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Synthetic Studies Toward 1a-Hydroxytestosterone from Testosterone

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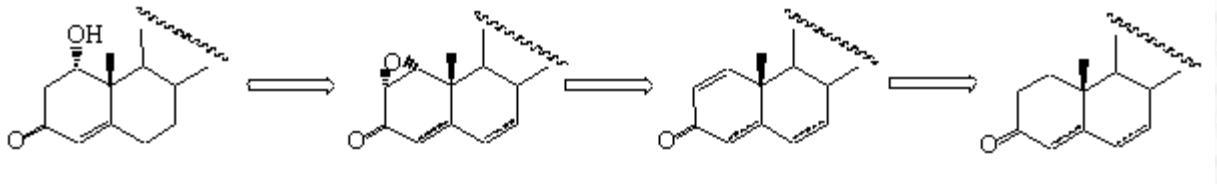
Abstract: Alternative synthetic routes to androst-4-ene-1a,17b-diol-3-one (1a-hydroxytestosterone) have been investigated. Within this objective numerous reported reductions have been reviewed and synthetically evaluated.

Introduction

1a-Hydroxytestosterone is of great interest in the enzyme conversion of androst-4-ene-3,17-dione into the A-ring aromatic estrone. The first synthesis of this compound other than *via* microbiological methods[1] was accomplished from 5a-androstan-17b-ol-3-one-17-benzoate (dihydrotestosterone benzoate) with nine steps and 3.7% yield.[2] Since it is desirable to make this compound more readily available for biological experimentation, we report our studies directed toward more efficient synthesis of 1a-hydroxytestosterone.

Retrosynthetic Analysis

Figure 1

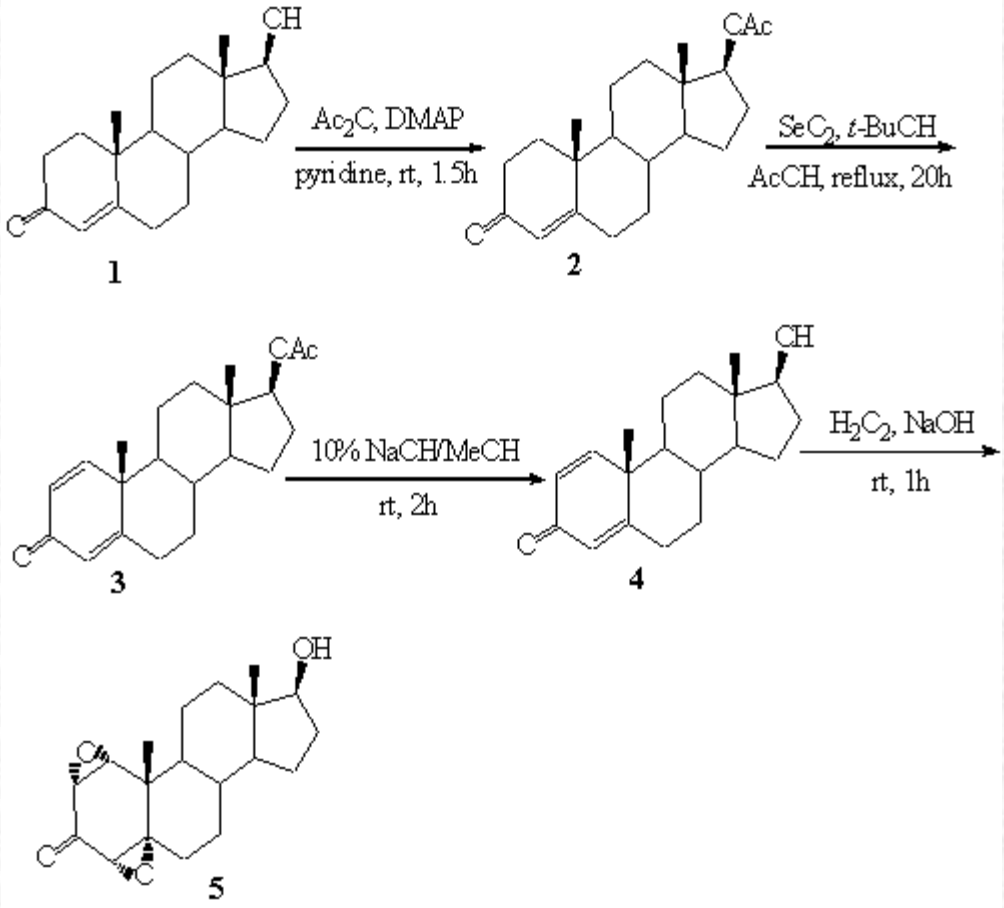


1a-Hydroxysteroids can be synthesized by catalytic hydrogenation;[3-9] sodium borohydride reduction;[10] lithium aluminum hydride reduction;[2, 11] or Birch reduction (lithium metal and ammonium chloride in ammonia-tetrahydrofuran)[11-17] of 1a,2a-epoxide steroids (Fig. 1). Double bonds in a,b-unsaturated keto steroids can be selectively oxidized with alkaline hydrogen peroxide to yield epoxy ketones. The nucleophilic attack of hydroperoxide ion on the D^{1}-3-ones yield predominantly a-oxiranes because of steric factors. The introduction of $D^{1, 2}$-double bond can be accomplished by dehydrohalogenation[2, 18-20] or DDQ[21-28], SeO_2[28-29] dehydrogenation. The $D^{4, 5}$-double bond can exist before the introduction of 1a,2a-epoxide[4] or be introduced after the introduction of 1a,2a-epoxide.[2] For the

