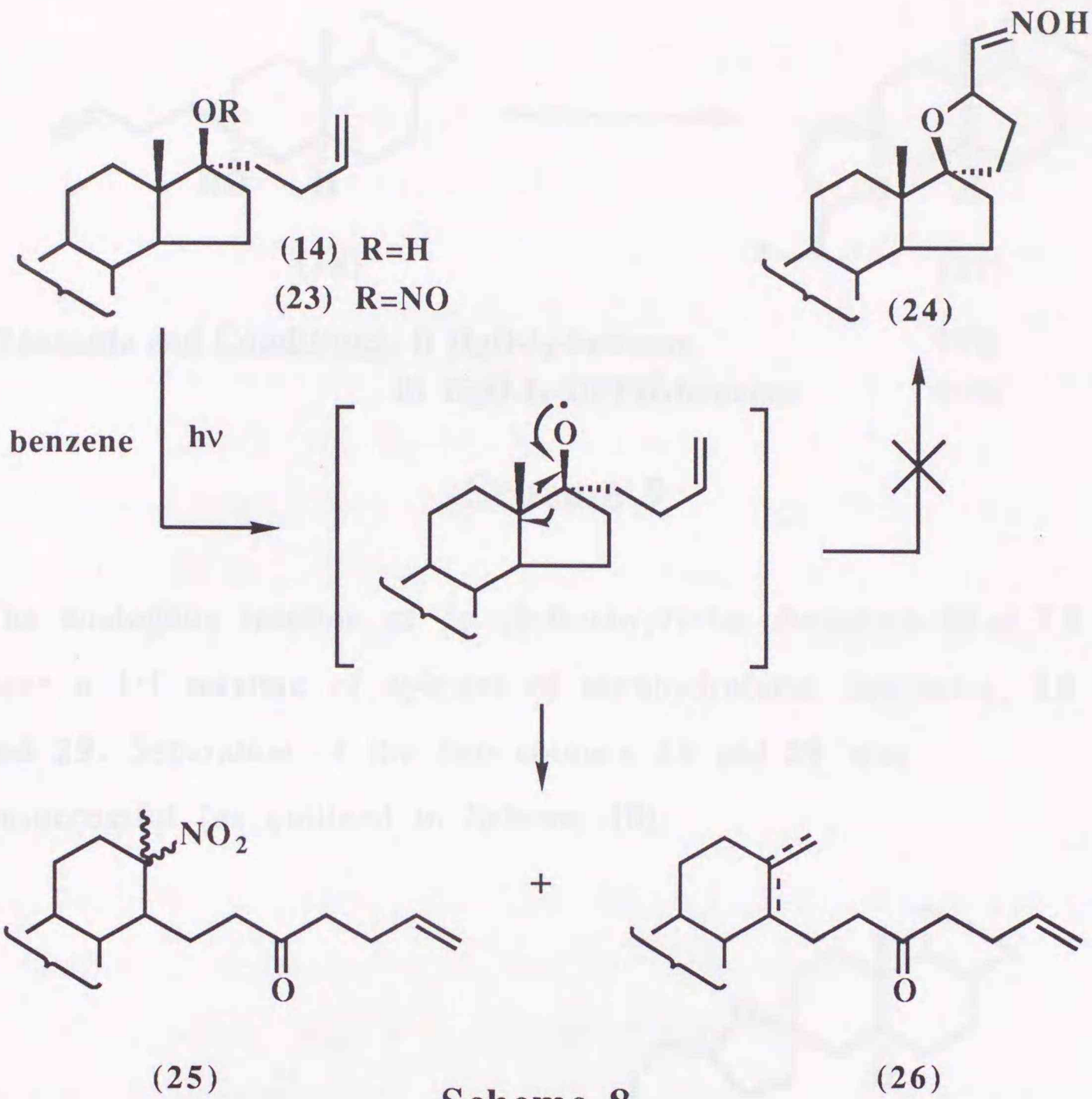
spirotetrahydrofurans **21** and **22**. It was unable to determine the configuration of the iodomethyl group of the epimers unambiguously by their spectral analysis. The configuration of the iodomethyl group of major epimer **21** was, however, tentatively assigned to be β on the basis of a consideration of the reaction stereochemistry. It was confirmed that hypoiodite of 17β-hydroxy-5α-androstane in benzene containing mercury(II) oxide and iodine was thermally stable and no products arising from β-scission were obtained when the solution was stirred at room temperature for 15 min in the dark. The starting 17β-ol was recovered unchanged after the work-up in the usual way. The spirotetrahydrofuran derivatives **21** and **22** were obtained in high yields even when the reaction of the hypoiodite of olefinic

alcohol **14** was carried out in the presence of a radical scavenger such as 2,2'-diphenyl-1-picrylhydrazyl (DPPH).

The foregoing results, thus, indicate that spirotetrahydrofurans **21** and **22** are produced exclusively *via* thermal cyclization of the hypoiodite of olefinic alcohol **14**.

