Transformation of epiandrosterone into 3-oxa-, 3-thia-, 3-selena-, and 3-aza-17-oxaandrostanes of the 5α series based on β-scission of alkoxyl radicals

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3β-Hydroxy-5α-androstan-17-one was transformed into 17-oxa-5α-androstan-3β-ol in five steps involving conversion of the 17-ketone via *the corresponding lactol to its hypoiodite and thence a regioselective β-scission under irradiation to give ring D seco iodoformate, from which the 17-oxasteroids were derived. Four bisheterosteroids 3,17-dioxa-5α-androstane, 3-thia-17-oxa-5α-androstane, 3-aza-17-oxa-5α-androstane, and 3-selena-17-oxa-5α-androstane) were synthesized from 17-oxa-5α-androstan-3β-ol* via *5, 8, 8, and 9 steps, respectively, involving a second regioselective β-scission of an alkoxyl radical as the key step. (Steroids* **55**:353–359, 1990)

Keywords: steroids; partial synthesis; alkoxyl radicals; 3-Hetero-17-oxa-5α-androstanes, mercuric oxide-iodine reagent

Introduction

The replacement of one or more carbon atoms of a steroid molecule with heteroatoms brings about notable modifications of its biologic activity; a number of investigations have been carried out on both the total and partial synthesis of heterosteroids and their physiologic activities by many investigators.[1–16]

In previous reports,[17–19] we have reported on the five- to six-step synthesis of various monoheterosteroids via substitution of a carbonyl group of steroidal ketones by a hetero atom (N, O, S, Se, and Te). The transformation involved conversion of appropriate ketones via the corresponding lactols to their hypoiodites and thence a regioselective β-scission under irradiation to give the corresponding seco iodoformates from which the heterosteroids were derived.

We report on the synthesis of 3,17-dioxa-5α-androstane **(16)**, 3-thia-17-oxa-5α-androstane **(20)**, 3-benzyl-3-aza-17-oxa-5α-androstane **(21)**, and 3-selena-17-oxa-5α-androstane **(25)** from 3β-hydroxy-5α-androstan-17-one (epiandrosterone) by methods devised by us and reported previously.[17,18]

Experimental

The melting points were recorded with a Yanagimoto micro mp apparatus. Infrared spectra were recorded for Nujol mulls with a JASCO IR 810 infrared spectrophotometer. ^{1}H-nuclear magnetic resonance (NMR) spectra were determined either with a JEOL JNM-FX 270 spectrometer (270 MHz) or with a Hitachi R22 FT NMR spectrometer (90 MHz) (solvent, $CDCl_3$; $SiMe_4$ as an internal standard; Faculty of Pharmaceutical Sciences, Hokkaido University). All of the high- and low-resolution mass spectra were recorded with a JEOL JMS-D 300 spectrometer (70 eV) (Faculty of Pharmaceutical Sciences, Hokkaido University). Preparative thin-layer chromatography (TLC) was carried out on a Merck Kieselgel 60 PF_{254}. Elemental analysis was performed in the Laboratory for Microanalysis of the Faculty of Pharmaceutical Sciences, Hokkaido University.

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3β-Hydroxy-17a-oxa-5α-D-homoandrostan-17-one **(2)**

To a solution of 3β-hydroxy-5α-androstan-17-one **(1)** (2 g) and *p*-toluenesulfonic acid (200 mg) in dichloromethane (30 ml), MCPBA (3 g) in dichloromethane (25 ml) was added slowly. The solution was stirred for 22 hours at room temperature. The solution was washed with a 5% $Na_2S_2O_2$ solution, aqueous Na_2CO_3 solution, saturated brine, and water, successively, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave lactone **2**, which was recrystallized from acetone in a nearly quantitative yield. The following values were determined: mp, 194–196° C; IR (Nujol), 3,426 (OH), 1,701 (C=O), 1,303, 1,061 cm^{-1}; ^1H NMR δ, 0.78 (3H, s, 19-H), 1.30 (3H, s, 18-H), 2.48–2.73 (2H, m, 16-H), 3.60 (1H, m, 3α-H); MS m/z, 306 (M^+, 1.3), 291 [$(M - Me)^+$, 46.6], 288 [$(M - H_2O)^+$, 3.8], 108 (100). Analysis calculated for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.32; H, 9.86.