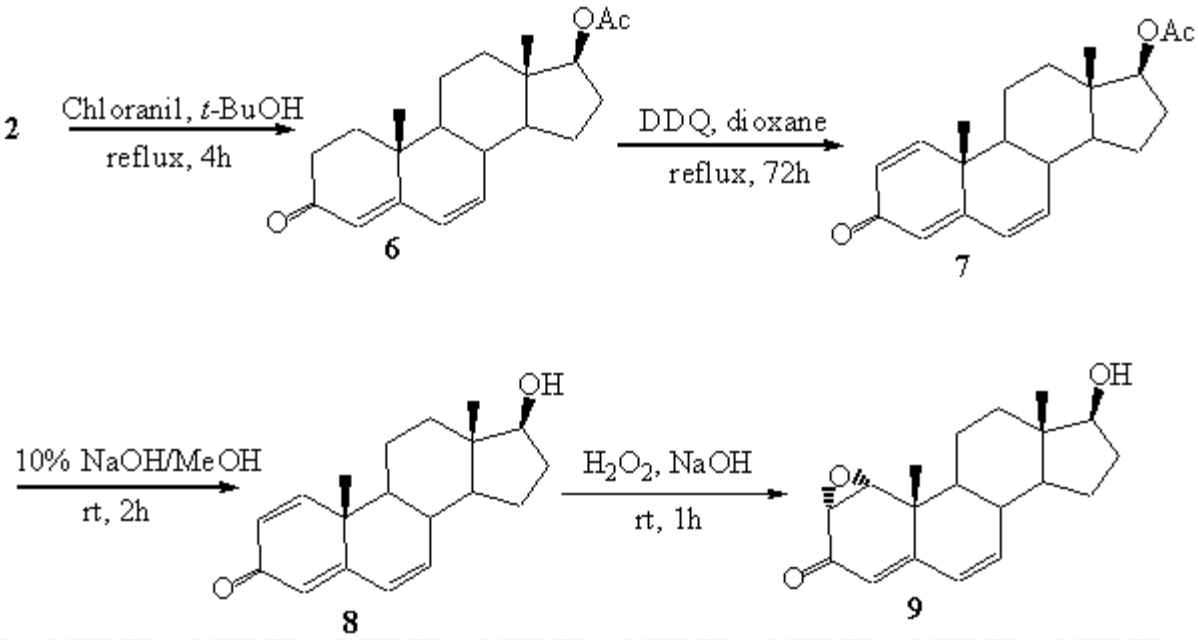
synthesis of 1a-hydroxytestosterone, the second strategy has been done by Mann and Pietrzak[2] and the first one has never been attempted. We report our results concerning the second strategy.

Results and Discussion

Scheme 1



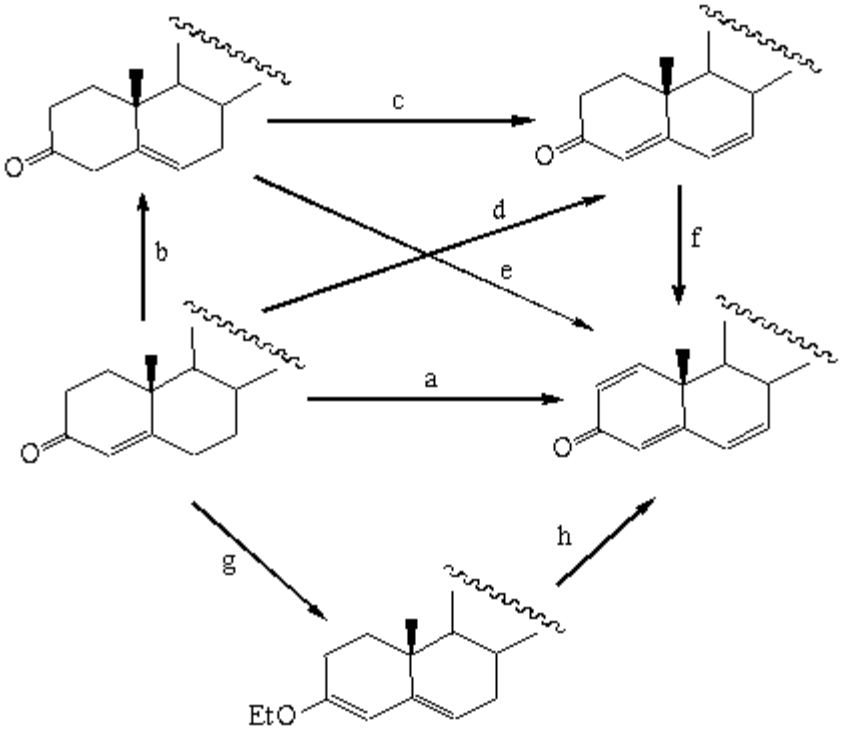
Scheme 2



The first synthetic route is showed in Scheme 1. The 17b-hydroxyl group (**1**) was first protected by acetate. The reaction was carried out in pyridine with 4-dimethylaminopyridine (DMAP) as the catalyst. Without DMAP, reaction can not be completed even with prolonged time. The $D^{1,2}$-double bond was introduced by SeO_2 the dehydrogenation.[28-29] The selective peroxidation of $D^{1,2}$-double bond was unsuccessful.