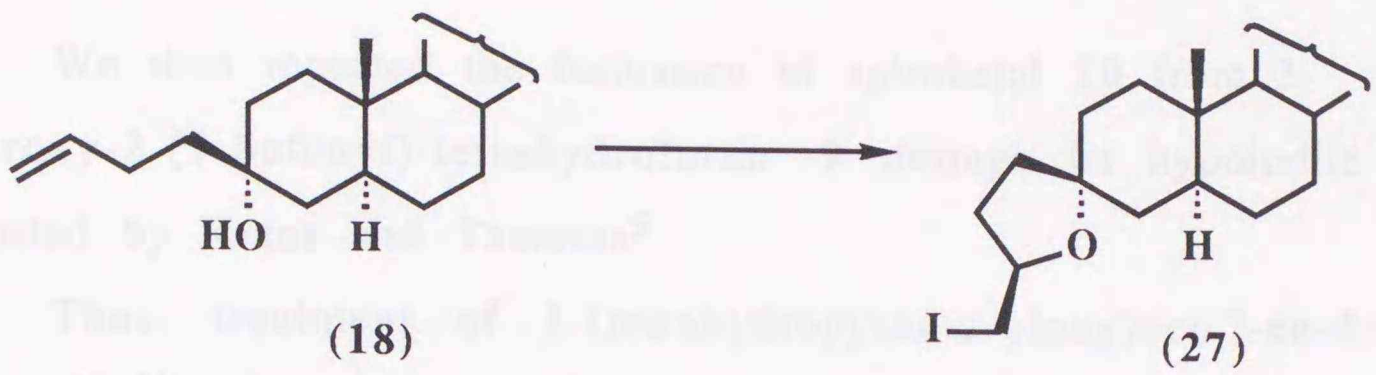
In order to confirm further this conclusion, we have examined products of the photolysis of the nitrite **23** of olefinic alcohol **14** prepared by the reaction with nitrosyl chloride in pyridine by the standard method. The photolysis of nitrite **23** in benzene with a high pressure mercury arc through a Pyrex-filter afforded none of tetrahydrofuranes **24** anticipated from an intramolecular addition of the corresponding alkoxyl radical but afforded a mixture of ill-defined products from which a mixture of products **25** and **26** arising from β-scission were isolated in poor yields as outlined in Scheme 8. The results indicate that a β-scission takes place in preference to an intramolecular addition from the alkoxyl radical generated from olefinic alcohol **14**.

It is of interest to note that the cyclization to spirotetrahydrofurans **21** and **22** takes place even under the standard photolytic conditions of hypoiodites. In view of the above-mentioned failure of the cyclization of the alkoxyl radical generated from the nitrite **23**, the formation of the spirotetrahydrofurans **21** and **22** under the photolytic conditions is considered to take place by an ionic process and not a radical process.



Scheme 8

Similar reaction of 3β-(3-butenyl)-5α-cholestan-3-α-ol **18** in benzene containing mercury(II) oxide and iodine under the same conditions as those for olefinic alcohol **14** in the dark gave the corresponding crystalline spirotetrahydrofuran derivative **27** in 93 % yield as a single product. The assigned β-configuration of the iodomethyl group attached to the tetrahydrofuran ring is based on merely a steric consideration and is not unambiguous as outlined in Scheme 9.



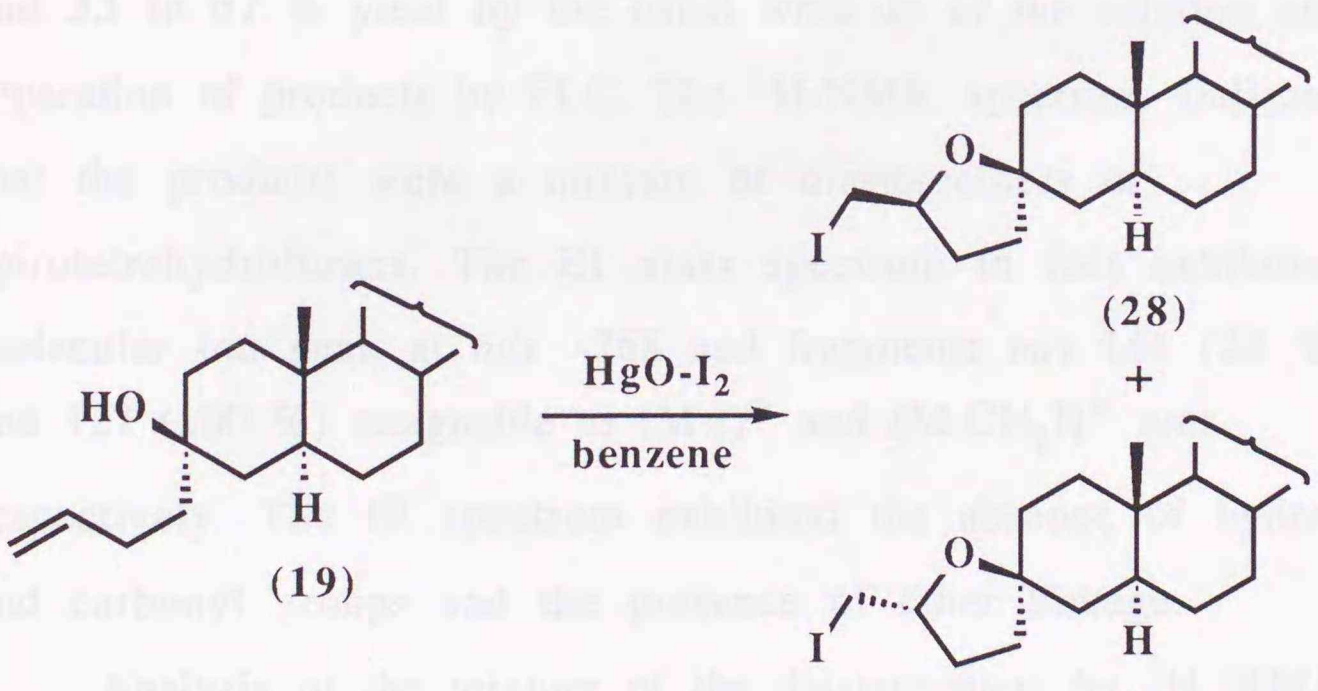
(18) (27)