3β-(1-Ethoxy)ethoxy-17a-oxa-5α-D-homoandrostan-17-one **(3)**

To a solution of the lactone **2** (1.56 g) and *p*-toluene sulfonic acid (35 mg) in dichloromethane (20 ml), ethyl vinyl ether (1.17 g) in dichloromethane (15 ml) was slowly added. The solution was stirred for 6 hours at room temperature. The solution was washed with 5% $NaHCO_3$ solution and then with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a product that was purified by column chromatography (silica gel). Elution with hexane/ethyl acetate (1 : 2) gave the ether **3** (1.557 g, 82%), with the following values: mp, 105–107° C (hexane/ethyl acetate); IR (Nujol), 1,730 (C=O), 1,115, 1,041 cm^{-1}; ^1H NMR δ, 0.77 (3H, s, 19-H), 1.30 (3H, s, 18-H), 2.50–2.72 (2H, m, 16-H), 3.41–3.67 (3H, m, 3α-H and -OC*H*$_2$CH$_3$), and 4.77 (1H, q, *J* 5.3 Hz, -OC*H*(Me)-O-); MS m/z, 363 [$(M - Me)^+$, 3.2], 289 [$(M - OCH(OC_2H_5)CH_3)^+$, 83.5], 73 (100). Analysis, calculated for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 73.04; H, 10.21.

Reduction of 1-Ethoxyethyl ether 3 with DIBAL

To a solution of the lactone **3** (2.40 g) in dry toluene (70 ml) cooled at −78° C in a nitrogen atmosphere, DIBAL (1.0 M in toluene) (9.23 ml) was added dropwise. The temperature of the solution was increased from −78° C to room temperature in the course of 2.5 hours while stirring. After water was added to the solution, the solution was stirred for a few minutes, then filtered. The solution was washed with saturated brine and then with water three times, and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent gave an unstable lactol **4** (2.249 g, 94%), with the following values; IR (neat), 3,318 (OH), 1,125 cm^{-1}; ^1H NMR δ, 0.69 (3H, s, 19-H), 1.09 (3H, s, 18-H), 3.29–3.66 (3H, m, 3α-H and OC*H*$_2$CH$_3$), 4.70 (1H, q, *J* = 5.3 Hz, OC*H*(Me)-O-), 4.99 (1H, m, 17-H); MS m/z, 380 (M^+, 0.11), 362 [$(M-H_2O)^+$, 4.5], 273 (8.1), 73 (100). High resolution MS calculated for $C_{23}H_{40}O_4$, M, 380.2927; found, 380.2928.

Irradiation of lactol 4 in benzene containing mercury(II) oxide and iodine

Lactol **4** (2.1 g) in dry benzene (150 ml) containing pyridine (2.0 ml), mercury(II) oxide (3.27 g), and iodine (3.8 g) was flushed with nitrogen and irradiated with a high-pressure 100-W Hg arc through a Pyrex-filter for 2.15 hours as previously described.[4] After the solution was filtered, the filtrate was washed with an aqueous 5% $Na_2S_2O_3$, and then with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude seco formate **5** that was purified by means of column chromatography. Elution with hexane/ethyl acetate (1 : 1) first gave a pure seco formate **5** (1.06 g, 38%) and then lactone **3** (approximately 1 g, 48%). The following values were obtained: IR (neat), 1,721 (C=O), 1,194, 1,170, and 1,119 cm^{-1}; ^1H NMR δ, 0.75 (3H, s, 19-H), 1.43 (3H, s, 18-H), 3.14–3.23 (2H, m, CH_2I), 3.41–3.67 (3H, m, 3α-H and MeC*H*$_2$-O-), 4.70 (1H, q, *J* = 5.1 Hz, -OC*H*(Me)-O-),and 8.03 (1H, s, OCHO). This formate was immediately subjected to the next cyclization.

17-Oxa-5α-androstan-3β-ol **(6)**

To a solution of seco formate **5** (950 mg) in dry tetrahydrofuran (THF) (95 ml) cooled −78° C, methyllithium (1.5 M in diethyl ether) (2.85 ml) was added dropwise at −78° C. The temperature of the solution was increased to room temperature in the course of 3.5 hours while stirring. After the addition of ethyl acetate to the solution, the solvent was evaporated to give a residue that was dissolved in diethyl ether. The solution was washed with on aqueous 5% $NaHCO_3$ solution, then with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent left a residue that was subjected to preparative TLC with hexane/ethyl acetate (1 : 1) to give 17-oxasteroid **6** (0.42 g, 81%): mp, 124–126° C and 146–148°C (reported in the literature [17]: 112–114°C and 135–139°C).

