Preparative chemical methods for aromatization of 19-nor-Δ^4-3-oxosteroids

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Two preparative chemical methods for aromatization of 19-nor-Δ^4-3-oxosteroids are described. The first method consists of an oxidative aromatization of 19-nor-Δ^4-3-oxosteroids with iodine-ceric ammonium nitrate in methanol to give a mixture of 3-methoxy ring-A aromatized derivatives consisting of the desired product, the $\Delta^{9,11}$ derivative, the 6-oxo derivative as well as some ring-A iodinated material. Conversion of this material to a mixture of the 3-methoxy ring-A aromatized derivative and its 6-oxo derivative was achieved by catalytic hydrogenation. Finally, reduction of the 6-oxo function with triethylsilane in trifluoroacetic acid gave the 3-methoxy-17-trifluoroacetate ring-A aromatized derivative as a single product. In the second method, reaction of 19-nor-Δ^4-3-oxosteroids with copper(II) bromide in acetonitrile at room temperature resulted in aromatic steroids in a single step in excellent yields. The second method was used in the first practical chemical synthesis of a 6-dehydroestrogen from a 19-nor-$\Delta^{4,6}$-3-oxosteroid. (*Steroids* **59**: 621–627)

Keywords: copper(II) bromide; ceric ammonium nitrate; iodine; aromatization; 19-nor-Δ^4-3-oxosteroids

Introduction

For the projected syntheses of some 13β-ethyl steroids, a method for the preparation of a large quantity of optically active D-(+)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one **4** was required. The published procedure for the synthesis of this material involves a total synthesis,[1] which was not considered to be a viable option. A reasonable alternative preparation of compound **4** is that outlined in Scheme 1, which consists of an initial de-ethynylation of the commercially available D-(-)-norgestrel **1**, followed by aromatization and methylation to give the desired compound **4**. The key step in this sequence would be an efficient method for the conversion of dione **2** to the ring-A aromatized derivative **3**.

The conversion of 19-nor-Δ^4-3-oxosteroids to the corresponding ring-A aromatized steroid is usually carried out by selective microbial procedures due to a lack of efficient chemical methods.[2] Usually, on a large preparative scale, the low solubility of steroidal substrates in aqueous systems renders the use of microbial procedures unwieldy due to the large volumes of fermentation media and extraction solvents required. The published chemical procedures for this transformation with such reagents as *N*-bromosuccinimide,[3,4] palladium black,[5] DDQ,[6] SeO_2,[7] and $CuBr_2$-LiBr in refluxing acetonitrile[8–10] are summarized in Table 1 and usually result in low yields of the desired aromatic steroid.

Two efficient procedures have been developed for the conversion of 19-nor-Δ^4-3-oxosteroids to the corresponding 3-hydroxestra-1,3,5(10)-trienes. In the first method, reaction of the 19-nor-Δ^4-3-oxosteroid with iodine-ceric ammonium nitrate (CAN-I_2) in refluxing methanol gave a mixture of ring-A aromatic products, which upon catalytic hydrogenation followed by reduction with triethylsilane in trifluoroacetic acid gave

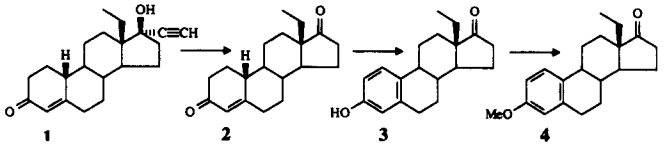

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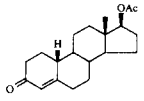
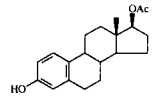
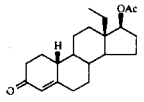
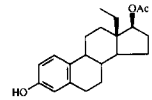
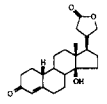
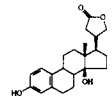
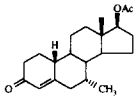
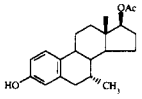
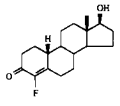
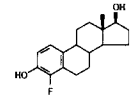
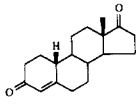
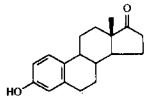
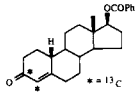
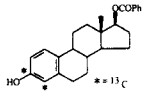
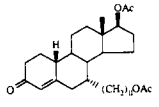
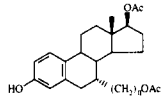
Table 1 Literature procedures for chemical aromatization of 19-nor-Δ^4-3-oxosteroids

