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15β-Hydroxysteroids (Part VI).* Steroids of the human perinatal period: The preparation and reactions of 3β-hydroxy-5,15-androstadien-17-one. The synthesis of 3β,15β-dihydroxy-5-androsten-17-one and derivatives

Anthony Y. Reeder and George E. Joannou

Department of Metabolic Mass Spectrometry, Royal Prince Alfred Hospital, Camperdown, New South Wales, Sydney, Australia

*A successful approach to the synthesis of 3β,15β-dihydroxy-5-androsten-17-one (**14d**) has been developed using trichloroethoxy ethers as intermediates in the synthesis of the corresponding alcohols. 3β-Methoxymethoxy-5,15-androstadien-17-one (**10c**) was prepared by a selenation/dehydroselenation strategy from 3β-methoxymethoxy-5-androsten-17-one (**14c**). Base-catalyzed reaction of trichloroethanol with **10c** gave 3β-methoxymethoxy-15β-trichloroethoxy-5-androsten-17-one (**14g**). Under the same conditions, 3β-acetoxy-5,15-androstadien-17-one (**10b**) gave 3β-hydroxy-15β-trichloroethoxy-5-androsten-17-one (**14f**) which was characterized after conversion to **14g**. Cleavage of the trichloroethoxy group in **14f** with zinc or zinc/copper couple gave **14d**. The acid-catalyzed hydrolysis of 17,17-ethylenedioxy-5,15-androstadien-3β-ol (**15**) gave 3β-hydroxy-5,15-androstadien-17-one (**10a**) as the major product along with **14d**. However, addition of water to **10a** in the presence of acid gave the desired product **14d** in poor yield (15%). (Steroids* **61**:22–26, 1996)

Keywords: 15β-hydroxysteroids; trichloroethoxy ethers; organoseleno-steroids; synthesis; 3β,15β-dihydroxy-5-androsten-17-one

Introduction

The identification of 3β,15β,17α-trihydroxy-5-pregnen-20-one (**1**) in the human neonate[1] and in maternal urine[2,3] had established this as the most probable precursor of 3,15β-dihydroxy-1,3,5(10)-estratrien-17-one (**8**)[4] and 5-pregnen-3β,15β,17α,20α-tetrol (**9**),[5] found earlier in maternal urine of late pregnancy. The identification and characterization of 3α,15β,17α-trihydroxy-5β-pregnan-20-one (**2**)[1] and more recently of 3α,15β,17α-trihydroxy-5α-pregnan-20-one (**3**), 3β,15β,17α-trihydroxy-5α-pregnan-20-one (**4**), 3β,15β,17α-trihydroxy-5β-pregnan-20-one (**5**), 5α-pregnan-3α,15β,17α,20α-tetrol (**6**) and 5β-pregnan-3α,15β,17α,20α-tetrol (**7**)[6] (Figure 1), in newborn infants affected with congenital adrenal hyperplasia, an adrenal cortisol dysfunction, lends support that these are probable products of metabolism of 17α-hydroxypregnenolone and 17α-hydroxyprogesterone. Although the biosynthesis of **8**

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Anthony Reeder's current address is Department of Chemistry, University of Western Australia, WA 6907, Australia.
Address reprint requests to Dr. George E. Joannou, Ray William Research Institute of Endocrinology, Diabetes & Metabolism, Royal Alexandra Hospital for Children, Westmead, P.O. Box 3515, Parramatta, NSW 2124, Sydney, Australia.
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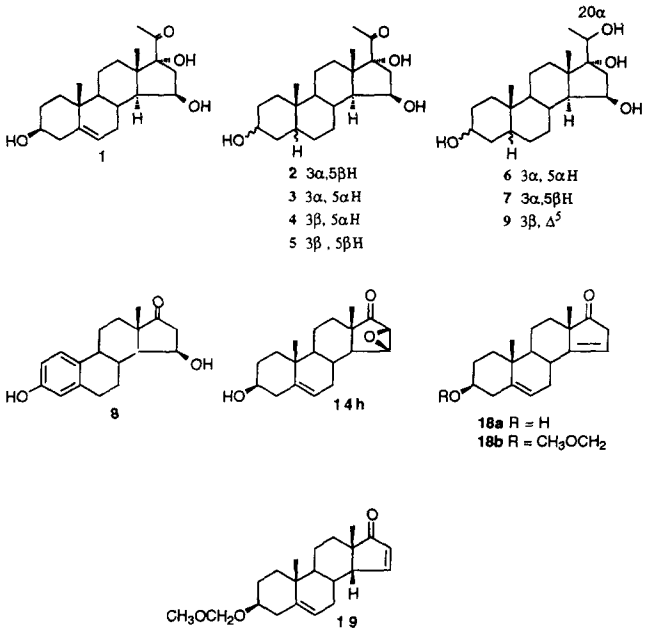