To selectively introduce 1a,2a-epoxide, the second synthetic route was showed in Scheme 2. The preparation of $D^{1,4,6}$-3-ones can be finished one step or two steps (Scheme 3). Oxidation of the D^4-3-one system preferentially gives the $D^{4,6}$-3-one system over the $D^{1,4}$-3-one system because their p_P -electronic system of the former is more stable than latter cross-conjugated system. In 1960, Agnello and Laubach[29] reported one step synthesis of $D^{1,4,6}$-3-ones by the treatment of D^4-3-ones with chloranil in *sec*-amyl or *n*-amyl alcohols. The followning research repeated the same reaction with low percent yield (30%).[4] As a preparative route to $D^{1,4,6}$-3-ones, the anhydrous reaction in benzene at room temperature gives 40-55% of product after chromatography and is inferior to a stepwise (*via* $D^{4,6}$).[23-24] The principal side reactiion (which also occur in the acid catalyzed reaction of D^4-3-ones with two moles of DDQ) appears to be

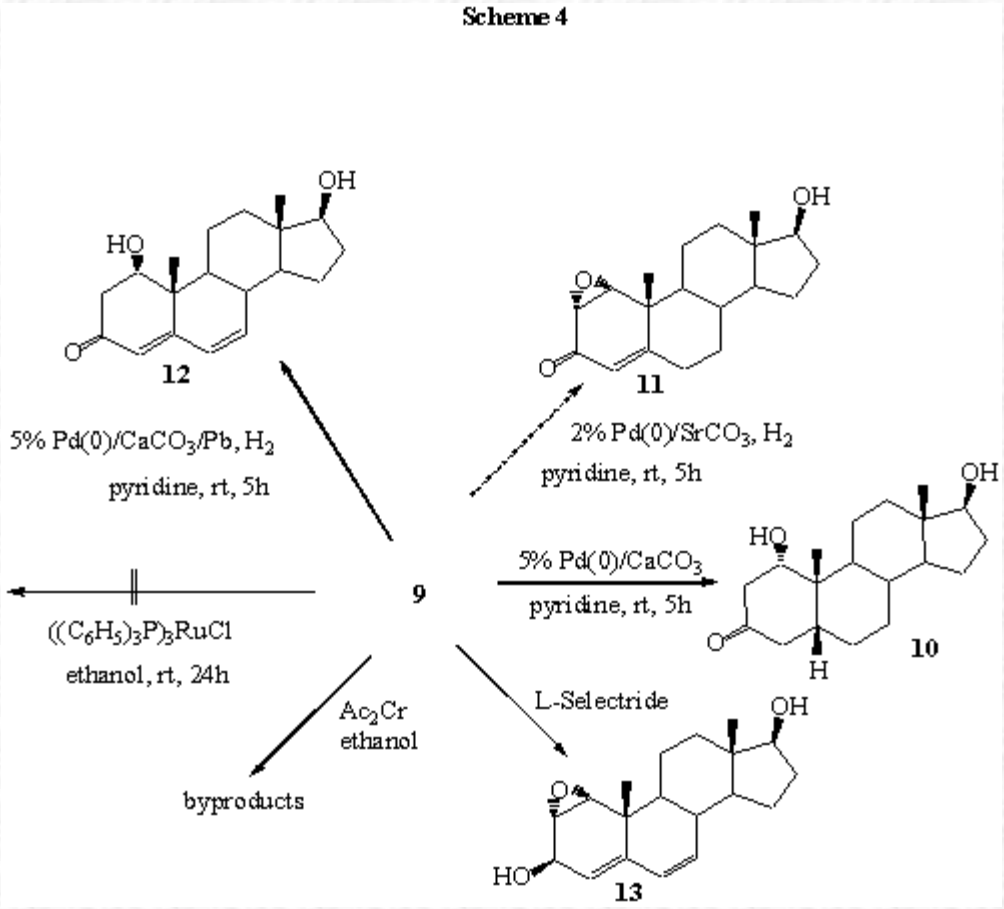
Scheme 3



a) chloranil, pentan-2-ol, reflux, 3h; b) *t*-BuOK, *t*-BuOH, rt, HOAc;
c) chloranil (1.1 equiv.), benzene, reflux, 15h; d) chloranil, *t*-BuOH, reflux, 3h
or DDQ, HCl, dioxane, 15 min; e) chloranil (2.0 equiv.), benzene, reflux, 2.5h;
f) DDQ, dioxane, reflux, 5h;g) EtOH, $HC(OEt)_3$, *p*-TsOH
or dioxane, $HC(OEt)_3$, *p*-TsOH, rt, 1h; h) DDQ, benzene, rt, 0.5h.