Substrate	Product	Reagents and Conditions	Yield	Ref.
		1) NBS/CCl_4 reflux, hν 2) H_2(1 atm), PtO/EtOH	60%	3
		1) NBS/CCl_4, reflux 20 min 2) DBU/toluene, reflux 30 min	39%	4
		Palladium black/EtOH 260°C	27%	5
		DDQ/dioxane, reflux	44%	6
		SeO_2/*t*-BuOH, AcOH, 75°C-reflux	26%	7
		$CuBr_2$, LiBr/CCH_3CN reflux	85%	8
		$CuBr_2$, LiBr/CH_3CN reflux	56%	9
		$CuBr_2$, LiBr/CH_3CN reflux	68%	10

the 3-methyl ether of the ring-A aromatized derivative in good yield. In the second method, excellent yields of 3-hydroxyestra-1,3,5(10)-trienes were obtained by the reaction of the corresponding 19-nor-Δ^4-3-oxosteroid with copper(II) bromide alone in acetonitrile. Contrary to the published procedures using $CuBr_2$-LiBr in refluxing acetonitrile,[8–10] significantly higher yields were obtained by (a) carrying out the reaction at room temperature, and (b) limiting the amount of $CuBr_2$ to 1.2 equivalents. Under these modified conditions, we have also discovered that the presence or absence of lithium bromide has no effect either on the rate of the reaction or the yield of the ring-A aromatic product.

Experimental

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 Mhz) spectrometer using tetramethylsilane (TMS) as an internal standard ($\delta = 0.0$). Infrared spectra were recorded on a Perkin-Elmer FTIR model 1600 instrument equipped with a diffuse reflectance accessory using a KBr matrix. Optical rotations were measured using a Rudolph Research Autopol II automatic polarimeter using a 1.0 dm cell. Mass spectral analyses$^{(EI)}$ were conducted by Dr. Susan Weintraub of the University of Texas Health Science Center at San Antonio using a Finnigan-MAT model 4615. Combustion analyses were performed by Midwest MicroLabs Ltd. (Indianapolis, IN, USA). Flash-column chromatography was performed on 32–63 μM silica gel obtained from Scientific Adsorbants Inc. (Atlanta, GA, USA). Thin-layer chromatography (TLC) analyses were carried out on silica gel GF (Analtech) glass plates (2.5 × 10 cm with 250 μM and prescored).

Most chemicals and solvents were analytical grade and used without further purification. Ceric ammonium nitrate, copper-(II) bromide, lithium bromide, triethylsilane, trifluoroacetic acid, tetrapropylammonium perruthenate, and *N*-methylmorpholine *N*-oxide were purchased from Aldrich Chemical Company (Milwaukee, WI, USA).

In reactions that gave known compounds, the products were compared (NMR, IR, optical rotation, TLC, and m.p.) with authentic samples and/or literature values.

D-(+)-*13β-Ethylgon-4-ene-3,17-dione* (2)

D-(−)-Norgestrel **1** (35 g) was de-ethynylated by reaction with silver carbonate on Celite according to the procedure of Lenz[11] to give the diketone **2** (32.8 g) in 98% yield, m.p. = 170–173.5°C (lit.[12] 174.5–175.5 C).

$[\alpha]_D^{24} = +98.0$ (c = 1.0, $CHCl_3$) [lit.[12] $[\alpha]_D^{25} = +97.7$ (c = 1.165, $CHCl_3$)]. ^1H NMR ($CDCl_3$) δ 0.80, (t, J = 8 Hz, 13β-CH_2CH_3), 5.87 (br.s, C-4 H) ppm. IR (cm^{-1}) 2958, 1730, 1668, 1610. Analysis calculated: C 79.68, H 9.15. Found: C 79.48, H 9.18.