<u>Reagents and Conditions</u>; i) $HgO\text{-}I_2$-benzene, 93%

ii) $HgO\text{-}I_2$-DPPH-benzene 93%

Scheme 9

The analogous reaction of 3α-(3-butenyl)-5α-cholestan-3β-ol **19** gave a 1:1 mixture of epimers of tetrahydrofuran derivative, **28** and **29**. Separation of the two epimers **28** and **29** was unsuccessful (as outlined in Scheme 10).



Scheme 10

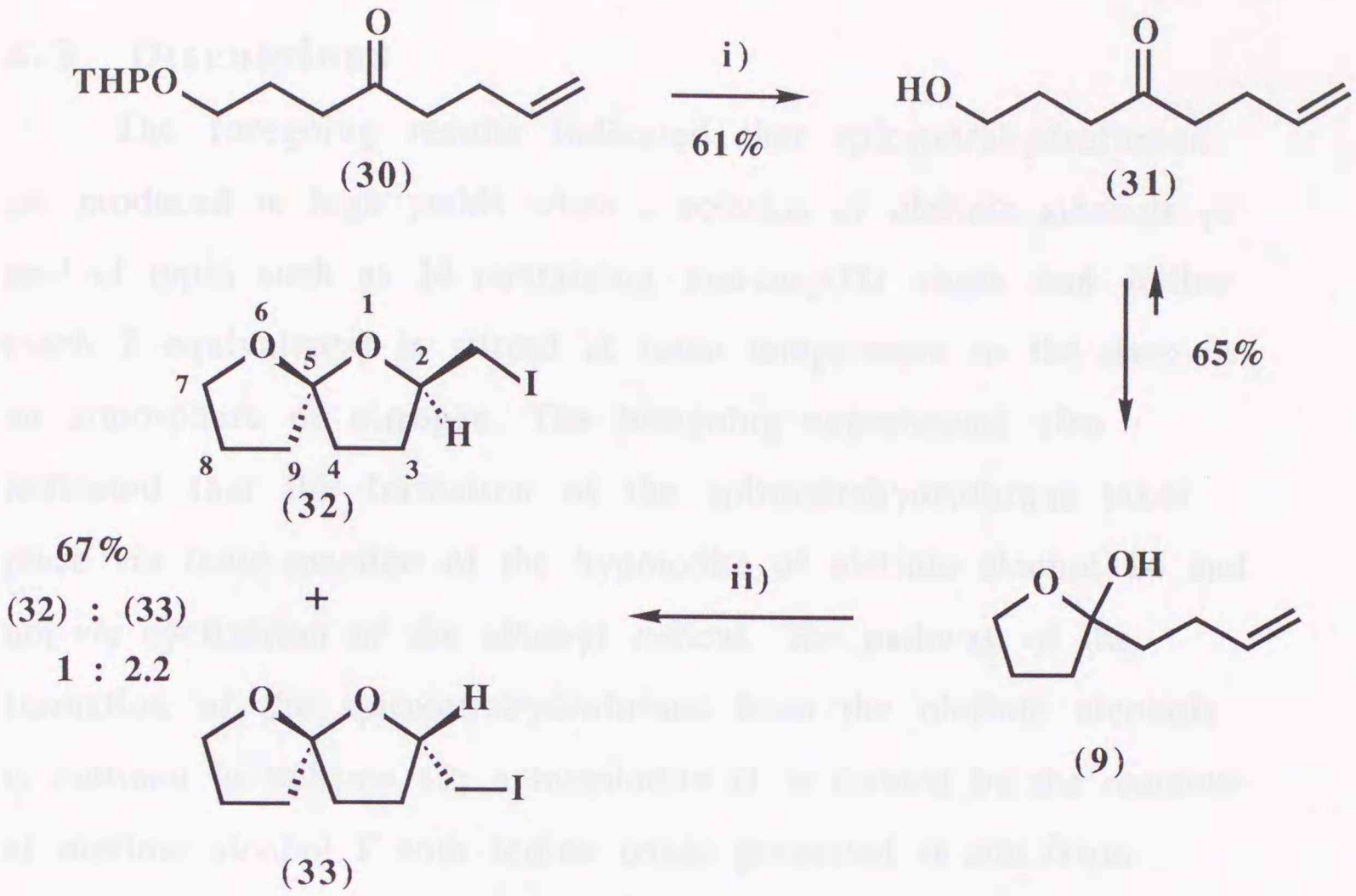
94% 1:1 mixture

We then repeated the formation of spiroketal **10** from 2-hydroxy-2-(3-butenyl)-tetrahydrofuran **9** through its hypoiodite reported by Kraus and Thurston[5].