Baeyer-Villiger oxidation of 17-oxa-5α-androstan-3-one **(7)**

To a solution of 17-oxa-5α-androstan-3-one **(7)** (540 mg), prepared according to a procedure described previously,[17,20] in dichloromethane (20 ml), was added MCPBA (540 mg). The solution was stirred at room temperature for 20 hours. The solution was then washed with aqueous 5% $Na_2S_2O_8$, aqueous 5% $NaHCO_3$ solution, saturated brine, and water, successively, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a residue (609 mg) that was recrystallized from hexane/ethyl acetate to yield a crystalline mixture of lactone isomers **8** and **9** (473 mg, 83%): mp, 194–196° C. Further amounts of lactones **8** and **9** (68 mg, 12%) were obtained by purifying the recovered lactones from the mother liquor by means of preparative TLC. The following values were determined: IR (Nujol), 1,737 (C=O), 1,296, 1,191, and 1,123 cm^{-1}; ^1H NMR δ, 0.93 (3H, s, 19-H of **8** and **9**), 0.96 (3H, s, 18-H of **8** and **9**), 2.53–2.71 (2H, m, $-CH_2COO$), and

4.25–4.33 (2H, m, CH_2OCO-); MS m/z, 292 (M^+, 0.75) and 277 [$(M - Me)^+$, 100]. Analysis calculated for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.69; H, 9.73.

Reduction of lactones 8 and 9 with DIBAL

A mixture of lactones **8** and **9** (530 mg, 1.80 mmol) was dissolved in dry toluene (20 ml) and cooled to −78° C. To this solution, DIBAL (1.0 M in toluene) (2 ml) was added at −78° to 20° C over the course of 2 hours. Iced water was added to the solution and the solution was filtered. The filtrate was washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent left a crude mixture of lactols **10** and **11** (532 mg). The mixture was purified by preparative TLC (hexane/ethyl acetate, 1 : 1) to give an oily mixture of lactols **10** and **11** (472 mg, 89%): IR (Nujol), 3,370 (OH) and 1,106 cm^{-1}; ^1H NMR δ, 0.83 (3H, s, 19-H), 0.95 (3H, s, 18-H), and 5.12 (1H, m, $-CH_2CH(OH)-O-$); MS m/z, 294 (M^+, 0.69), 279 [$(M - Me)^+$, 100], and 261 [$(M - Me - H_2O)^+$, 3.6].

The photolysis of hypoiodites of lactols 10 and 11 in the presence of mercury(II) oxide and iodine

A solution containing lactols **10** and **11** (400 mg, 1.36 mmol), mercury(II) oxide (864 mg, 4.00 mmol), and iodine (1,016 mg, 4.00 mmol) in benzene (50 ml) was placed in a Pyrex vessel, flushed with nitrogen, and irradiated with a 100-W Hg arc lamp for 3 hours at room temperature. The solution was filtered and the filtrate was washed with aqueous $Na_2S_2O_3$ solution, water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent left a product mixture that was subjected to preparative TLC (hexane/ethyl acetate, 1 : 1) to give two fractions. The more mobile fraction **A** (124 mg) was a mixture of oily diol diformates **14** and **15**. This mixture was again subjected to preparative TLC (hexane/ethyl acetate, 1 : 2) to give a less mobile diformate **14** (60 mg, 7.8%) and a more mobile diformate **15** (61 mg, 8.0%), both of which were virtually pure. The following values were determined for diformate **14:** IR (neat), 1,719, 1,174 cm^{-1}; ^1H NMR δ, 0.75 (3H, s, 19-H), 1.56 (3H, s, 18-H), 4.15 (2H, t, J = 7.25 Hz, $-CH_2OCHO$), 7.99 (1H, s, OCHO), 8.04 (1H, s, OCHO); MS m/z, 470 [$(M - 2HOCHO)^+$, 12.7], 389 [$(M - HOCHO - I)^+$, 77.5], 343 [$(M - 2HOCHO - I)^+$, 100]; analysis calculated for $(M - 2HOCHO)^+$, 469.9966; found, 469.9960. The following values were determined for diformate **15:** IR (neat), 1,721 and 1,166 cm^{-1}; ^1H NMR δ, 0.79 (3H, s, 19-H), 1.56 (3H, s, 18-H), 8.01 (1H, s, OCHO), 8.08 (1H, s, OCHO); MS m/z, 470 [$(M - 2HOCHO)^+$, 8.07], 389 [$(M - HCHO - I)^+$, 54.2], 343 [$(M - 2HOCHO - I)^+$, 100]; analysis calculated for $C_{16}H_{24}I_2$ $(M - 2HOCHO)^+$, 469.9966; found, 469.9984. The less mobile fraction **B** (296 mg) was a mixture of oily formates **12** and **13.** This mixture was again subjected to preparative TLC (hexane/ethyl acetate, 1 : 1) to give a less mobile formate **12** (146 mg, 25.6%) and a more mobile formate **13** (145 mg, 25.4%).