addition of the hydroquinone.[21, 24] A related reaction involving attack at C-6 was also reported.[30] The two step synthesis of $D^{1, 4, 6}$-3-ones from D^4-3-ones can be concluded by three ways: 1) The D^4-3-ones were converted to 3-ethoxy-3,5-dienesteroids and then the reaction of DDQ leads to $D^{1, 4, 6}$-3-ones;[23-25] 2) Treatment of D^4-3-ones with chloranil in *t*-butanol[23, 29] or DDQ in dioxane[31-33] gave the corresponding $D^{4, 6}$-3-ones. Subsequent dehydrogenation with DDQ in dioxane or benzene gave $D^{1, 4, 6}$-3-ones; [23, 26-29] 3) The D^4-3-ones were deconjugated by kinetic protonation to give the b,g-unsaturated ketones.[34-35] Treatment of 5-en-3-ones with two equivalents of DDQ in benzene or dioxane gave $D^{1, 4, 6}$-3-ones.[26] Our investigations found that the direct dehydrogenation of **2** to **7** by either DDQ or chloranil proceeded in only low yields and it was very difficult to separate $D^{1, 4, 6}$-3-ones from dienones. The two step dehydrogenation (*via* $D^{4, 6}$-3-ones) gave satisfactory results. Treatment of $D^{4, 6}$-3-ones **6** with DDQ in dioxane[23, 26, 29, 33] in 24 hours only gave 30-40% **7**. We have found that a separated addition of DDQ and prolonged reaction time (72 hours) is quite essential to improve the yield (68%). Subsequent ester hydrolysis provide the corresponding alcohol **8**.

Scheme 4



We first repeated the same epoxidation on **8** and found that the overnight reaction[2, 3] gave a polar side product which may be due to the base open the epoxide. TLC in ethyl acetate-hexane (1:1) showed that the reaction could be accomplished after 1 hour instead of 3 hours.[4] The following hydrogenation in pyridine over Pd(II)/$CaCO_3$[3, 4] on **9** gave 1a,17b-dihydroxy-5b-androstan-3-one (**10**) even with shorter reaction time (5 hours) (Scheme 4). The orientation of the 5 proton in **10** is presumably mainly b. A similar reduction of cholesta-1a,2a-epoxy-4,6-dien-3-one gave mainly 5b proton.[5] The TLC ($CHCl_3$: CH_3OH=9:1) showed that most of reactants can not be reduced with further shorter reaction time (2-3 hours). The pre-hydrogenated 5% Pd(0)/$CaCO_3$ catalyst can not improve the selectivity. In 1996, Liu and co-workers reported that the selective hydrogenation of 17-substituted 13b-ethyl-11b-hydroxy-gona-4,9-dien-3-ones in Pd(0)/$SrCO_3$-pyridine media gives the corresponding 11b-hydroxy-gon-4-en-3-ones.[36] According to Jeger and Wehrli's results on 1a,2a-epoxy-17b-3-oxoandrosta-4,6-diene, compound **11** should be synthesized.[37] We found that this catalyst gave the same results as Pd(0)/$CaCO_3$ on reduction of **9**. Compared with the 6a,7a-epoxide, the chromium (II) acetate reduction[38] on 1a,2a-epoxide gave a complex mixture. Compared with the $D^{1, 4}$-3-one system, the Wilkinson's catalyst [chlorotris(triphenylphosphine)rhodium (I)] in our hands did not reduce $D^{4, 6}$-3-one system.[38] In 1956, Howe and McQuillin found that Pd(II)/$CaCO_3$/Pb (Lindlar catalyst) was effective on selective reduction the terminal bond of a dienone of b-cyperone.[39] A similar selective hydrogenation of b-damascenone was reported by Büchi and Wüest in 1971.[40] We found that this catalyst can only reduce 1a,2a-epoxide within 5 hours reaction. Both $D^{6, 7}$-double bond and $D^{1, 2}$-double bond will be reduced with prolonged time. In 1989, Jansen and co-workers[41, 42] reported that the dienone dienone can be selectively 1,6 reduced with Li-selectride to give enone. Our investigation showed that Li-selectride selectively reduced only the 3-ketone to give the 3b-hydroxy group.

1H NMR Spectra: All the ^1H NMR spectra are summarized in Table 1. The 17a-H show triblet because of coupling with the hydrogens at C-16. After the esterification of 17b-OH, both 17a-H and 18-methyl group shifts downfield

from 3.66 to 4.60 ppm and from 0.80 to 0.84 ppm, respectively. The 6,7-dehydrogenation has shielding effect on 4-H from 5.73 to 5.68 ppm. The 1,2-dehydrogenation has deshielding effect on 4-H from 5.73 to 6.02-6.08 ppm. After the epoxidation of 1,2-double bond, 4-H shift back to 5.66 from 6.01-6.04 ppm. After the reduction of 3-ketone, 4-H (from 5.66 to 5.21 ppm), 6-H (from 6.01-6.13 to 5.62 ppm) and 7-H (from 6.01-6.13 to 5.91 ppm) are shielded. In compound **13**, 7-H show a double-doublet because the couplings from 6-H and 8-H.