Figure 1 The structures of compounds **1–9, 14f, 18a, 18b,** and **19.**

has not been established, the identification of **1** supports a pathway via 3β,15β-dihydroxy-5-androsten-17-one **(14d).**

As part of an investigation into the chemistry and metabolism of 15β-hydroxylated steroids, we required a synthesis of **14d.** 15β-Hydroxylation has been reported by either epoxidation of 3β-hydroxy-5,15-androstadien-17-one **(10a)** to give 15β,16β-epoxy-3β-hydroxy-5-androsten-17-one **(14h)**[7,8] followed by reduction or by Michael-type addition of an alcohol to give 15β-alkoxy-3β-hydroxy-5-androsten-17-one **(14e)** followed by ether cleavage.[9,10] The synthesis of required Δ^{15}-17-ketosteroids has been achieved by either dehydrobromination[11] of 16α-bromo-17,17-ethylenedioxy-5-androsten-3β-ol **(11)** or by thermal elimination of a 16α-phenylsulphoxide.[12]

We describe a new approach in the synthesis of **14d** and give further insight into the reactions of steroid intermediates.

Experimental

All solvents were distilled and the light petroleum used had a boiling point of 60–80°C. All apparatus, when required dry, were heated in an oven at 150°C for more than 4 h, stoppered with a Supa Seal stopper, and cooled to room temperature over silica gel in a desiccator before use. THF was dried by refluxing over calcium hydride overnight followed by distillation. *n*-Butyl lithium concentration was determined by titration of 2,5-dimethoxybenzyl alcohol.[13] All reagents were obtained from commercial suppliers and used without further purification. 3β-Hydroxy-5-androsten-17-one **14a** was purchased from Sigma-Aldrich Pty. Ltd. and was used as received. 3β-Hydroxy-5,15-androstadien-17-one **10a** was prepared according to Kelly and Sykes[11] and also via a selenation/dehydroselenation route (data submitted for publication). Methoxymethyl chloride was prepared from dimethoxymethane, methanol and acetyl chloride.[14]

Melting points were determined using a Reichert Hot Stage Apparatus and are uncorrected. Ultraviolet spectra were obtained

on a Varian Techtron ultraviolet-visible spectrophotometer. Infrared spectra were recorded on a Perkin Elmer 297 infrared spectrophotometer using a nujol mull or carbon tetrachloride solution. Only the more characteristic frequencies are quoted. Proton nuclear magnetic resonance spectra were recorded in deuterochloroform at 90 MHz using a JEOL FX-90Q Fourier Transform spectrometer and for compound **14d** on at 400 MHz on a Bruker 400 Fourier Transform spectrometer. Solid probe chemical ionisation mass spectra (SP-CIMS), were obtained on Finnigan MAT TSQ-46 and TSQ-70 tandem quadrupole systems using methane as plasma. Microanalyses were carried out by the Australian Microanalytical Service (Ferntree Gully, Victoria, Australia). Preparative column chromatography was carried out using the technique of short column vacuum chromatography.[15]

3β-Hydroxy-5,15-androstadien-17-one (10a)