The following are values for formate **12:** IR (neat), 1,725 (C=O), 1,169 cm^{-1}; ^1H NMR (270 MHz) δ, 0.78 (3H, s, 19-H), 0.95 (3H, s, 18-H), 2.83 (1H, dd, J = 10.63 and 9.89 Hz, $-CH_2I$), 3.61 (1H, dd, J = 9.71 and 2.2 Hz, CH_2I), 3.81–3.97 (2H, m, 16-H), 4.20 (2H, dd, J = 7.33 and 7.69 Hz, 3-H), 8.07 (1H, s, OCHO); FI (field ionization) −MS, m/z, 421 [$(MH)^+$, 57.2], 405 (100); analysis calculated for $C_{18}H_{30}O_3I$, $(M + H)^+$, (FI-HRMS), 421.1238; found, 421.1177. The following are values for formate **13:** IR (neat), 1,727 (C=O), 1,170 cm^{-1}; ^1H NMR (270 Hz) δ, 0.81 (3H, s, 19-H), 0.95 (3H, s, 18-H), 3.02–3.29 (2H, m, CH_2I), 3.80–3.96 (3H, m, 16-H and 2-H), 4.32 (1H, ddd, J = 10.99, 4.40, and 0 Hz, 2-H), 8.09 (1H, s, OCHO); FI-MS m/z, 421 [$(MH)^+$, 51.3], 405 (100); analysis calculated for $C_{18}H_{30}O_3I$, $(M + H)^+$, (FI-MS), 421.1238; found, 421.1183.

3,17-Dioxa-5α-androstane (16)

Formate **13** (31 mg, 0.074 mmol) and sodium borohydride (34 mg) in THF (5 ml) was heated under reflux in a nitrogen atmosphere. The solvent was evaporated and the residue dissolved in dichloromethane. The solution was washed with brine, then water, and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent left dioxaandrostane **16,** which was purified by preparative TLC (hexane/ethyl acetate, 3 : 1) (15 mg, 77%): mp, 105–107° C (acetone/hexane); IR (Nujol), 1,220, 1,112, 992 cm^{-1}; ^1H NMR (270 MHz) δ, 0.93 (3H, s, 19-H), 0.96 (3H, s, 18-H), 3.31–3.48 (2H, m, 16-H), 3.61–3.96 (4H, m, 2-H and 4-H); MS m/z, 264 (M^+, 0.9) 249 [$(M - Me)^+$, 100]. Analysis calculated for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.11; H, 10.75.

2-Iodo-2,3-seco-17-oxa-5α-A-norandrostan-3-ol (17)

To the formate **12** (120 mg, 0.29 mmol) in dry toluene (15 ml), DIBAL (0.7 ml, 1.0 M in toluene) was added dropwise at −78° C. The solution was stirred for 5 hours at −78° to 20° C. To this solution iced water was added. The solution was stirred for 5 minutes, then filtered. The filtrate was washed with brine, water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent left crystals that were purified by preparative TLC (hexane/ethyl acetate, 1 : 1) to give pure iodo alcohol **17** (100 mg, 90%): mp, 152–154° C (acetone); IR (Nujol), 3,400 (OH), 1,221, 1,193 cm^{-1}; ^1H NMR (90 MHz) δ, 0.77 (3H, s, 19-H), 0.95 (3H, s, 18-H), 3.36–3.96 (6H, m, CH_2I, CH_2OH and 16-H); MS m/z, 392 (M^+, 0.35), 377 [$(M - Me)^+$, 100]; high resolution MS calculated for $C_{17}H_{29}O_2I$: M, 392.1212. Found: 392.1205.

2-Iodo-2,3-seco-17-oxa-5α-A-norandrostan-3-ol mesylate (18)

Iodoalcohol **17** (88 mg, 0.22 mmol) and mesyl chloride (0.6 ml) in dry pyridine (12 ml) were stirred for 18 hours at room temperature. After the addition of diethyl ether, the solution was washed with brine, water, and dried over anhydrous $MgSO_4$. Evaporation of the sol-

vent left a residue that was subjected to preparative TLC (hexane/ethyl acetate, 1 : 1) to give an oily mesylate **18** (103 mg, 98%). The following values were determined: IR (neat), 1,172 (S=O) and 950 cm^{-1}; ^1H NMR (270 MHz) δ, 0.80 (3H, s, 18-H), 0.95 (3H, s, 19-H), 3.08 (3H, s, CH_3SO_2-), 3.80–3.97 (2H, m, 16-H), 4.23–4.31 (2H, m, $-CH_2SO_2$); MS m/z, 470 (M^+, 0.78), 455 [$(M - Me)^+$, 100]. High resolution MS calculated for $C_{18}H_{31}O_4IS$: M, 470.0989. Found: 470.0980.