D-(+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17β-yl trifluoroacetate (6)

a. Reaction with CAN, I_2/MeOH. In dry glassware, the dione **2** (25.0 g, 87.3 mmol), ceric ammonium nitrate (71.9 g, 131.1 mmol), iodine (33.2 g, 131.1 mmol) and dry methanol (1 L) were combined and heated to reflux under nitrogen for 2.5 h. At the end of this time, TLC (2% acetone in CH_2Cl_2) indicated complete conversion of starting material. The dark brown mixture was cooled to room temperature and concentrated in vacuo at 40–50 C to ~200 mL. This residue was diluted with water (1200 mL) and extracted with ether (2 ×) and ethyl acetate (1 ×). The organic fractions were washed with water (2 ×), sodium thiosulfate solution (10%, 2 × 500 mL), water (2 ×), brine, and then combined and dried over anhydrous sodium sulfate. Filtration followed by concentration in vacuo gave 26.6 g residue as a grayish foam.

b. Catalytic reduction. The residue from the above reaction was dissolved in ethyl acetate (1 L), and added to palladium on calcium carbonate (5%, 15.0 g) in a 2-L Parr shaker flask and was hydrogenated overnight at 40 psi. Filtration followed by concentration in vacuo gave 26.2 g of a grayish oil indicated by TLC (2% acetone in CH_2Cl_2) to consist of a mixture of the desired product **4** and the 6-oxo derivative **6**.

D-(+)-13β-Ethyl-3-methoxygona-1,3,5(10)-triene-6,17-dione (6)

The crude product from a 1 g batch reaction of dione **2** with CAN-I_2/MeOH followed by catalytic hydrogenation was separated by flash column chromatography (2% acetone in CH_2Cl_2) to give 0.54 g of the methoxy ketone **4** and 0.38 g of 13β-ethyl-3-methoxygona-1,3,5(10)-triene-6,17-dione **6**, m.p. = 157–159°C. $[\alpha]_D^{24} = +55.0$ (c = 0.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 13β-CH_2CH_3), 3.87 (s, 3-OCH_3), 7.13 (d of d, J = 9 Hz, J' = 3 Hz, C-2H), 7.39 (d, J = 9 Hz, C-1H), 7.61 (d, J = 3 Hz, C-4H) ppm. IR (cm^{-1}) 2967, 1724, 1678. MS (m/z): M^+ = 312. Analysis calculated: 76.89, H 7.74. Found: C 76.89, H 7.71.

c. Silane reduction. The residue obtained from the catalytic reduction (step b.) was dissolved in benzene (1 L) and concentrated in vacuo at 50°C to remove any moisture. Under nitrogen, dry trifluoroacetic acid (150 mL, 2.0 mol) was added and the residue dissolved with stirring. Triethylsilane (35 mL, 2.17 mol) was introduced via syringe and the mixture stirred at room temperature for 4 h. At that time, TLC indicated incomplete reaction. Additional triethylsilane (5 mL) was added and the mixture was stirred for an additional 1 h. The mixture was then diluted with water (1 L), cooled in an ice bath, and carefully neutralized by the slow addition of sodium hydroxide (4N) at such a rate as to maintain the reaction at or below 20°C. The reaction mixture was then extracted with CH_2Cl_2 (4 ×). The organic fractions were washed with saturated sodium bicarbonate solution (1 ×), water (1 ×), brine (1 ×), and then combined and dried (Na_2SO_4). Filtration followed by concentration in vacuo gave the crude residue which was crystallized twice from methanol to give 17.9 g of the pure trifluoroacetate **7**. The mother liquors were concentrated in vacuo and the residue purified by flash column chromatography (20% CH_2Cl_2 in hexanes) to give an additional 4.2 g solid **7**. Total yield of **7** was 22.1 g (63.9% from **2**), m.p. = 132–135°C. $[\alpha]_D^{24} = +26.8$ (c = 1.1, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7 Hz, 13β CH_2CH_3), 2.87 (m, C-6H_2), 3.77 (s, 3-OCH_3), 4.93 (br.t, J = 9 Hz, 17α-H), 6.69 (s, C-4H), 6.73 (d of d, J = 8 Hz, J' = 3 Hz, C-2H), 8.4 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 2948, 1779. MS (m/z): M^+ = 396. Analysis calculated: C 66.65, H 6.86. Found: C 66.73, H 6.90.