A solution of toluene-*p*-sulfonic acid (50 mg, 0.3 mmol) in water (5 mL) was added to a solution of 17,17-ethylenedioxy-5,15-androstadien-3β-ol **(15;** 1 g, 3 mmol), m.p. 160–161°C, prepared from 3β-hydroxy-5-androsten-17-one according to Kelly and Sykes,[11] in acetone (50 mL) and stirred at room temperature for 5 h. Water (15 mL) was added and the mixture was evaporated to half volume. The precipitate was filtered and air-dried to give 0.68 g (80%) of **10a;** m.p. 188–190°C; ^{1}H NMR δ 7.50 (1 H, dd $J_{15,16}$ = 7 Hz, $J_{14\alpha,15}$ = 2 Hz, H-15), 6.03 (1 H, dd $J_{15,16}$ = 7 Hz, $J_{14\alpha,16}$ = 3 Hz, H-16), 5.39 (1 H, m $W_{1/2}$ = 10 Hz, H-6), 3.54 (1 H, m $W_{1/2}$ = 26 Hz, H-3), 1.08 (6 H, s, H-18,19); λ_{max} = 231 (Log ε 3.86); υ cm^{-1} 3480, 1705, 1555, 1090, 1015, 865; SP-CIMS m/z (relative intensity %) 315 (12) $[M+29]^+$, 287 (100) $[M+1]^+$, 269 (94) $[MH-46]^+$; (lit.[11] m.p. 185–190°C; ^{1}H NMR δ 7.52 (1 H, d, H-16), 6.06 (1 H, q, H-15), 5.45 (1 H, m, H-6), 1.09 (6 H, s, H-18,19)).

The filtrate was extracted with ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4), evaporated to dryness, and the residue was chromatographed on silica gel eluting with ethyl acetate/light petroleum (1:2, v/v) to give 9 mg (10%) of **10a,** identical to that obtained above. Further elution with ethyl acetate/light petroleum (1:1, v/v) gave, after crystallization from ethyl acetate, 5 mg (5%) of 3β,15β-dihydroxy-5-androsten-17-one **(14d):** m.p. 181–183°C; ^{1}H NMR δ 5.39 (1 H, $W_{1/2}$ = 10 Hz, H-6), 4.54 (1 H, $J_{15\alpha,14\alpha}$ = 5 Hz, $J_{16\alpha,15\alpha}$ = 6 Hz, $J_{16\beta,15\alpha}$ = 1 Hz, H-15), 3.54 (1 H, $W_{1/2}$ = 26 Hz, H-3), 2.58 (1 H, $J_{16\beta,15\alpha}$ = 1 Hz, $J_{16\beta,16\alpha}$ = 20 Hz, H-16β), 2.51 (1 H, $J_{15\alpha,16\alpha}$ = 6 Hz, $J_{16\beta,16\alpha}$ = 20 Hz, H-16α), 1.30 (1 H, $J_{14\alpha,15\alpha}$ = 5 Hz, $J_{14\alpha,8\beta}$ = 11 Hz, H-14α), 1.19 (3 H, s, H-18), 1.08 (3 H, s, H-19); SP-CIMS m/z (%); 333 (11) $[M+29]^+$, 305 (58) $[M+1]^+$, 287 (100) $[MH-18]^+$, 269 (48) $[MH-36]^+$; (lit.[7] m.p. 182–184°C; ^{1}H NMR δ 5.36 (1 H, m, H-6), 4.68 (1 H, m, $J_{14,15}$ = $J_{15,16\alpha}$ = 4 Hz, $J_{15,16\beta}$ = 2 Hz, H-15), 3.53 (1 H, m, H-3), 2.67 (2 H, d, H-16), 1.21 (3 H, s, H-18), 1.09 (3 H, s, H-19)).