2,3-Diiodo-2,3-seco-17-oxa-5α-A-norandrostane (19)

The mesylate **18** (103 mg, 0.22 mmol) and NaI (200 mg, 1.33 mmol) in acetone (20 ml) were heated under reflux for 3 days. The solvent was evaporated, and the residue dissolved in diethyl ether was washed with brine, water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent left a residue that was subjected to preparative TLC to give diiodide (105 mg, 96%): mp, 107–108° C (acetone/hexane); IR (Nujol), 1,214, 1,174, 1,121, and 1,008 cm^{-1}; ^1H NMR (270 MHz) δ, 0.74 (3H, s, 18-H), 0.94 (3H, s, 19-H), 2.81 (1H, dd, J = 9.89 and 10.63 Hz, $-CH_2I$), 3.06–3.13 (2H, m, CH_2I), 3.49 (1H, dd, J = 9.89 and 2.57 Hz, CH_2I), 3.81–3.97 (2H, m, 16-H); MS m/z, 502 (M^+, 0.48), 486 (100), 375 [$(M - I)^+$, 13.6]. High-resolution MS calculated for $C_{17}H_{28}OI_2$: M, 502.0230. Found: 502.0223.

3-Thia-17-oxa-5α-androstane (20)

Diiodide **19** (25 mg, 0.05 mmol) in ethanol (4 ml) containing an excess (150 mg) of $Na_2S \cdot 9H_2O$ was heated under reflux for 6 hours. Evaporation of the solvent left a residue that was dissolved in diethyl ether. The ethereal solution was washed with brine, then water, and finally dried over anhydrous $MgSO_4$. The usual work-up gave a residue that was subjected to preparative TLC (benzene) to give 3-thia-17-oxa-5α-androstane (12 mg, 86%): mp, 118–120° C (hexane); IR (Nujol), 1,295, 1,167, 1,127, 1,035, 995 cm^{-1}; ^1H NMR (270 MHz), 0.83 (3H, s, 19-H), 0.95 (3H, s, 18-H), 2.63–2.97 (2H, m, -CH_2S-), 2.83–3.96 (2H, m, -CH_2O-); MS m/z, 280 (M^+, 21.6), 265 [$(M - Me)^+$, 100]. Analysis calculated for $C_{17}H_{28}OS$: C, 72.80; H, 10.06; S, 11.41. Found; C, 72.69; H, 10.06; S, 10.95.

3-Benzyl-3-aza-17-oxa-5α-androstane (21)

Diiodide **19** (35 mg, 0.07 mmol) in dioxane (0.5 mol) containing benzylamine (0.5 ml) was heated under reflux for 27 hours. The solvent was evaporated to leave a residue that was subjected to a preparative TLC (ethyl acetate/hexane, 75 : 25 vol/vol) to give bisheterosteroid **21** (24 mg, 96%): mp, 148–150° C (hexane); IR (Nujol), 1,654, 1,373, 1,297, 1,007 cm^{-1}; ^1H NMR (270 MHz), 0.80 (3H, s, 19-H), 0.94 (3H, s, 18-H), 3.52 (2H, s, $C_6H_5CH_2$), 3.81–3.94 (2H, m, 16-H); MS m/z, 353 (M^+, 100), 338 [$(M - Me)^+$, 34.7], 262 [$(M - C_6H_5CH_2$-$)^+$, 45.73], 91 ($C_6H_5CH_2^+$, 39.0). Analysis calculated for $C_{24}H_{35}NO$: C, 81.59; H, 9.92; N, 3.96. Found: C, 81.64; H, 10.15; N, 3.85.

Monoselenocyanates 22 and 23

Diiodide **19** (68 mg, 0.135 mmol) in acetone (15 ml) containing potassium selenocyanate (20 mg, 0.135 mmol) was heated under reflux for 2 hours. The solvent was evaporated to give a residue that was dissolved in diethyl ether. The ethereal solution was washed with brine, then water, and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent left a residue that was subjected to preparative TLC (hexane/diethyl ether, 3 : 1) to give a more mobile starting material **19** (60 mg) and a less mobile oily mixture of monoselenocyanates **22** and **23** (5 mg, 65% based on consumed starting diiodide): IR (neat), 2,150 cm^{-1} (C≡N); ^1H NMR (270 MHz) δ, 0.78 (3H, s, 19-H), 0.80 (3H, s, 19-H), 0.94 (6H, s, 18-H), 3.79–3.93 (2H, m, 16-H); MS m/z, 366 [$(M - Me)^+$, 100], 375 [$(M - SeCN)^+$, 2.6], 328 [$(M - ICN)^+$, 22.2], 313 [$(M - ICN - Me)^+$, 59.1].