Thus, treatment of 1-(tetrahydropyran-2-yloxy)oct-7-en-4-one **30**[10, 11] with *p*-toluenesulphonic acid in a mixed solvent of methanol and water at 50°C for 1h gave the corresponding alcohol **31** in 61 % yield. This alcohol **31** was set aside for 5 days at room temperature and column chromatography through Florisil gave lactol **9** in 65 % as a thick liquid (as outlined in Scheme 11).

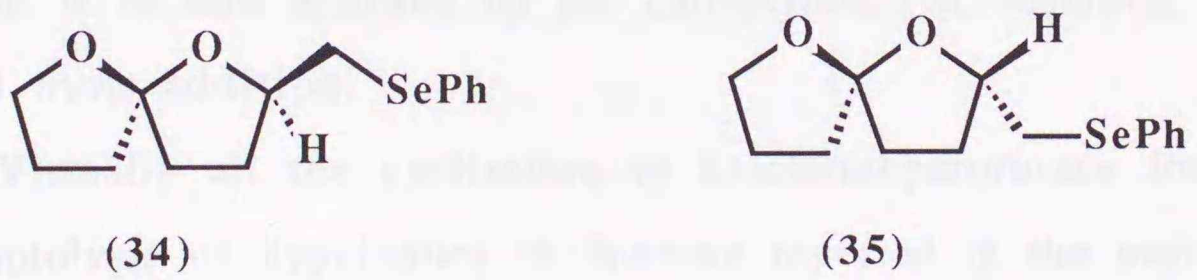
To a solution of lactol **9** in benzene in a vessel covered by an aluminium foil was added mercury(II) oxide and iodine (each 2 equiv.). The solution was stirred for 1h 45 min at room temperature in the dark to give a 1:2 mixture of two products **32** and **33** in 67 % yield by the usual work-up of the solution and the separation of products by PLC. The ^{1}H-NMR spectrum indicated that the products were a mixture of diastereomers of spirotetrahydrofurans. The EI mass spectrum in fact exhibited the molecular ion peak at *m/z* 268 and fragments *m/z* 141 (23 %) and 127 (100 %) assignable to $(M\text{-}I)^+$ and $(M\text{-}CH_2I)^+$ ions, respectively. The IR spectrum exhibited the absence of hydroxyl and carbonyl groups and the presence of ether linkage.

Analysis of the mixture of the diastereomers by ^{1}H-NMR (400 MHz) by comparing the spectrum with those of diastereomers of closely related spirotetrahydrofurans **34**[11] and **35**[11] aided with double reasonance technique enabled to determine it to be a 1:2 mixture of *cis* and *trans* spirotetrahydrofurans **32** and **33**.



Reagents and Conditions; i) TsOH-H_2O-MeOH, 50°C
ii) HgO-I_2-benzene, 20°C

Scheme 11



The result conflicts with the report by Kraus and Thurston[5] in two respects; the first, the spirotetrahydrofurans are formed by an ionic reaction in the dark while the previous workers claim that the reaction is a radical addition[5]; the second, a mixture of the diastereomers is obtained as the product while Kraus and Thurston report that a single isomer is obtained[5].