3β-Methoxymethoxy-16α-phenylseleno-5-androsten-17-one (16c)

To a solution of 3β-methoxymethoxy-5-androsten-17-one **(14c;** 0.5 g, 1.5 mmol), m.p. 124–126°C, prepared from 3β-hydroxy-5-androsten-17-one according to Weisz-Vincze,[18] in ethyl acetate (13 mL), benzeneselenenyl chloride (400 mg, 2 mmol) was added and after 24 h the solution was washed with sodium bicarbonate (saturated, aqueous), water, dried (Na_2SO_4) and evaporated to dryness. Chromatography of the residue on silica gel eluting with light petroleum removed the excess reagent and further elution with dichloromethane gave, after crystallization from dichloromethane/hexane, 660 mg (90%) of **16c:** m.p. 114–117°C, ^{1}H NMR δ 7.66 (2 H, $W_{1/2}$ = 21 Hz, aromatic), 7.32 (3 H, $W_{1/2}$ = 10 Hz, aromatic), 5.34 (1 H, $W_{1/2}$ = 10 Hz, H-6), 4.56 (2 H, s, MOM), 4.07 (1 H, $W_{1/2}$ = 13 Hz, H-16), 3.46 (1 H, $W_{1/2}$ = 26 Hz, H-3), 3.38 (3 H, s,

MOM), 1.00 (3 H, s, H-19), 0.91 (3 H, s, H-18); υ cm^{-1} 3075, 1730, 1585, 1160, 1115, 1030, 750, 690; SP-CIMS m/z (%); 529 (6) $[M+41]^+$, 517 (20) $[M+29]^+$, 489 (50) $[M+1]^+$, 471 (97) $[MH-18]^+$, 457 (12) $[MH-32]^+$, 441 (10) $[MH-48]^+$, 427 (100) $[MH-62]^+$, 409 (25) $[MH-80]^+$, 271 (37) $[MH-118]^+$, 251 (85) $[MH-138]^+$; found C 66.1%, H 7.3%, $C_{27}H_{37}O_3Se$ requires C 66.4%, H 7.6%.

To a solution at –78°C of lithium diisopropylamine, from diisopropylamine (0.27 mL) and *n*-butyl lithium in hexane (0.96 mL; 1.96 M), in anhydrous tetrahydrofuran (20 mL) a solution of **14c** (0.5 g, 1.5 mmol) in anhydrous tetrahydrofuran (7.5 mL) was added and the mixture was stirred for 20 min at –78°C. A solution of benzeneselenenyl bromide, prepared by the addition of bromine (58 µl) to a solution of diphenyldiselenide (0.35 g, 1.1 mmol) in anhydrous tetrahydrofuran (3.75 ml), was added slowly and the reaction mixture was poured into hydrochloric acid (1 M) and extracted with diethyl ether. The organic phase was washed successively with hydrochloric acid (1 M), sodium bicarbonate (saturated, aqueous), water. The organic phase was then dried (Na_2SO_4) and evaporated to dryness. Chromatography of the residue on silica gel eluting initially with hexane followed by dichloromethane gave after crystallization from dichloromethane/hexane, 0.55 g (75%) of **16c:** m.p. 114–117°C; identical to that obtained above.

3β-Methoxymethoxy-5,15-androstadien-17-one (10c)

To a cooled (–40°C) stirred solution of **16c** (50 mg, 0.1 mmol) in dichloromethane (4 mL), *m*-chloroperbenzoic acid (28 mg, 0.16 mmol) in dichloromethane (3 mL) was slowly added in 0.2 mL portions over a period of 10 min. After 45 min at –40°C, diisopropyl amine (0.5 mL, 4 mmol) was added and the cold reaction mixture was poured into a refluxing solution of diisopropyl amine (1.5 mL) in carbon tetrachloride (50 mL). After 15 min, the mixture was cooled to room temperature, washed with hydrochloric acid (1 M) then sodium bicarbonate (saturated, aqueous), water, and dried (Na_2SO_4). Evaporation to dryness and chromatography of the residue on silica gel eluting with hexane followed by ethyl acetate gave after crystallization from aqueous methanol 31 mg (91%) of **10c:** m.p. 128–130°C; ^{1}H NMR δ 7.53 (1 H, dd $J_{15,16}$ = 6 Hz, $J_{14\alpha,15}$ = 2 Hz, H-15), 6.04 (1 H, dd $J_{15,16}$ = 6 Hz, $J_{14\alpha,16}$ = 3 Hz, H-16), 5.40 (1 H, m, $W_{1/2}$ = 10 Hz, H-6), 4.67 (2 H, s, MOM), 3.46 (1 H, m, $W_{1/2}$ = 26 Hz, H-3), 3.38 (3 H, s, MOM), 1.08 (6 H, s, H-18,19); λ_{max} = 232 (log ε 3.86); υ cm^{-1} 3500, 1705, 1555, 1140, 1080, 1065; SP-CIMS m/z (%); 371 (4) $[M+41]^+$, 359 (10) $[M+29]^+$, 331 (36) $[M+1]^+$, 299 (11) $[MH-32]^+$, 269 (100) $[MH-62]^+$; found C 76.3%, H 9.1%; $C_{21}H_{30}O_3$ requires C 76.3%, H 9.2%.