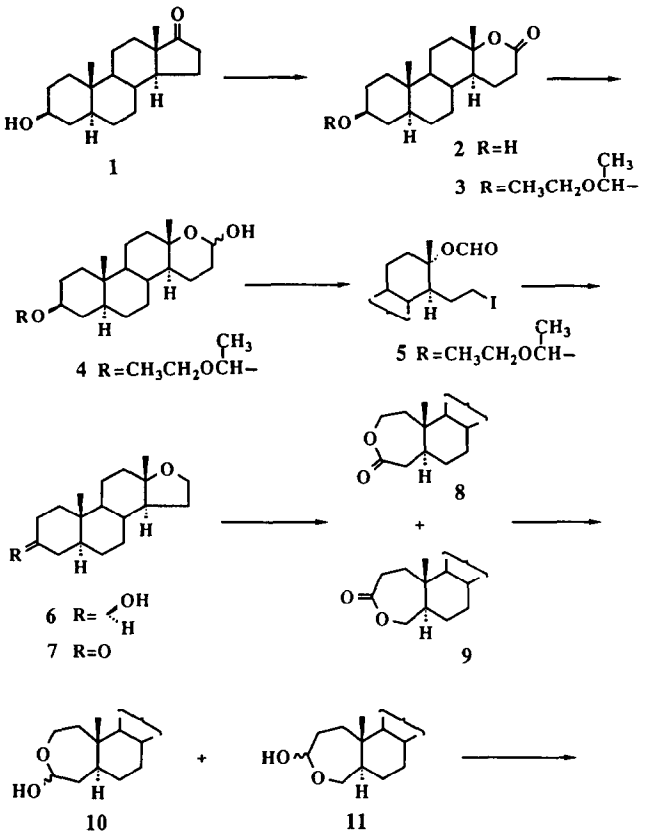
Diselenocyanate **24** ^1H NMR (270 MHz) δ, 0.84 (3H, s, 19-H), 0.94 (3H, s, 18-H), 3.79–3.96 (2H, m, 16-H); MS m/z, 445 [$(M - Me)^+$, 100], 338 [$(M - Me - HScCN)^+$, 14.7] can only be formed when an excess of potassium selenacyanate in a smaller volume of solvent is used.

3-Selena-17-oxa-5α-androstane (25)

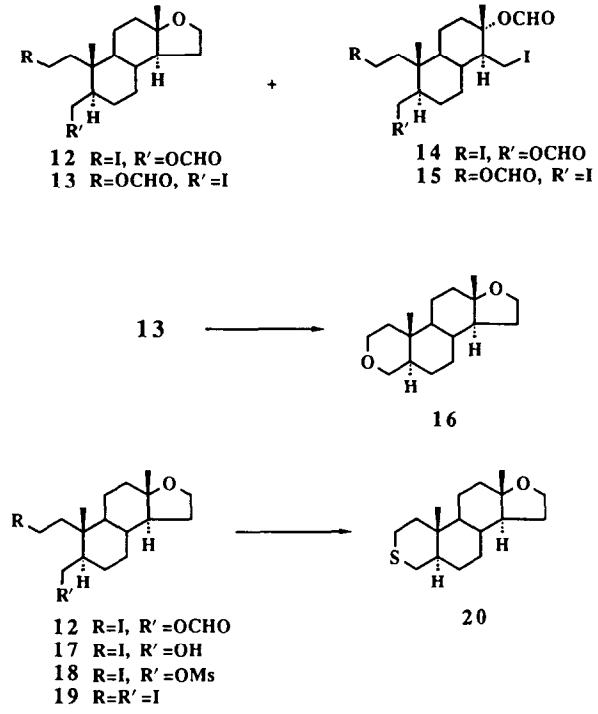
To a solution containing a mixture of monoselenocyanates **22** and **23** (25 mg, 0.052 mmol) in THF/ethanol (4 : 1), $NaBH_4$ in THF ethanol (4 : 1) (20 ml) was slowly added. The solution was stirred for 3 days at 40° C. The solution was then evaporated, leaving a residue that was dissolved in diethyl ether. The solution was washed with a brine, then with water, and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent gave bisheterosteroid **23,** which was recrystallized from hexane to give pure compound **23** (13 mg, 77%): mp, 114–115° C; IR (Nujol), 1,217, 1,122, and 9,92 cm^{-1}; ^1H NMR (270 MHz) δ, 0.81 (3H, s, 19-H), 0.95 (3H, s, 18-H), 2.78–2.99 (2H, m, -CH_2Se-), 3.79–3.96 (2H, m, 16-H); MS m/z, 328 (M^+, 62.0); 313 [$(M - Me)^+$, 100]. Analysis calculated for $C_{17}H_{28}OSe$: C, 62.44; H, 8.63. Found: C, 62.65; H, 8.72.