13C NMR Spectra: All the ^{13}C NMR spectra are summarized in Table 2. The assignments of these spectra are through comparisons with closely related compounds tabulated by Blunt and Stothers.[43] From these tables, we can see: 1) After acetate protection of the 17-hydroxyl group, the 18-methyl group deshielded 0.91 ppm; 2) After the formation of 6(7)-double bond, C-5 shift from 171.04 to 163.46 ppm and C-9 shift from 53.72 to 48.10 ppm. The two more sp^2 peaks demonstrated the 6(7)-double bond. Compared with C-7, C-6 is in the higher field because it is closer to 4(5)-double bond; 3) After the formation of 1(2)-double bond, C-3 shift up-field (199.48-186 ppm) and C-10 shift down-field (36.57-43.07 ppm). The two more sp^2 peaks demonstrated the 1(2)-double bond; 4) The reduction of 1a,2a-epoxide deshielding C-1 from 59.44 to 78.12 ppm. 5) After the reduction of $D^{4,5}$-double bond, 3-ketone deshield from 194.69 to 210.52 ppm.

Conclusion

The synthesis of 1a-hydroxytestosterone from testosterone *via* its 1,2,6,7-tetradehydro- and 1a,2a-epoxy-6,7-didehydro-derivatives has been attempted and various problems identified. The characterization of numerous intermediates of this study was accomplished by ^1H NMR, ^{13}C NMR and MS.

Experimental Section

Column chromatography was carried out using Grade 62 (60-200 mesh) silica gel and eluted by cyclohexane-ethyl acetate solvent system. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were measured at 250 MHz or 63 MHz (Bruker) in $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a VG20-253 or VGZAB-HS Spectrometer.

17b-**Acetoxy-androst-4-en-3-one (2):** To a cooled (0^0C) suspension of **1** (5.0g; 17.36 mmol) in acetic anhydride (5 mL) and pyridine (8 mL), DMAP (0.4g; 3.27 mmol) were added. The reaction mixture was stirred at 25^0C for 1.5 hr. The solvent was concentrated in vacuo, 50 mL ethyl acetate was added and the solution was washed with 1.0 M HCl, $NaHCO_3$ and NaCl solution. The organic layer was dried with Na_2SO_4 and solvent was evaporated to afford 5.35g (93.4%) **2** as a colorless crystal, m.p. 128-130^0C [ref.[44] m.p. 142-142^0C]. ^1H NMR ($CDCl_3$): 0.84 (s, 3H, 18-H_3); 1.19 (s, 3H, 19-H_3); 2.05 (s, 3H, 17-OAc); 4.60 (t, 1H, 17a-H); 5.73 (s, 1H, 4-H).

17b-**Acetoxy-androsta-1,4-dien-3-one (3):** To a solution of **2** (0.7g, 2.12 mmol) in *t*-BuOH (50 mL) and acetic acid (1.0 mL) was added SeO_2 (0.3g, 2.7 mmol), and then the reaction mixture was reflux for 20 h. A further SeO_2 (0.3g, 2.7 mmol) was added and the mixture was refluxed for 30h. After cooling, the precipitated Se was removed, the filtrate was evaporated in vacuo, and the residue extracted with ethyl acetate. The extracts were washed with 0.5M $Na_2S_2O_3$ solution, H_2O and brine. The dried extract was purified by chromatography through silica gel affording 0.47g (67.5%) **3** as a yellow crystal, m.p. 157-159^0C [ref.[22] m.p. 155^0C]. ^1H NMR ($CDCl_3$): 0.82 (s, 3H, 18-H_3); 1.24 (s, 3H, 19-H_3); 2.05 (s, 3H, 17-OAc); 4.58 (t, 1H, 17a-H); 6.08 (s, 1H, 4-H); 6.23 (d, 1H, 2-H); 7.05 (d, 1H, 1-H). MS(m/z): 328.2 $[M]^{+\cdot}$.

Androsta-1,4-dien-3-one-17b-**ol (4):** Compound **3** (0.4g, 1.22 mmol) was hydrolyzed by treatment with 10% methanolic NaOH solution (15 mL) for 2 hours at rt. After neutralization with 1.0M HCl, the solution was concentrated *in vacuo*, and the residue was extracted with methylene chloride. The organic layer was washed with aqueous $NaHCO_3$, water, brine and dried with Na_2SO_4. The solvent was evaporated to afford **4** (0.34g, 97.5%) as colorless

crystals, m.p. 160-162^{0}C. ^{1}H NMR ($CDCl_3$): 0.82 (s, 3H, 18-H_3); 1.25 (s, 3H, 19-H_3); 3.65 (t, 1H, 17a-H); 6.08 (s, 1H, 4-H); 6.23 (d, 1H, 2-H); 7.07 (d, 1H, 1-H). MS(m/z): 286.2 $[M]^{+\cdot}$.