To a solution of **10a** (1 g, 3.5 mmol) in dichloromethane (10 mL) and ethyldiisopropylamine (0.9 mL), methoxymethyl chloride solution[14] (1 mL) was added and the solution stirred overnight at room temperature. The mixture was diluted with ethyl acetate, washed with hydrochloric acid (1 M), sodium bicarbonate (saturated, aqueous), water, and dried (Na_2SO_4). Evaporation gave a solid which was recrystallized from aqueous methanol yielding 1.05 g (91%) of **10c:** m.p. 128–130°C; identical to that obtained above.

3β-Hydroxy-15β-(2',2',2'-trichloroethoxy)-5-androsten-17-one (14f)

To a solution of **10a** (1.5 g, 5 mmol) dissolved in THF (37.5 mL) and trichloroethanol (15 mL), aqueous sodium bicarbonate (37.5 mL, 10%) was added and the mixture was stirred at room temperature for 5 days before being evaporated to dryness. The residue was extracted with diethyl ether, washed with water, dried (Na_2SO_4), and evaporated to yield a gum which was purified by chromatography on silica gel. Elution with ethyl acetate/light petroleum (1:1, v/v) gave after crystallization from ethyl acetate 150 mg (10%) of **10a:** m.p. 188–190°C (lit.[11] m.p. 185–190°C) identical with that obtained above and 2 g (88%) of **14f** as a gum: ^{1}H NMR δ 5.37 (1 H, $W_{1/2}$ = 10 Hz, H-6), 4.31 (1 H, t *J* = 6 Hz, H-15), 4.08 (1 H, d *J* = 11 Hz, O-HCH-CCl_3), 3.98 (1 H, d *J* = 11 Hz, O-HCH-CCl_3), 3.53 (1 H, $W_{1/2}$ = 26 Hz, H-3), 1.21 (3 H, s, H-18), 1.09 (3 H, s, H-19); SP-CIMS m/z (%); 435 (40) $[M+1]^+$, 417 (68) $[MH-18]^+$, 399 (20) $[MH-36]^+$, 287 (98) $[MH-148]^+$, 269 (100) $[MH-166]^+$.

3β-Methoxymethoxy-15β-(2',2',2'-trichloroethoxy)-5-androsten-17-one (14g)

To a solution of **10c** (3 g, 9 mmol) dissolved in THF (75 mL) and trichloroethanol (20 mL), aqueous sodium bicarbonate (75 mL, 10%) was added and the mixture was stirred at room temperature for 5 days before being evaporated to dryness. The residue was extracted with diethyl ether, washed with water, dried (Na_2SO_4), and evaporated to yield a gum which was purified by chromatography on silica gel. Elution with ethyl acetate/light petroleum (1:1, v/v) gave 3 g (90%) of **14g:** m.p. 121–123°C; ^{1}H NMR δ 5.38 (1 H, $W_{1/2}$ = 10 Hz, H-6), 4.66 (2 H, s, MOM), 4.30 (1 H, $W_{1/2}$ = 10 Hz, H-15), 4.06 (1 H, d *J* = 11 Hz, O-HCH-CCl_3), 3.91 (1 H, d *J* = 11 Hz, OHCHCl_3), 3.48 (1 H, $W_{1/2}$ = 26 Hz, H-3), 3.38 (3 H, s, MOM), 1.12 (3 H, s, H-18), 1.04 (3 H, s, H-19); υ cm^{-1} 1730, 1160, 1120, 1035, 725; SP-CIMS m/z (%); 519 (3) $[M+41]^+$, 507 (6) $[M+29]^+$, 479 (25) $[M+1]^+$, 447 (31) $[MH-32]^+$, 417 (100) $[MH-62]^+$, 381 (40) $[MH-98]^+$, 331 (18), $[MH-148]^+$, 299 (45) $[MH-180]^+$, 269 (66) $[MH-210]^+$; found C 57.4%, H 6.6%; $C_{23}H_{33}O_4Cl_3$ requires C 57.6%, H 6.9%.