Results and discussion

We have previously reported the transformation of 5α-androstan-3α,17β-diol 3-acetate into 17-oxa-5α-androstan-3-one **(7)** in four steps.[17] The 17-oxasteroid **7** used for the synthesis of 17-oxa-3-heterosteroids in the present experiments was prepared from 3β-hydroxy-5α-androstan-17-one **(1)** in six steps (Scheme 1). A Baeyer-Villiger oxidation of 3β-hydroxy-5α-androstan-17-one **(1)** with MCPBA (*m*-chloroperbenzoic acid) gave 3β-hydroxy-17a-oxa-5α-D-homoandrostan-17-one **(2)** in a nearly quantitative yield. The 17a-oxasteroid **2** was transformed into the 1-ethoxyethyl ether **3** with ethyl vinyl ether and *p*-toluene sulfonic acid in dichloromethane in 82% yield. The protected lactone **3** was then subjected to reduction with DIBAL (diisobutyl aluminum hydride) to give an unstable lactol **4**,



Scheme 1

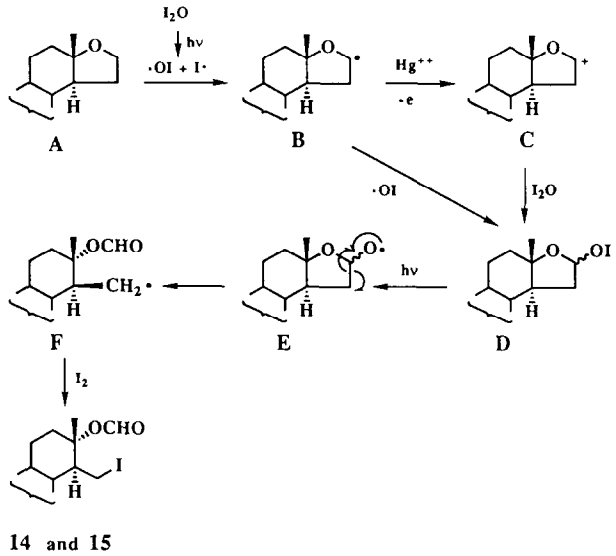


Scheme 2

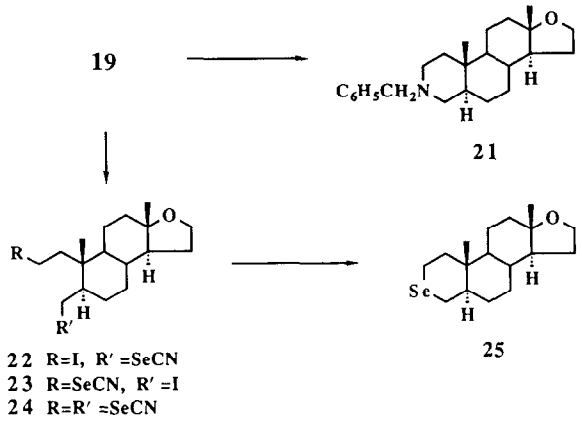
which readily lost the element of water, in 94% yield. Irradiation of lactol **4** in benzene containing mercury (II) oxide and iodine with Pyrex-filtered light under the conditions reported previously[18,19] gave a seco formate **5** and lactone **3** in 38% and 48% yields. Treatment of the seco formate **5** with methyllithium at −78° C in dry THF under the conditions reported previously[17] directly gave 17-oxa-5α-androstan-3β-ol **(6)** in 81% yield. The oxidation of the 3β-alcohol **6,** as described in a previous report,[17] gave 17-oxa-5α-androstan-3-one **(7).**[18,20]