4-3 Discussions

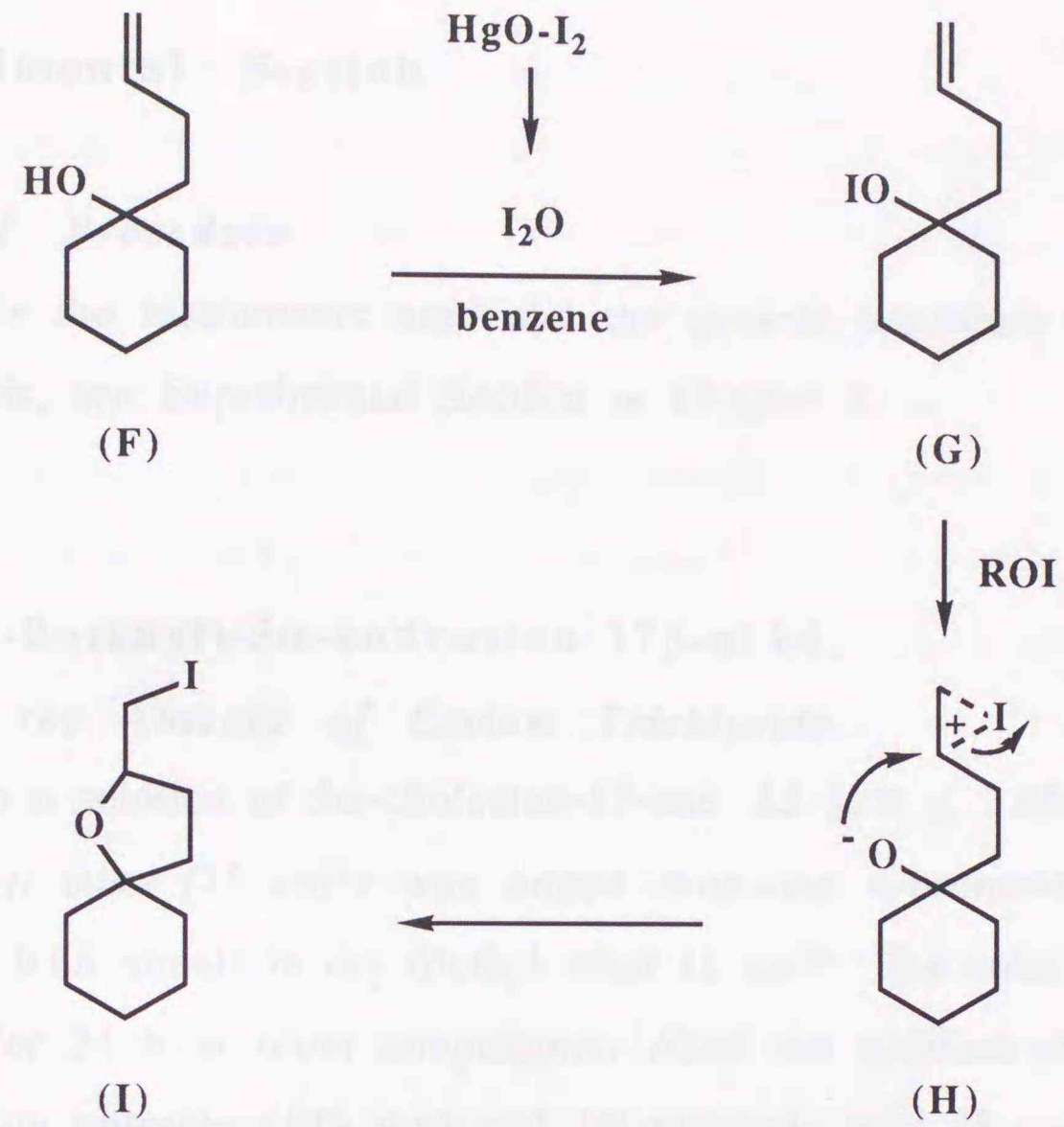
The foregoing results indicated that spirotetrahydrofurans are produced in high yields when a solution of olefinic alcohols (4-en-1-ol type) such as **14** containing mercury(II) oxide and iodine (each 2 equivalents) is stirred at room temperature in the dark in an atmosphere of nitrogen. The foregoing experiments also indicated that the formation of the spirotetrahydrofurans takes place *via ionic* reaction of the hypoiodite of olefinic alcohol **14** and not *via* cyclization of the alkoxyl radical. The pathway of the formation of the spirotetrahydrofurans from the olefinic alcohols is outlined in Scheme 12; a hypoiodite **G** is formed by the reaction of olefinic alcohol **F** with iodine oxide generated *in situ* from mercury(II) oxide and iodine in benzene.

An intramolecular reaction of iodonium ion **H** generated by the reaction of the hypoiodite **G** with another hypoiodite molecule gives the spirotetrahydrofuran **I**. This pathway is entirely analogous to that of the addition of acyl hypoiodites to olefins[12] where the acyl hypoiodite attacks the olefin to form an iodonium ion that is in turn attacked by the carboxylate ion, resulting in overall *trans* addition.

Virtually all the cyclization to halotetrahydrofurans found in the photolysis of hypoiodites in benzene reported in the past is considered to be formed by ionic reactions.

There have been a number of reports concerning the formation of cyclic ethers by electrophilic halocyclization of alcohols of 4-en-1-ol type involving halonium ions and others.

A variety of reagents used include (a) NBS-*t*-BuOH-H_2O[13a];



Scheme 12

NBS-CCl_4[13b]; Br_2-CCl_4[13c]; Br_2-Pyridine-CCl_4[13d], (b) I_2-KI-H_2O[14], (c) I_2-$NaHCO_3$-Et_2O-H_2O[15a]; KI_3-$NaHCO_3$-Et_2O-H_2O[15b], (d) $Pb(OAc)_4$-NaI or $ZnBr_2$-DME[16], (e) N-Phenylselenophthalimide (NPSP)-$ZnBr_2$-CH_2Cl_2[11], (f) PhSSPh + e → PhS^+-CH_2Cl_2[17], (g) I_2-CH_3CN[18a]; 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO)-CH_2Cl_2[18b].

The electrophilic cyclization of unsaturated alcohols *via* their hypoiodites generated *in situ* with mercury(II) oxide and iodine described in this paper is complementary to these methods; it takes place at room temperature under essentially neutral conditions and gives high yields of functionalized tetrahydrofuran derivatives.

Experimental Section

General Procedure

For the instruments used and the general procedure of the photolysis, see Experimental Section in Chapter 2.