D-(+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol (8)

A solution of the trifluoroacetate **7** (32.6 g, 82.2 mmol) in tetrahydrofuran (200 mL) was diluted with methanol (100 mL) and the system flushed with nitrogen. A solution of 1N KOH (90 mL, 90 mmol) was then added over a period of 5 min and the reaction mixture stirred at room temperature for 1 h. At the end of that time TLC (5% acetone in CH_2Cl_2) indicated a complete reaction. The solution was then concentrated to ~150 mL under a stream of nitrogen in a warm water bath, then diluted with water (~100 mL) and the resulting precipitate was extracted with ether (3 ×). The organic fractions were washed with water (3 ×), brine (1 ×), combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to give 25 g of the crude 17β alcohol **8**. Crystallization from ethanol/water gave the pure compound **8** (21 g, 85%). m.p. = 105–107°C (lit.[1] 103–106). $[\alpha]_D^{24} = +50.0$ (c = 1.0, $CHCl_3$) {lit.[1] $[\alpha]_D^{20} = +51$}.

^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7 Hz, 13β-CH_2CH_3), 3.78 (s, 3-OCH_3), 3.83 (br.t, 17α-H), 6.68 (br.s, C-4H), 6.74 (d of d, J = 7 Hz, J' = 2 Hz, C-2H), 7.2 (d, J = 7 Hz, C-1H) ppm. IR (cm^{-1}) 3299, 2940, 1610.

D-(+13)β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (4)

A mixture of the 17β-alcohol **8** (26 g, 86.5 mmol), *N*-methylmorpholine *N*-oxide (21 g, 174 mmol), and powdered 4-Å molecular sieves (100 g) in dry CH_2Cl_2 (1.5 L) was stirred mechanically under nitrogen for 1.5 h. Solid tetrapropylammonium perruthenate (1.5 g, 4.3 mmol) was added and the mixture was stirred at room temperature. After 30 min, TLC (2% acetone in CH_2Cl_2) indicated complete reaction. The mixture was filtered through Celite and the filtrate concentrated to dryness in vacuo. The residue was taken up in CH_2Cl_2 (150 mL), diluted with ether (150 mL) and passed through a column of neutral alumina, eluting with ether. Evaporation of the solvent followed by crystallization of the residue from CH_2Cl_2/MeOH gave the pure 17-ketone **4** (25 g, 97%), m.p. = 144–146°C (lit.[1] 146–148 C). $[\alpha]_D^{24} = +102$ (c = 1.0, $CH_3OH/CHCl_3$ 1:1) {lit.[1] $[\alpha]_D^{20} = +104$ (c = 1, $CH_3OH/CHCl_3$ 1:1)} ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 13β-CH_2CH_3), 3.80 (s, 3-OCH_3), 6.65 (s, C-4H). 6.7 (d of d, J = 9 Hz, J' = 3 Hz, C-2H), 7.19 (d, J = 9 Hz, C-1H) ppm. IR (cm^{-1}) 2948, 1779. Analysis calculated: C 80.50, H 8.78. Found: C 80.51, H 8.82.

3-Methoxyestra-1,3,5(10)-triene-17-one (10) and 3-methoxy-1,3,5(10)-triene-6,17-dione (11)

In dry glassware, a mixture of estr-4-ene-3,17-dione **9** (0.5 g, 1.84 mmol), ceric ammonium nitrate (1.01 g, 1.84 mmol), and iodine (0.47 g, 1.85 mmol) in dry methanol (20 mL) was heated to reflux under nitrogen for 2 h. At the end of that time, TLC (ether) indicated that the majority of the starting material

had reacted. The mixture was cooled to room temperature and the methanol removed under a stream of dry nitrogen. The residue was diluted with water (~50 mL) and extracted with ether (3×). The organic fractions were washed with water (2×), sodium thiosulfate solution (10%, 1×), water (1×), brine, and then combined and dried over anhydrous sodium sulfate. Filtration followed by concentration in vacuo gave 0.45 g residue indicated by TLC (ether) to consist of two major components. Separation by flash column chromatography (20% hexanes in ether) gave 3-methoxyestra-1,3,5(10)-trien-17-one **10** (0.25 g, 48%), m.p. = 167–169C (lit.[13] 164–167°C), ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 18-CH_3), 3.80 (s, 3-OCH_3), 6.68 (br.s, 4-CH), 6.75 (d of d, J = 8 Hz, J' = 3 Hz, 2-CH), 7.25 (d, J = 8 Hz, 1-CH) ppm. IR (cm^{-1}) 2916, 1738, 1610, and 3-methoxyestra-1,3,5(10)-triene-6,17-dione **11** (0.15 g, 27%), m.p. = 142–144°C. (lit.[14] 144–146 C), ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 18-CH_3), 3.89 (s, 3-OCH_3), 7.15 (d of d, J = 9 Hz, J' = 3 Hz, 2-CH), 7.40 (d, J = 9 Hz, 1-CH), 7.63 (d, J = 3 Hz, 4-CH) ppm. IR (cm^{-1}) 2954, 1742, 1672, 1602.