Androstan-1a,2a;4a,5a-diepoxy-3-one-17b-ol (5): To a solution of **4** (0.1g, 0.35 mmol) in methanol (2 mL) was treated with 10% methanolic NaOH (0.036 mL) and 30% H_2O_2 (0.2 mL) for 3 hours at rt. Sodium sulphite (0.1g) was added, followed by brine (5 mL), and the product was extracted three times with methylene chloride (10 mL). The organic phase was washed with 0.1M HCl, NaCl solution, dried, and evaporated to give the crude epoxide. Further purification of the crude epoxide by column chromatography gave **5** (0.09g, 81%) as colorless crystal, m.p. 189-191^{0}C. ^{1}H NMR ($CDCl_3$): 0.80 (s, 3H, 18-H_3); 1.25 (s, 3H, 19-H_3); 3.15 (s, 1H, 4b-H); 3.41 (d, 1H, 2b-H); 3.59 (d, 1H, 1b-H); 3.66 (t, 1H, 17a-H). MS(m/z): 318.4 $[M]^{+\cdot}$.

17b-Acetoxy-androsta-4,6-dien-3-one (6): To a solution of **2** (5.0g, 15.15 mmol) in *t*-BuOH (60 mL) was added chloranil (4.5g, 18.3 mmol), and then the reaction mixture was reflux for 4 hours. After cooling, the reaction mixture was poured into saturated Na_2CO_3 solution and the products were extracted with CH_2Cl_2. The extracts were washed with 0.5M $Na_2S_2O_3$ solution and again wiith saturated Na_2CO_3 solution. The dried extract was evaporated and the residue was purified by chromatography through silica gel affording 2.72g (54.7%) **6** as a yellow crystal, m.p. 138-140^{0}C. ^{1}H NMR ($CDCl_3$): 0.89 (s, 3H, 18-H_3); 1.12 (s, 3H, 19-H_3); 2.06 (s, 3H, 17-OAc); 4.63 (t, 1H, 17a-H); 5.68 (s, 1H, 4-H); 6.11 (m, 2H, 6-H, 7-H). MS(EI): 328.2 $[M]^{+\cdot}$ (44), 268.2 $[M\text{-}HOAc]^{+\cdot}$ (36), 253.3 $[M\text{-}HOAc\text{-}CH_3]^+$ (14), 136.1 (34), 133.1 (50), 43.0 (100).

17b-Acetoxy-androsta-1,4,6-trien-3-one (7): To a solution of **6** (2.5g, 7.58 mmol) in dioxane (30 mL) was added DDQ (2.22g, 9.78mmol) three times during 72 hours refluxing. After cooling, the solution was filtered and treated in the same manner as used in **6**. Chromatography gave **7** (1.7g, 68.4%) as colorless crystals, m.p. 148-150^{0}C [ref.[45] m.p. 151-153^{0}C]. ^{1}H NMR ($CDCl_3$): 0.92 (s, 3H, 18-H_3); 1.21 (s, 3H, 19-H_3); 2.06 (s, 3H, 17-OAc); 4.62 (t, 1H, 17a-H); 6.02 (m, 2H, 2-H, 4-H); 6.23-6.27 (m, 2H, 6-H, 7-H); 7.06 (d, 1H, 1-H). MS(EI): 326.2 $[M]^{+\cdot}$ (34), 266.1 $[M\text{-}HOAc]^{+\cdot}$ (17), 251.1 $[M\text{-}HOAc\text{-}CH_3]^+$ (11), 134.1 (34), 133.1(56), 43.0 (100). **Androsta-1,4,6-trien-3-one-17b-ol (8)** was prepared in similar fashion as **4**, m.p. 153-155^{0}C [ref.[46] m.p. 156-158^{0}C] (94%). ^{1}H NMR ($CDCl_3$): 0.88 (s, 3H, 18-H_3); 1.21 (s, 3H, 19-H_3); 3.69 (t, 1H, 17a-H); 6.01-6.04 (m, 2H, 2-H, 4-H); 6.22-6.27 (m, 2H, 6-H, 7-H); 7.08 (d, 1H, 1-H). MS(m/z): 284.4 $[M]^{+\cdot}$.

Androsta-1a,2a-epoxy-4,6-dien-3-one-17b-ol (9) was prepared in similar fashion as **5**, m.p. 163-165^{0}C [ref.[6] m.p. 169-171^{0}C] (80%). ^{1}H NMR ($CDCl_3$): 0.87 (s, 3H, 18-H_3); 1.20 (s, 3H, 19-H_3); 3.46 (d, 1H, 2b-H); 3.60 (d, 1H, 1b-H); 3.72 (t, 1H, 17a-H); 5.66 (s, 1H, 4-H); 6.01-6.13 (m, 2H, 6-H, 7-H). MS(EI): 300.2 $[M]^{+\cdot}$ (100), 267.1 (35), 133.1 (81), 97.1 (93).

5b-Androstan-1a,17b-diol-3-one (10): To a suspension solution of pre-hydrogenated 5% Pd(0)/$CaCO_3$ catalyst (0.1g)[33] and epoxide **9** (0.1g, 0.33 mmol) in pyridine (8 mL) was bubbled a stream of hydrogen with stirring at rt for 5 h. The catalyst was filtered through a small silica-gel column and washed with pyridine (15 mL). The pyridine removed in a stream of air and the residue was chromatographyed afforded **10** (63mg, 61.8%) as colorless crystal, m.p. 163-165^{0}C [ref.[7] m.p. 168-170^{0}C]. ^{1}H NMR ($CDCl_3$): 0.76 (s, 3H, 18-H_3); 1.22(s, 3H, 19-H_3); 2.56-2.67 (m, 2H, 2-H); 3.64 (m, 1H, 17a-H); 3.71 (m, 1H, 1b-H). MS(m/z): 306.2 $[M]^{+\cdot}$.