17α-(3-Butenyl)-5α-androstan-17β-ol 14.

(a) In the Absence of Cerium Trichloride.

To a solution of 5α-cholestan-17-one **13** (1.0 g, 3.65 mmol) in diethyl ether (15 cm^3) was added dropwise 4-bromo-1-butene (1 cm^3, 9.86 mmol) in dry diethyl ether (1 cm^3). The solution was stirred for 24 h at room temperature. After the addition of ammonium chloride (195 mg) and 1N-sulphuric acid (5 cm^3) to the solution the organic layer was worked up in usual manner. The product was subjected to PLC (7:1 hexane-ethyl acetate) to give three fractions A, B, and C. The most mobile fraction (382 mg, 38 %) was the starting 17-one **13**. The second mobile fraction (112 mg, 9 %) was 17α-(3-butenyl)-5α-androstan-17β-ol **14**, m.p. 138~140°C (from acetone). (Found: C, 83.41; H, 11.51 $C_{23}H_{38}O$ requires C, 83.57; H, 11.59%). IR 3496 (OH), 1641 (C=C), and 905 cm^{-1}; δ (400 MHz) 0.79 (3H, s, 19-H), 0.85 (3H, s, 18-H), 4.93~5.10 (2H, m, -CH=C$\underline{H}_2$), 5.83-5.95(1H, m, -C$\underline{H}$=CH_2); *m/z* 330 (M^+, 13), 312 [$(M-H_2O)^+$, 12], 297 [$(M-H_2O-Me)^+$, 17], 275, [$(M-C_4H_7)^+$, 75], and 109 (100 %).

The most polar fraction C was 5α-androstan-17β-ol **15** (471 mg, 47 %) identical with the authentic sample.

(b) In the Presence of Cerium Trichloride.

Cerium trichloride hydrate ($CeCl_3 \cdot 7H_2O$)(560 mg, 1.5 mmol) was dried at *ca.* 140°C in *vacuo* (0.1 mm Hg) for 3h. To this dehydrated cerium chloride cooled at 0°C in an ice-bath was added tetrahydrofuran (5 cm^3). The solution was stirred for 16h. To this suspension cooled at 0°C by ice-bath was added a solution of 3-butenylmagnesium bromide prepared by the reaction of magnesium (61 mg, 2.54 mmol) with 4-bromo-1-butene (0.2 cm^3, 1.9 mmol) in THF (5 cm^3). The solution was stirred for 1h 20 m at 0°C. To this solution was added 17-ketone **13** (274 mg, 1 mmol) in THF (5 cm^3) at 0°C. The solution was stirred for 17h at room temperature. After 10% acetic acid (10 cm^3) was added, the solution was extracted with diethyl ether. The organic layer was worked up by the usual way to give a product (228 mg, 69 %) which was almost pure alcohol **14**.

3α- ***And*** **3β-*(3-butenyl)*-5α-*cholestan*-3-*ols*** **19** ***and*** **18.**

To a solution of 5α-cholestan-3-one **17** (670 mg, 1.74 mmol) in dry diethyl ether (8 cm^3) was added dropwise 4-bromo-1-butene (1 cm^3, 9.85 mmol) in dry diethyl ether (2 cm^3). The solution was stirred for 2h at room temperature. To the solution were added ammonium chloride (60 mg) and 1N-hydrochloric acid (3 cm^3). The organic layer was then washed with 2N-sodium hydroxide, water, and brine, successively, dried over anhydrous sodium sulphate. Evaporation of the solvent gave a mixture of product which was subjected to PLC (5:1 hexane-ethyl acetate) to give three fractions A, B, and C. The most mobile fraction (337 mg, 44 %) was 3β-(3-butenyl)-5α-cholestan-3α-ol **18**, m.p. 104~107°C

(from methanol). (Found: M^+, 442.4147. $C_{31}H_{54}O$ requires *M*, 442.4174); IR 3496 (OH), 1641 (C=C), 1163, 943, 947, and 905 cm^{-1}; δ (400 MHz) 0.65 (3H, s, 18-H), 0.74 (3H, s, 19-H), 4.90~5.07 (2H, m, -CH=C<u>H</u>$_2$), and 5.78~5.91 (1H, m, -C<u>H</u>=CH$_2$; *m/z* 442 (M^+, 2.2), 424 [$(M-H_2O)^+$, 2.4], 409 [$(M-H_2O-Me)^+$, 8], and 387 [$(M-C_4H_7)^+$, 100 %].

The second mobile fraction B (182 mg, 24 %) was 3α-(3-butenyl)-5α-cholestan-3β-ol **19**, m.p. 38~42°C (from methanol) (Found: M^+, 442.4176. $C_{31}H_{54}O$ requires *M*, 442.4174). IR 3344 (OH), 1645 (C=C), and 905 cm^{-1}; δ (400 MHz) 0.65 (3H, s, 18-H), 0.82 (3H, s, 19-H), 4.90~5.10 (2H, m, -CH=C<u>H</u>$_2$), and 5.80~5.95 (1H, m, -C<u>H</u>=CH$_2$). *m/z* 442 [$(M-H_2O-Me)^+$, 7.9] and 387 [$(C-C_4H_9)^+$, 100 %].