General procedure for aromatization with $CuBr_2/CH_3CN$

a. Reaction in the presence of LiBr. Under nitrogen, the 19-nor-Δ^4-3-oxosteroid was dissolved in anhydrous acetonitrile (10 mL/mmol of steroid if readily soluble, exceptions noted in Table 2) and solid $CuBr_2$ (2.1 equiv) and LiBr (1.1 Eq) were added and the dark green mixture stirred at room temperature and monitored by TLC until disappearance of starting material (2–2.5 h). Water was added until disappearance of the green color and the acetonitrile was removed in vacuo at 40–50°C. The residue was extracted with ethyl acetate (3×) and the organic fractions were washed with water (2×), brine (1×), combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. Isolation of the product was carried out by flash column chromatography (1–10% acetone in CH_2Cl_2) followed by crystallization from a suitable solvent to give the pure product.

b. Reaction in the absence of LiBr. Solid $CuBr_2$ (1.2 Eq) was added to a solution of the steroid in acetonitrile (0.1 M except where noted in Table 2) and the mixture was stirred at room temperature overnight (16 h). Workup as described above gave the pure compound.

13β-Ethyl-3-hydroxygona-1,3,5(10)-trien-17-one **(3)**

M.p. = 242–245°C. (EtOAc/benzene, lit.[1] 245–251°C.) ^{1}H NMR ($CDCl_3$ + D_7DMF) δ 0.73 (t, J = 7 Hz, 13β-CH_2CH_3), 6.59 (br.s, C-4H), 6.63 (d of d, J = 8 Hz, J' = 2 Hz, C-2H), 7.12 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 3398, 2923, 1718.

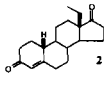
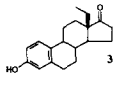
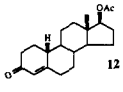
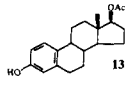
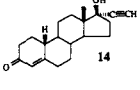
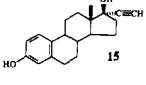
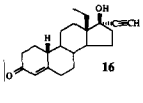
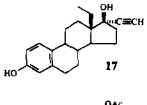
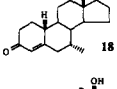
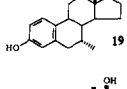
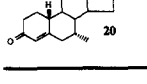
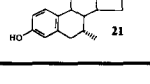
3-Hydroxyestra-1,3,5(10)-triene-17β-yl acetate **(13)**

M.p. = 213–217°C. (acetone/hexanes, lit.[15] 217–222°C.) ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 18-CH_3), 2.09 (s, 3-OAc), 4.76 (br.t, 17α-H), 6.63 (br.s, C-4H), 6.68 (d of d, J = 8 Hz, J' = 2 Hz, C-2H), 7.22 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 3419, 2932, 1703.

19-Nor-17α-pregna-1,3,5(10)-triene-20-yne-3,17β-diol **(15)**

M.p. = 142–144°C. (MeOH/H_2O, lit.[16] 145–146°C.) ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 18-CH_3), 2.61 (s, 17α- C≡C*H*), 6.62 (br.s, C-4H), 6.67 (d of d, J = 8 Hz, J' = 2 Hz), 7.15 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 3286, 2932, 1610.

Table 2 $CuBr_2$ aromatization of 19-nor-Δ^4-3-oxosteroids at room temperature

Substrate	Steroid concentration (*M*)	Equiv $CuBr_2$	Equiv LiBr	Reaction time (h)	Isolated yield %	Product
	0.1	2	1	2.5	71	
		1.5	0	16	82.1	
	0.1	2	1	2.5	68	
		2	0	4	82.5	
		1.1	1	3	50.4	
		1.1	1	16	84.7	
		1.1	0	16	85.5	
	0.033	2	1	2.5	65	
		1.2	0	16	79	
	0.007	2	1	2.5	72.5	
		1.2	0	16	67.6	
	0.1	2	1	2.5	77	
	0.033	2	1	2.5	85.9	
		1.2	0	16	81.0	

13β-Ethyl-18,19-dinor-17α-pregna-1,3,5(10)-triene-20-yne-3,17β-diol **(17)**

M.p. = 144–146°C. (acetone/pentane, lit.[1] 134–136°C, MeOH). ^{1}H NMR ($CDCl_3$ + D_6DMSO) δ 0.97 (t, J = 10 Hz, 13β-CH_2CH_3), 2.62 (s, 17α- C≡C*H*), 6.62 (br.s, C-4H), 6.67 (d of d, J = 8 Hz, J' = 2 Hz), 7.15 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 3239, 2932, 1610.