Baeyer-Villiger oxidation of the 3-ketone **(7)** with MCPBA gave the corresponding isomeric lactones, **8** and **9,** in a combined yield of 95%. The reduction of a mixture of lactones **8** and **9** in toluene with DIBAL gave a mixture of the corresponding lactols, **10** and **11,** in a combined yield of 89% (Scheme 1). A mixture of lactols **10** and **11** was then subjected to a β-scission reaction by dissolving it in benzene containing mercury (II) oxide and iodine and irradiating the solution with Pyrex-filtered light under the above-mentioned conditions (Scheme 2). This photolysis gave the expected oily formates, **12** and **13,** in 25.6% and 25.4% yields, together with two unexpected isomeric compounds, **14** and **15,** which were separated by preparative TLC (Scheme 2). The ^{1}H NMR spectra of the less mobile compound **14** (7.8%) and the more mobile compound **15** (8.0%) each exhibited two 1H singlets (δ 7.99 and 8.04 for **14,** δ 8.01 and 8.08 for **15**), assignable in each case to a formyloxy group. The electron impact mass spectra of both products **14** and **15** exhibited no molecular ions, but did exhibit $(M - 2HOCHO)^+$ ions. The molecular formulae of products **14** and **15** were then each confirmed as being $C_{18}H_{28}O_4I_2$ by means of high-resolution mass spectrometry. The IR, ^{1}H NMR, and MS spectra suggested that the structures of products **14** and **15** are diformyl esters **14** and **15** arising from a cleavage of the D ring of formates **12** and **13.** The pathway by which the D ring of seco steroids **12** and **13** is cleaved is outlined in Scheme 3. Thus, the iodoxy radical generated from iodine oxide abstracts a hydrogen attached to C(16) of the D ring of 17-oxasteroid **(A)** to give a carbon radical **(B).** Lactol hypoiodite intermediate **(D)** is then formed from the carbon radical **(B)** either by the reaction of a carbocation **(C),** formed by one-electron oxidation, with iodine oxide. A regioselective β-scission of an alkoxyl radical **(E)** generated by irradiation gives ω-iodoalkyl formates **14** and **15** via a carbon radical **(F).** The results that support the pathway outlined in Scheme 3 will be reported elsewhere.[21]

Treatment of the iodo formate **13** in THF with sodium borohydride under reflux (as described previously[18]) gave 3,17-dioxa-5α-androstane **(16)** in 77% yield (Scheme 2). Treatment of the isomeric iodo formate **12** with sodium borohydride, however, gave no dioxasteroid **16** but, rather, a product arising from a reductive elimination of iodine. It should be noted that the corresponding iodo formate of the cholestane series gave 5α-3-oxacholestane on treatment with sodium borohydride.[18] Thus, a modification of the D ring of



Scheme 3



Scheme 4

iodo formate **12** apparently affects the direction of the reactions that take place at C-2 and C-3. These effects are probably due to some slight alterations in the conformations of the two relevant substituents and the distance between the two reaction centers. The exact reason, however, is not yet clear.

We next synthesized 3-thia-17-oxa-5α-androstane **(20)** and 3-benzyl-3-aza-17-oxa-5α-androstane **(21).** A reduction of iodo formate **12** in toluene with DIBAL gave 2-iodo-2,3-seco-17-oxa-5α-A-norandrostan-3-ol **(17)** in 90% yield. Iodoalcohol **17** gave its mesylate **18** by the standard procedure in 98% yield. Heating of a solution of mesylate **18** and sodium iodide in acetone under reflux for 3 days gave 2,3-diiodo-2,3-seco-17-oxa-5α-A-norandrostane **(19)** in 96% yield. Heating the diiodide **19** and sodium sulfide in ethanol under reflux for 6 hours as reported previously[19] gave 3-thia-17-oxa-5α-androstane **(20)** in 86% yield (Scheme 2).

Similarly, heating the diiodide **19** and benzylamine in dioxane for 27 hours gave 3-benzyl-3-aza-17-oxa-5α-androstane **(21)** in 96% yield (Scheme 4).

Finally, the synthesis of 3-selena-5α-17-oxaandrostane **(25)** was accomplished (Scheme 4). Diiodide **19** was transformed into a mixture of monoselenocyanates, **22** and **23,** in 65% yield (based on consumed diiodide) by heating it in acetone containing an equivalent of potassium selenocyanate[19,22] for 2 hours. The use of excess potassium selenocyanate in this reaction resulted only in the formation of diselenocyanate **24.** Treatment of monoselenocyanates **22** and **23** in a mixed solvent of THF/ethanol (4 : 1) with sodium borohydride for 3 days at 40° C (as reported previously[19]) gave a crystalline-3-selena-17-oxa-5α-androstane **(25)** in 77% yield (Scheme 4).

The biologic activities of 3-hetero-17-oxa-5α-androstanes **16, 20, 21,** and **25** synthesized in this work will be reported elsewhere.

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