Androst-4,6-dien-1a,17b-diol-3-one (12): To a suspension solution of 5% Pd(II)/$CaCO_3$/Pb catalyst (Lindlar catalyst, 0.1g) in pyridine (8 mL), was bubbled with hydrogen for 12 h. Then, the epoxide **9** (0.1g, 0.33 mmol) was added and hydrogen was bubbled for another 5 h. The catalyst was filtered through a small silica-gel column and the pyridine removed in a stream of air. Column chromatography gave **9** (35mg, 35%) and **12** (50mg, 49.7%), m.p. 213-215^{0}C. ^{1}H

NMR ($CDCl_3$): 0.82 (s, 3H, 18-H_3); 1.15(s, 3H, 19-H_3); 3.71 (m, 1H, 17a-H); 4.20 (m, 1H, 1b-H); 5.79 (s, 1H, 4-H); 6.14-6.17 (m, 2H, 6-H, 7-H). MS(m/z): 302.2 $[M]^{+\cdot}$.

Androsta-1a,2a-epoxy-4,6-diene-1a,3b,17b-triol (13): To a solution of **9** (0.1g, 0.33 mmol) in THF (2 mL) amd HMPA (0.35 mL) was added Li-selectride (0.88 mL, 1.0 M THF solution) at 0^0C. The reaction mixture was stirred for 10 h at 0^0C and quenched with water. The product was extracted with ethyl acetate and the combined extracts were washed with brine, dried and evaporated. The residue was purified by column chromatography gave colorless crystal **13** (55 mg, %), m.p. 187-189^{0}C. ^{1}H NMR ($CDCl_3$): 0.83 (s, 3H, 18-H_3); 1.00 (s, 3H, 19-H_3); 3.33 (d, 1H, 2b-H); 3.54 (d, 1H, 1b-H); 3.67 (t, 1H, 17a-H); 4.51 (broad s, 1H, 3a-H); 5.21 (s, 1H, 4-H); 5.62 (d, 1H, 6-H); 5.91 (dd, 1H, 7-H). MS(EI): 302.2 $[M]^{+\cdot}$ (1), 286.2 $[M-H_2O]^{+\cdot}$ (21), 151.2 (5), 122.1 (100), 41.1 (10).

Acknowledgment

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Table 1. Partial ^{1}H NMR Spectra

Cpd.	C-18	C-19	17b-OAc	17a-H	4-H	2-H	6,7-H	1-H
1	0.80(s)	1.20(s)	----	3.66(t)	5.74(s)	---	----	----
2	0.84(s)	1.19(s)	2.05(s)	4.60(t)	5.73(s)	----	----	----
3	0.82(s)	1.24(s)	2.05(s)	4.58(t)	6.08(s)	6.23(d)	----	7.05(d)
4	0.82(s)	1.25(s)	----	3.65(t)	6.08(s)	6.23(d)	----	7.07(d)
5	0.80(s)	1.25(s)	----	3.66(t)	3.15(s)	3.41(d)	----	3.59(d)
6	0.89(s)	1.12(s)	2.06(s)	4.63(t)	5.68(s)	----	6.11(m)	----
7	0.92(s)	1.21(s)	2.06(s)	4.62(t)	6.02(m)	6.02(m)	6.23-6.27(m)	7.06(d)
8	0.88(s)	1.21(s)	----	3.69(t)	6.01-6.04(m)	6.22-6.27(m)	7.08(d)	
9	0.87(s)	1.20(d)	----	3.72(t)	5.66(s)	3.46(d)	6.01-6.13(m)	3.60(d)
10	0.76(s)	1.22(d)	----	3.64(m)	----	2.56-2.67(m)	----	3.71(m)
12	0.82(s)	1.15(d)	----	3.71(m)	5.79(s)	----	6.14-6.17(m)	4.20(m)
13	0.83(s)	1.00(d)	----	3.67(t)	5.21(s)	3.33(d)	5.62-5.91(m)	3.54(d)