3-Hydroxy-7α-methylestra-1,3,5(10)-triene-17β-yl acetate **(19)**

M.p. = 136–139°C (acetone/pentane lit.[6] 133–136°C). ^{1}H NMR ($CDCl_3$) δ 0.83 (overlapping s and t, J = 7 Hz, 7 and 18-CH_3's), 2.07 (s, 17β-OAc), 4.75 (br.t, 17α-H), 6.60 (br.s, C-4H), 6.67 (d of d, J = 8 Hz, J' = 2 Hz, C-2H), 7.18 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 3321, 2954, 1730, 1699.

7α-Methyl-19-nor-17α-pregna-1,3,5(10)-triene-20-yne-3,17β-diol **(21)**

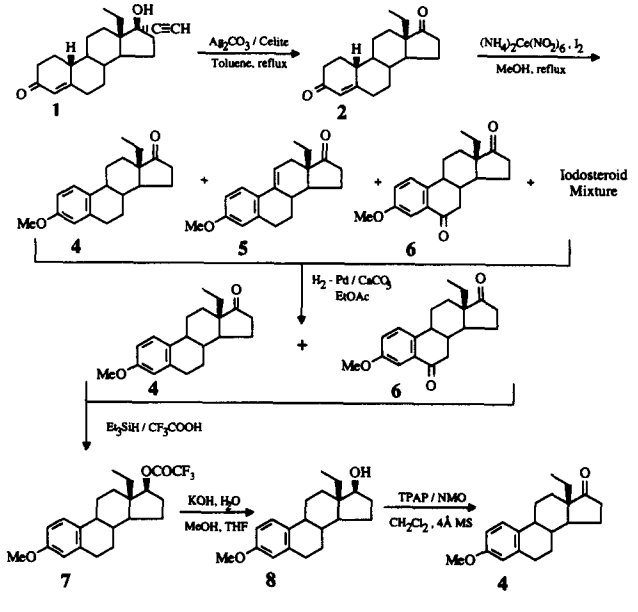
M.p. = 161–165°C ($MeOH/H_2O$, lit.[6] 122–123°C, Et_2O/petroleum ether). ^{1}H NMR ($CDCl_3$ + D_6DMSO) δ 0.89 (overlapping s and t, J = 7 Hz, 7 and 18-CH_3's), 2.60 (s, 17α-C≡CH), 6.70 (br.s, C-4H), 6.72 (d of d, J = 8 Hz, J' = 2 Hz), 7.20 (d, J = 8 Hz, C-1H) ppm. IR (cm^{-1}) 3296, 2952, 1610.

3-Hydroxyestra-1,3,5(10),6-tetraene-17β-yl acetate **(23)**

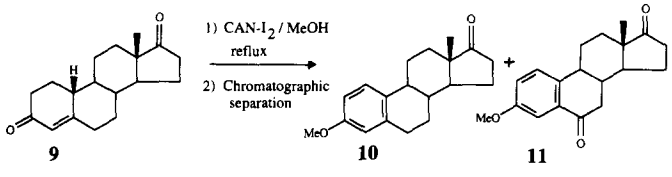
Solid $CuBr_2$ (1.8 g, 8.06 mmol) was added to a solution of estra-4,6-dien-3-one-17β-yl acetate **22** (0.629 g, 2 mmol) in acetonitrile (30 mL). The system was flushed with nitrogen and stirred at room temperature overnight (16 h). At the end of that time, TLC (2% acetone in CH_2Cl_2) indicated complete conversion of starting material. Sufficient water was added to decolorize the reaction mixture (~5–10 mL). The mixture was concentrated in vacuo at 40–50°C to remove acetonitrile and the residue was taken up in ethyl acetate and washed with water (3×) and brine (1×). The organic fractions were combined, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. To the oily residue was added ether (20 mL), glacial acetic acid (3 mL), and acid washed zinc powder (2 g) and the mixture was stirred under nitrogen at room temperature overnight. The mixture was diluted with ethyl acetate (30 mL), filtered free of solids, and extracted with ethyl acetate (3×). The organic fractions were washed with water (2×), brine (1×), combined, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (1% acetone in CH_2Cl_2) gave the pure 3-hydroxyestra-1,3,5(10),6-tetraene-17β-yl acetate **23** (0.322 g, 51%), m.p. = 247–249°C (acetone/pentane, lit.[17] 250–251 C). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.82 (s, 18-CH_3), 2.07 (s, 17β-OAc), 4.74 (br.t, 17α-H), 5.96 (d, J = 9 Hz, C-7H), 6.46 (d of d, J = 9 Hz, J' = 2 Hz, C-6H), 6.63 (br.s, C-4H), 6.71 (d of d, J = 8 Hz, J' = 2 Hz), 7.12 (d, J = 8 Hz) ppm. IR (cm^{-1}) 3450, 2926, 1714, 1615.