To a solution of **14f** (1.5 g, 3.4 mmol) dissolved in anhydrous dichloromethane (10 mL) and *N,N*-dimethylaniline (1.0 mL), methoxymethyl chloride solution[14] (1.2 mL) was added and the mixture stirred at room temperature overnight before being washed with hydrochloric acid (1 M), then water, dried (Na_2SO_4), and evaporated to dryness. Chromatography of the residue on silica gel eluting with ethyl acetate/light petroleum (1:2, v/v) gave a gum which crystallized from dichloromethane/methanol to give 1.6 g (96%) of **14g:** m.p. 121–123°C identical to that obtained above.

3β,15β-Dihydroxy-5-androsten-17-one (14d)

Zinc/copper couple[19] (0.112 g) was added as an ethanol slurry to a solution of **14f** (50 mg, 0.1 mmol) in ethanol (3 mL). The reaction mixture was refluxed for 30 min, then celite was added, the mixture was filtered, evaporated to dryness, and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), evaporated to dryness, and the residue was chromatographed on silica gel eluting with ethyl acetate/light petroleum (1:2, v/v) to give after recrystallization from ethyl acetate, 24 mg (70%) of **14d:** m.p. 182–184°C (lit.[7] m.p. 182–184°C); identical to that obtained above.

To a solution of **10a** (0.7 g, 2.4 mmol) dissolved in acetone (25 mL), a solution of toluene-*p*-sulfonic acid (0.2 g) in water (5 mL) was added. After stirring for 16 h, the mixture was neutralized with aqueous sodium bicarbonate (saturated, 5 mL), evaporated to low volume and the residue extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to dryness, yielding a gum which was chromatographed on silica gel eluting with ethyl acetate/light petroleum (1:4, v/v) to give after recrystallization from ethyl acetate, 200 mg (29%) of **10a** identical to that obtained above. Further elution gave after recrystallization from acetone 110 mg (15%) of **14d:** m.p. 182–184°C (lit.[7] m.p. 182–184°C) identical to that obtained above.

Results and discussion

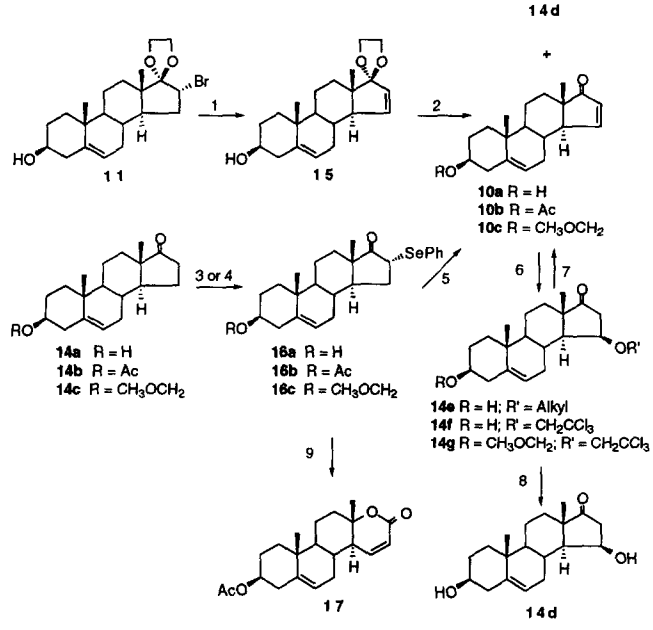
A new high-yielding synthesis of Δ^{15}-17-ketosteroids has been developed via 16α-phenylselenosteroids (e.g., **16c**)[20,21] (Scheme 1). 3β-Methoxymethoxy-16α-phenylseleno-5-androsten-17-one (**16c**) was prepared from 3β-methoxymethoxy-5-androsten-17-one (**14c**) using either benzeneselenenyl chloride in ethyl acetate[21] or by the addition of benzeneselenenyl bromide to the 16 anion of **14c** which was prepared by deprotonation of **14c** with lithium diisopropylamide in anhydrous THF.[20] A minor amount of the starting material (**14c**) was recovered due to the failure of the reaction to go to completion. Furthermore, pure crystalline 16α-phenylselenosteroids (e.g., **16c**) were found to undergo a photochemically catalyzed degradation to give the saturated deselenated steroid (e.g., **14c**).