Table 2. ^{13}C NMR Spectra of 6-12

Assignment	**1**[43]	**1**	**2**	**6**	**7**	**8**	**9**	**10**	**12**
C-1	35.6	35.71	35.72	33.92	152.72	153.07	59.44	78.12	**71.75**
C-2	33.8	33.95	33.90	(33.92)	128.03	127.73	54.71	40.94	**43.97**
C-3	199.4	199.66	199.24	199.48	**188.44**	**194.69**	**210.52**		
C-4	123.6	123.82	123.91	123.85	124.03	123.79	119.60	42.52	123.19
C-5	171.0	171.46	171.04	**163.46**	162.24	162.71	158.66	45.97	
C-6	32.7	32.81	32.71	**128.23**	128.22	128.10	128.03	25.05	128.58
C-7	31.5	31.58	31.48	**139.98**	137.25	137.79	139.44	25.78	140.83
C-8	35.0	(35.71)	35.36	37.42	37.91	38.20	37.55	36.03	36.22
C-9	53.9	53.93	53.72	**48.10**	48.30	49.28	48.22	40.27	48.28
C-10	38.6	38.70	38.57	(36.57)	43.07	43.50	38.94	40.03	37.61
C-11	20.6	20.68	20.50	20.20	21.41	21.53	20.98	**23.17**	19.84
C-12	36.4	36.45	36.63	36.57	36.51	36.33	36.15	36.94	(36.22)
C-13	42.7	42.82	42.46	(48.10)	41.18	41.30	43.49	42.76	42.94
C-14	50.4	50.52	50.22	50.65	(48.30)	49.51	46.27	50.94	(48.28)
C-15	23.2	23.35	23.47	23.11	23.11	23.00	22.99	23.65	23.10
C-16	30.1	30.38	**27.48**	27.47	27.48	30.33	30.33	30.23	29.73
									(30.39)
C-17	81.0	81.51	82.43	82.12	82.00	81.10	81.15	82.00	81.33
C-18	11.0	11.10	**12.01**	12.01	12.07	11.16	10.98	11.23	11.04
C-19	17.3	17.41	17.41	**16.37**	20.81	20.75	18.50	19.17	17.83
C_{17OAc}-CH_3	----	-----	21.11	21.17	21.12	-----	-----	-----	-----
C_{17OAc}-CO	----	-----	170.86	170.11	-----	-----	-----	-----	

Table 2a. ^{13}C NMR Spectra of 1-5

Assignment	**1**[43]	**1**	**2**	**3**	**4**	**5**
C-1	35.6	35.71	35.72	**155.63**	**155.94**	**63.26**
C-2	33.8	33.95	33.90	**127.61**	**127.49**	**56.69**
C-3	199.4	199.66	199.24	**186.32**	**186.38**	**201.55**
C-4	123.6	123.82	123.91	124.01	123.85	**52.83**
C-5	171.0	171.46	171.04	**168.80**	**169.22**	**66.42**
C-6	32.7	32.81	32.71	33.12	33.18	33.06
						(33.42)
C-7	31.5	31.58	31.48	**32.76**	**32.81**	31.96
C-8	35.0	(35.71)	35.36	35.39	35.60	35.12
C-9	53.9	53.93	53.72	52.28	52.59	**48.83**
C-10	38.6	38.70	38.57	**43.55**	**43.67**	**38.10**
C-11	20.6	20.68	20.50	21.17	22.56	21.84
C-12	36.4	36.45	36.63	36.58	36.39	36.15
C-13	42.7	42.82	42.46	42.76	43.12	43.00
C-14	50.4	50.52	50.22	49.93	50.16	50.35
C-15	23.2	23.35	23.47	23.72	23.55	23.65
						(22.81)
C-16	30.1	30.38	**27.48**	**27.48**	**30.39**	30.61
						(29.72)
C-17	81.0	81.51	**82.43**	**82.37**	**81.41**	81.76
C-18	11.0	11.10	**12.01**	**12.14**	**11.20**	11.35
C-19	17.3	17.41	17.41	**18.77**	**18.74**	18.99
C_{17OAc}-CH_3	----	-----	21.11	22.38	-----	-----
C_{17OAc}-CO	----	-----	170.86	171.10	-----	-----

Table 2b. ^{13}C NMR Spectra of 6-13

Assignment	**6**	**7**	**8**	**9**	**10**	**12**	**13**
C-1	33.92	152.78	153.07	59.44	78.12	**71.75**	58.71
C-2	(33.92)	128.03	127.73	54.71	40.94	**43.97**	55.80
C-3	199.48	186.32	**188.44**	**194.69**	**210.52**	65.69	
C-4	123.85	124.02	123.79	119.60	42.52	123.19	120.88
C-5	**163.46**	162.30	162.71	158.66	45.97		130.82
C-6	**128.23**	128.21	128.10	128.03	25.05	128.58	128.10
C-7	**139.98**	137.26	137.79	139.44	25.78	140.83	140.10
C-8	37.42	37.91	38.20	37.55	36.03	36.22	36.75
C-9	**48.10**	48.31	49.28	48.22	40.27	48.28	48.65
C-10	(36.57)	43.06	43.50	38.94	40.03	37.61	42.03
C-11	20.20	21.41	21.53	20.98	**23.17**	19.84	20.92
C-12	36.57	36.51	36.33	36.15	36.94	(36.22)	36.33
C-13	(48.10)	41.18	41.30	43.49	42.76	42.94	43.43
C-14	50.65	(48.31)	49.51	46.27	50.94	(48.28)	45.67
C-15	23.11	23.11	23.00	22.99	23.65	23.10	23.11
C-16	27.47	27.48	30.33	30.33	30.23	29.73	30.27
						(30.39)	
C-17	82.12	82.00	81.10	81.15	82.00	81.33	81.33
C-18	12.01	12.07	11.16	10.98	11.23	11.04	11.04
C-19	**16.37**	20.80	20.75	18.50	19.17	17.83	17.30
C_{17OAc}-CH_3	21.17	21.14	-----	-----	-----	-----	-----
C_{17OAc}-CO	170.11	171.09	-----	-----	-----	-----	-----

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