The most polar fraction (115 mg, 17 %) was identified to be 5α-cholestan-3β-ol **20**.

***Intramolecular Addition of the Hypoiodite of* 17α-(3-*Butenyl*)-5α-*androstan*-17β-*ol* 14.**

A solution of 17β-ol **14** (52 mg, 0.158 mmol) in benzene (8 cm^3) containing mercury(II) oxide (68 mg, 0.314 mmol) and iodine (80 mg, 0.315 mmol), placed in a vessel covered with aluminium foil, was flushed with nitrogen gas and stirred for 15 m at room temperature. After the solution was filtered, the organic layer was worked up in the usual way. The product was subjected to PLC (7:1 hexane-ethyl acetate) to give two products **21** and **22**. The more mobile major product **21** (46 mg, 64 %) was a spirotetrahydrofuran derivative, m.p. 121~122°C (from acetone). (Found: C, 60.47; H, 8.28; I, 27.65. $C_{23}H_{37}OI$ requires C, 60.52; H,

8.17; I, 27.80 %);IR 1197, 1055, 1024, 969, and 892 cm^{-1}; δ (400 MHz) 0.78 (3H, s, 19-H), 0.85 (3H, s, 18-H), 1.93~2.02 (1H, m), 2.03~2.15 (2H, m), 3.08 (1H, dd, *J* 7.8 and 9.8, $-CH_2I$), 3.27 (1H, dd, *J* 4.4 and 9.8, $-CH_2I$), and 3.91~4.00 (1H, m, -OCH-); *m/z* 456 (M^+, 23), 441[$(M-Me)^+$, 6], 329 [$(M-I)^+$, 4], 315 [$(M-CH_2I)^+$, 12], and 237 (100 %).

The less mobile minor product **22** (21 mg, 29 %) was an epimer of the spirotetrahydrofuran derivative, m.p. 116~117°C (from acetone). (Found; M^+, 456. 1910. $C_{23}H_{37}OI$ requires *M*, 456.1889);IR1302, 1275, 1206, 1162, 1090, 1005, 967, and 895 cm^{-1}; δ (400 MHz) 0.79 (3H, s, 19-H), 0.86 (3H, s, 18-H), 1.85~1.94 (1H, m), 2.03~2.15 (2H, m), 3.06 (1H, dd, *J* 7.8 and 9.8, $-CH_2I$), 3.21 (1H, dd, *J* 4.4 and 9.8, $-CH_2I$), and 3.98~4.06 (1H, m, -OCH-). *m/z* 456 (M^+, 27), 441 [$(M-Me)^+$, 7], 329 [$(M-I)^+$, 3], 315 [$(M-CH_2I)^+$, 12], and 237 (100 %). The ratio of the two epimers **21** and **22** was, thus, 2.2:1.

***Intramolecular Addition of the Hypoiodite of 3β-(3-Butenyl)-5α-cholestan-3α-ol* 18.**

(a) In the Absence of 2,2'-Diphenyl-1-Picrylhydrazyl (DPPH).

To a solution of steroidal 3α-ol **18** (50 mg, 0.113 mmol) in benzene (6 cm^3) placed in a vessel covered by aluminium foil were added mercury(II) oxide (50 mg, 0.231 mmol) and iodine (62 mg, 0.244 mmol) in the dark. The solution was flushed with nitrogen and then stirred for 2h and 20 m at room temperature in the dark. The soluton was then filtered and the filtrate was washed with 5 % $Na_2S_2O_8$ solution, water, and brine, and dried

over anhydrous sodium sulphate. Work-up in the usual way gave a product which was purified by PLC (benzene) to give a spirotetrahydrofuran derivative **27** (60 mg, 93 %), m.p. 88.5~90.0°C (from acetone). (Found; C, 65.60; H, 9.27; I, 22.50. $C_{31}H_{53}OI$ requires C, 65.49; H, 9.39; I, 22.32 %). IR1160, 1040, and 900 cm^{-1}; δ (400 MHz) 0.64 (3H, s, 18-H), 0.75 (3H, s, 19-H), 3.13 (1H, dd, *J* 9.8 and 8, $-CH_2I$), 3.30 (1H, dd, *J* 9.8 and 3.9, $-CH_2I$), and 3.96~4.06 (1H, m, -OCH-); *m/z* 568 (M^+, 54), 553 [$(M-Me)^+$, 20], 441 [$(M-I)^+$, 14], 413 (37), 263 (56), 250 (66), 238 (80), 95 (86), 81 (95), and 55 (100%).

(b) In the Presence of* 2,2'-*Diphenyl*-1-*Picrylhydrazyl* *(DPPH).

To a solution of 3α-ol **18** (51 mg, 0.115 mmol) in benzene (6 cm^3) placed in a vessel covered by aluminium foil were added DPPH (136 mg, 0.345 mmol), mercury(II) oxide (50 mg, 0.231 mmol), and iodine (59 mg, 0.232 mmol) successively. The solution was flushed with nitrogen and then stirred for 2h at room temperature in the dark. Work up as described above gave spirotetrahydrofuran derivative **27** (60 mg, 93 %) as a single isomer.