Previously reported dehydroselenation of 16α-phenylselenosteroids (**16b**) using hydrogen peroxide resulted in a Baeyer-Villiger oxidation and an α,β-unsaturated lactone (e.g., 3β-acetoxy-17α-oxo-D-homo-5,15-androstadien-17-one (**17**)) being isolated (Figure 1).[16,21,22] Oxidation of **16c** using *m*-chloroperbenzoic acid at –40°C prepared the desired phenylselenoxide. Subsequent thermal elimination of the phenylselenoxide in the presence of a dialkyl amine avoided the undesired Baeyer-Villiger oxidation by the preparation of a selenamide (PhSeNR2)[20] and gave 3β-methoxymethoxy-5,15-androstadien-17-one (**10c**) in good yield (88%).

Although reportedly unstable,[9,23] in our hands the Δ^{15}-17-keto steroids once crystalline were stable. Only in our initial attempts to prepare 3β-methoxymethoxy-5,15-androstadien-17-one (**10c**) from 3β-hydroxy-5,15-androstadien-17-one (**10a**),[24,25] which resulted in ring D isomerization to give 3β-methoxymethoxy-5,14-androstadien-17-one (**18b**) and 3β-methoxymethoxy-14β-androsta-5,15-dien-17-one (**19**; Figure 1), was instability noticed. Reaction of **10a** with methoxymethyl chloride and ethyldiisopropyl-amine in dichloromethane gave **10c.** Conversely, 17,17-ethylenedioxy-5,15-androstadien-3β-ol (**15**) was found to be very unstable decomposing during chromatography on silica gel and on standing at room temperature. Acid-catalyzed hydrolysis of **15** gave two products, the expected **10a** and 3β,15β-dihydroxy-5-androsten-17-one (**14d**) formed by hydration of **10a.**

Trichloroethoxy esters can be cleaved by normal acid or base hydrolysis and under very mild conditions using metallic zinc.[26] Trichloroethoxy ethers should similarly be cleaved by the action of metallic zinc. 3β-Hydroxy-15β-trichloroethoxy-5-androsten-17-one (**14f**) was prepared by the base-catalyzed Michael-type addition of trichloroethanol to **10b** (Scheme 1).

Heating of **14f,** for example, during work-up, resulted in the thermal elimination of trichloroethanol and the formation of **10a** suggesting an Ei type mechanism with the *syn* elimination of the trichloroethoxy group and the C-16β proton. This product was surprising, as it is known that **10a** readily rearranges to give 3β-hydroxyandrosta-5,14-dien-17-one (**18a**).[9,12] This rearrangement has been attributed to the inherent strain of the steroidal *trans*-C,D-ring junction[27] as the ring-strain can be relieved by either isomerization of the proton at C-14 with formation of a *cis*-C,D-ring junction (e.g., **19**) or, alternatively, isomerization of the olefin out of conjugation to the C-14,15 position (e.g., **18a**). Reaction of **14f** with zinc-copper couple in boiling methanol[19] gave **14d,** the desired product, in good yield (70%). Attempted acid-catalyzed hydration of **10a** gave only a low yield of **14d,** proving less efficient that the route via the trichloroethoxy ethers.



Scheme 1. The synthesis of 3β,15β-dihydroxy-5-androsten-17-one.

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