Results and discussion

Currently, there are no satisfactory chemical methods for aromatization of 19-nor-Δ⁴-3-oxosteroids on a preparative scale. While reviewing the literature on general chemical aromatization methods, we came across a publication by Horiuchi et al.[18] which describes a procedure for the conversion of α,β-unsaturated cyclohexenones to the methoxy aromatic derivatives in high yield using ceric ammonium nitrate and iodine (CAN-I_2) in refluxing methanol. Although the authors did not apply their method to steroids, we felt this method could be employed for the aromatization of dione **2** (Scheme 2), obtained in quantitative yield from D-(-)-Norgestrel **1** by reaction with Fétizon's reagent according to the procedure of Lenz.[11] When applied to the dione **2**, the CAN-I_2 reaction gave a mixture of ring-A aromatized products as well as a 50% recovery of starting material. The published procedure employs one half of an equivalent each of iodine and ceric ammonium nitrate. By increasing both of the reagents to 1.5 Eq, we were able to obtain a complete conversion of dione **2** to the mixture of ring-A aromatized products. Evidence for the formation of some iodinated derivatives was obtained by sodium fusion of an aliquot of the crude material followed by a positive halide test using silver nitrate solution. The crude reaction mixture was separated into two main fractions via flash chromatography. The more polar of the two fractions was determined to consist solely of the 6-oxo compound **6**. The NMR data of the less polar fraction was consistent with a mixture of compounds **4** and **5**. In addition to the aromatic pattern expected for compound **4** a doublet at δ 7.55 and a multiplet at δ 6.13 are consistent with the values observed for the C-1H and the C-11H of other estra-1,3,5(10),9(11)-tetraenes.[3,19] Catalytic hydrogenation of the total crude mixture using palladium on calcium carbonate followed by chromatographic separation gave compound **4** in 48% yield and the 6-oxo derivative **6** in 38% yield. A further transformation of a mixture of **4** and **6** was achieved by reduction with triethylsilane in trifluoroacetic acid according to the procedure of West et al.[20] to give the 17-trifluoroacetate **7** as a single product. With no purification of intermediates, the overall yield of the trifluoroacetate **7** from D-(-)-norgestrel **1** was 63%.



Finally, base hydrolysis of compound **7** followed by tetrapropylammonium peruthenate oxidation[21] of alcohol **8** gave the desired compound **4** in 52% overall yield from D-(-)-norgestrel **1**. Extension of this method to another example is shown in Scheme 3. The reaction of estr-4-ene-3,17-dione **9** with CAN-I_2 in refluxing methanol gave a product mixture determined by NMR to be similar to that obtained from compound **2**. Without any subsequent reduction, chromatographic separation gave estrone methyl ether **10** (48%) and 6-oxoestrone 3-methyl ether **11** (27%).