***Intramolecular Addition of the Hypoiodite of* 3α-(3-*Butenyl*)-5α-*cholestan*-3β-*ol* 19.**

A solution of 3β-ol **19** (58 mg, 0.131 mmol), mercury(II) oxide (57 mg, 0.263 mmol) and iodine (67 mg, 0.264 mmol) in benzene (7 cm^3), made up as described above, was flushed with nitrogen and stirred for 40 m at room temperature in the dark,

The solution was then worked up as mentioned above to give a 1:1 mixture of two isomers **28** and **29**, m.p. 101~103°C (from acetone). (Found: C, 65.50; H, 9.52; I, 22.39. $C_{31}H_{53}OI$ requires C, 65.49; H, 9.39; I, 22.32 %); IR 1171, 1078, 1051, 930, and 672 cm^{-1}; δ (400 MHz) 0.64 (3H, s, 18-H), 0.81 (3H, s, 19-H), 3.129 (1H, dd, *J* 7.8 and 9.8; $-CH_2I$), 3.268 (1H, dd, *J* 3.9 and 9.8, $-CH_2I$), 3.284 (1H, dd, *J* 3.9 and 9.8, $-CH_2I$), and 3.96~4.07 (1H, m, -OCH-); *m/z* 568 (M^+, 70), 553 [$(M-CH_3)^+$, 11], 441 [$(M-I)^+$, 15], 427 (40), 413 (15), 331 (56), 263 (84), 250 (100), 238 (93), and 237 (77 %).

1-*Hydroxy-oct-7-en-4-one* 31.

To a solution of 1-(tetrahydropyran-2-yloxy)oct-7-en-4-one **30**[10] (122 mg, 0.54 mmol) in methanol (1.2 cm^3) and water (1.2 cm^3) was added a catalytic amount of *p*-toluenesulphonic acid. The solution was stirred for 1h at 50°C. The reaction mixture was then extracted with diethyl ether. The ethereal solution was worked up in the usual manner. Evaporation of the solvent gave a product which was subjected to column chromatography (Florisil, 2g). Elutions with 10:1 hexane - ethyl acetate gave the alcohol **31** (47 mg, 61 %).

2-*Hydroxy-2-(3-butenyl)-tetrahydrofuran* 9.

The open-chain alcohol **31** (neat) was set aside for 5 days at room temperature and was subjected to column chromatography (Florisil, 10g). Elutions with 5:2 hexane - ethyl acetate gave lactol **9** (237 mg, 65 %).

***The Formation of Spirotetrahydrofurans* 32 *and* 33 *from the Hypoiodite of Lactol* 9.**

To a solution of lactol **9** (237 mg, 1.67 mmol) in benzene (82 cm^3) placed in a vessel covered by aluminium foil was added mercury(II) oxide (724 mg, 3.34 mmol) and iodine (849 mg, 3.34 mmol). The solution was stirred for 1h 45 m at room temperature in the dark. The solution was then filtered and the filtrate was washed with 5 % sodium thiosulphate solution, water and brine, successively and dried over anhydrous sodium sulphate. Evaporation gave a product mixture which was subjected to PLC (5:1 hexane - ethyl acetate) to give a 1:2 mixture of diastereoisomers **32** and **33** (301 mg, 67 %). (Found M^+, 267.9985. $C_8H_{13}O_2I$ requires *M*, 267.9960). IR (neat) 1166, 1152, 1112, 1052, 1008, 933 cm^{-1}, and 920; δ (400 MHz) 1.69~1.77 (1H, m, 3-H of **33**), 1.82~2.16 (13H, m), 2.20~2.30 (2H, m, 3-H of **32** and **33**), 3.16 (1H, dd, *J* 8.3 and 9.3, $-CH_2I$ of **32**), 3.22 (1H, dd, *J* 6.3 and 9.8, $-CH_2I$ of **33**), 3.28 (1H, dd, *J* 4.2 and 9.8, $-CH_2I$ of **33**), 3.36 (1H, dd, *J* 5.9 and 9.3, $-CH_2I$ of **32**), 3.82-3.98 (4H, m, 7-H of **32** and **33**), 4.07~4.13(1H, m, 2-H of **33**), and 4.23~4.30 (1H, m, 2-H of **32**). The assignments of the signals at δ 1.69~1.77 and δ 2.20~2.30 were made by irradiating signals at 4.07~4.13 (2-H of **33**) and those at 4.23~4.30 (2-H of **32**). All the assigments are based on the comparisons with the signals of diastereoisomers **34** and **35** of spirotetrahydrofurans. *m/z* 268 (M^+, 6.3), 141 [$(M-I)^+$, 23], 127 [$(M-CH_2I)^+$, 100], 85 (48), and 55 (97 %).

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Inches 1 2 3 4 5 6 7 8

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

Centimetres

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Kodak
LICENSED PRODUCT

Blue Cyan Green Yellow Red Magenta White 3/Color Black

Kodak Gray Scale

C Y M

A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19