9 **10** **11**

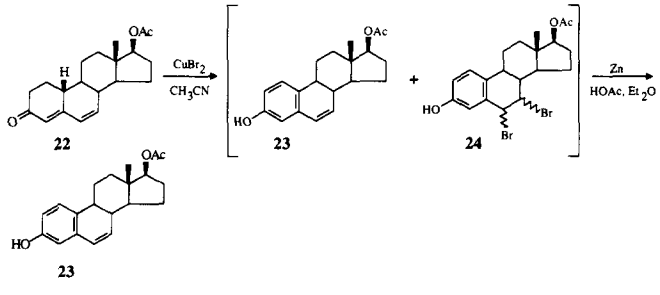
While the CAN-I_2 procedure for the preparation of compound **4** presents a substantial improvement in yield over the published procedure,[4] it is somewhat time-consuming, and on a large scale, workup of the silane reduction step involves the neutralization of large amounts of trifluoroacetic acid. In order to further simplify the preparation of compound **4**, we reexamined some of the aromatization methods outlined in Table 1.

We were attracted in particular to a procedure described by Bondon et al.[8] in which they have reported the conversion of estr-4-ene-3,17-dione to estrone in 85% yield by reacting the 19-norsteroid with two equivalents of $CuBr_2$ and one equivalent of LiBr in refluxing acetonitrile. When this reaction was attempted on compound **2** following the published procedure, 50% of the starting material was recovered and about 10% of the desired aromatic product was obtained. Monitoring the reaction by TLC, we observed an initial rapid formation of the expected aromatic product **3** along with several unidentified by-products. After about 30 min, no further change in the reaction composition could be observed. Increasing the amount of $CuBr_2$ and LiBr increased the conversion of starting material, but also appeared to increase the amount of by-products. Attempting to limit the formation of by-products, the reaction was run at room temperature for a longer period of time (2.5 h), and a substantial increase in the yield of the aromatic product (70%) was obtained. Further variation of reaction conditions revealed that maximum yield could be obtained by decreasing the number of equivalents of $CuBr_2$ from 2 to 1.1–1.2 and increasing the reaction time to 16 h.

The data presented in the original publication on $CuBr_2$-LiBr aromatization suggest this reaction is catalyzed by bromide ion.[8] Using 19-nortestosterone **12** as substrate, the reaction run under the modified conditions presented above gave essentially identical yields (85%) with and without the addition of one equivalent of LiBr. These data are presented in Table 2. Furthermore, when the reaction with added LiBr was run for a shorter period of time (3 h), we obtained only a 50% yield of product. This result would seem to indicate that under our modified conditions, the LiBr is not catalytic.

Our findings shown in Table 2 indicate a variety of 17-substituents survive the reaction conditions. The reactions with the 17-ethynylated substrates were carried out at a higher dilution due to the low solubility of these compounds in acetonitrile. Attempting to run these reactions as a suspension of the 19-nor-Δ^4-3-oxosteroid in acetonitrile resulted in precipitation of an unidentified intermediate (possibly the 2-bromo-3-oxo derivative) and a much lower yield of ring-A aromatized product.

The $CuBr_2$ aromatization reaction was extended to a related conjugated dien-3-one steroid. The conversion of estra-4,6-dien-3-one-17β-yl acetate **22** to 3-hydroxyestra-1,3,5(10),6-tetraen-17β-yl acetate **23** was achieved as shown in Scheme 4. Reaction of the dienone **22** with $CuBr_2/CH_3CN$ following the procedure outlined above gave a mixture consisting of the starting material **22**, the expected Δ^6-aromatic derivative **23** and some slightly less polar material that gave a positive halide test upon sodium fusion and testing with $AgNO_3$ solution. According to Baird et al.,[22] olefins are readily halogenated by $CuBr_2$ in acetonitrile at room temperature suggesting that the halide positive component of the reaction mixture was probably the 6,7-dibromo derivative **24** as is shown in Scheme 4. Increasing the $CuBr_2$ to 4 Eq, followed by a zinc/acetic acid reduction in ether gave the Δ^6-estradiol derivative **23** in 51% yield. This two-step procedure for the formation of compound **23** represents the first practical chemical method for synthesizing a 6-dehydroestrogen from a 19-nor-$\Delta^{4,6}$-3-oxosteroid.



22 **23** **24**

23

In summary, two practical preparative chemical methods for the aromatization of a variety of 19-nor-Δ^4-3-oxosteroids have been developed. The first method consists of reaction of the 19-nor-Δ^4-3-oxosteroid with ceric ammonium nitrate and iodine in refluxing methanol followed by catalytic hydrogenation and triethylsilane reduction in trifluoroacetic acid. The second method employs the reaction of 19-nor-Δ^4-3-oxosteroids with copper(II) bromide in acetonitrile at room temperature.

Acknowledgments

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