# Preparation of 16-formylestradiol and the 16-($\alpha$-methylenebutanolide) derivative

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*Routes to the preparation of 16-formylestradiol are described. Estrone was converted to (E)-16-methoxymethylene estrone via the 16-hydroxymethylene estrone. Reduction of the methoxymethylene estrone with $NaBH_4$ in the presence of $CeCl_3$ gave 16-methoxymethylene estradiol. Deprotection by acid afforded the desired 16-formylestradiol. Attempts to prepare the 16-formylestradiol via the 16-butylthiomethylene derivative gave only 16-formylestra-1,3,5(10),16-tetraen-3-ol, and a route through the 16-dimethoxymethyl derivative gave a mixture of the 16-formyltetraen-3-ol and the 16-formylestradiol in low yield. The 16-formylestradiol was subsequently converted to the $\alpha$-methylene lactone conjugate, 4-(3,17$\beta$-dihydroxyestra-1,3,5(10)trien-16-yl)-2-methylene-4-butanolide by reaction with methyl $\alpha$-(bromomethyl) acrylate and zinc.* (*Steroids* **58:**234–238, 1993)

**Keywords:** steroids; estrogens; 16-formylestradiol; butanolide; methyl $\alpha$-(bromomethyl)acrylate

## Introduction

Functionalization of estradiol at various positions of the molecule has been a target for modifying it with a view toward obtaining derivatives that may possess better estrogenic property or different pharmacological activity altogether.[1–3] However, routes for the preparation of the 16-aldehydic derivative have not been established, possibly because of the notion that $\beta$-hydroxyaldehydes are not stable and thus very difficult to obtain.

The synthesis of steroidal $\alpha$-methylene lactone conjugates has been of great interest because of the cytotoxicity conferred on such compounds by the $\alpha$-methylene lactone moiety.[4]

Thus, although the conjugate could possibly be cytotoxic, the steroid could additionally act as a biological carrier with increased lipophilicity and be able to cross cell membrane barriers in vivo. In this regard, some steroidal $\alpha$-methylene lactones have been synthesized.[5,6] However, these were found to lack specificity of action in vivo.

The use of estrogens as carriers has been conceived to lead to target-specific lactones that could be of advantage in hormone-receptive tumors, such as breast, cervix, and prostate cancer.[7,8]

Reported here are routes to the preparation of 16-formylestradiol and the derived $\alpha$-methylene lactone, which it is hoped will have greater affinity for estrogen receptor than others synthesized earlier.

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## Experimental

Preparative thin-layer chromatography (TLC) plates were prepared from Kieselgel 60 PF 254 (Merck). Infrared (IR) absorption spectra were determined with a Perkin-Elmer 177 spectrophotometer. $^1$H nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ containing tetramethylsilane (TMS) at 60 MHz with a Varian EM 350A spectrometer or at 90 MHz with a Perkin-Elmer R32 spectrometer. Melting points (mp) were measured on a Reichert Kofler hot stage apparatus and are uncorrected. Mass spectra were recorded on a Kratos MS 80 mass spectrometer using a DS-55 data system. Ether refers to diethyl ether. Solutions were dried over anhydrous magnesium sulfate and evaporated in vacuo.

### *16-Hydroxymethylene-3-hydroxyestra-1,3,5(10)-trien-17-one* (2)

Sodium hydride (8 g, 60% in oil dispersion) was washed three times with petroleum ether [boiling point (bp) 40-60 C]. The flask was flushed with nitrogen to remove the last traces of the petroleum ether. Dry benzene (100 ml) was introduced and estrone (1) (5 g) added. The mixture was stirred for 1 hour, before adding

ethyl formate (20 ml, freshly distilled over $P_2O_5$). The reaction mixture was stirred at room temperature until there was no estrone left (24–36 hours). The reaction mixture was poured onto ice/dilute HCl, and the white precipitate formed was filtered off. The precipitate was washed thoroughly with water and dried under vacuum at 80 C to give the desired product (5 g, 91%); mp 227–229 C (lit.[9] 229–231 C), infrared (IR) (mull) 3,400 (OH, broad), 1,720 (C=O). 1,635 (C=C) and 1590 $cm^{-1}$ (C=C).

### *16-Dimethoxymethyl-3-hydroxyestra-1,3,5(10)-trien-17-one (3)*

16-Hydroxymethylene estrone **(2)** (0.8 g), dry methanol (50 ml), and trimethyl orthoformate (5 ml) were heated to reflux under nitrogen in an oil bath, and p-toluene sulfonic acid (pTSA) (50 mg) was added as a catalyst. After about 4 hours the reaction mixture was diluted with $CHCl_3$ (100 ml), washed with brine (twice), dried, and evaporated. Preparative TLC of the crude product [petroleum ether (bp 40–60 C)/acetone, 2 : 1] gave the acetal (0.16 g, 16%), which was recrystallized from $CHC_{13}$/petroleum ether (40-60) to give crystalline sample (0.1 g, 10%); mp 213–245 C, $(\alpha)_D$ + 16° [c, 1%, tetrahydrofuran (THF)]; IR $\nu_{max}$ (mull) 3,380 (OH, broad), 1,720 (C=O) and 1,600 $cm^{-1}$ (C=C); $^1$H NMR δ 0.92 (s, 3H, 18-Me), 3.48 (s, 6H, $CH(OMe)_2$), 4.7 (d, J ~ 4 Hz, 1H, $CH(OMe)_2$), 6.64 (m, 2H, 4-H and $\overline{2}$-H), 7.2 (d, J ~ 10 Hz, 1H, 1-$\overline{H}$). Found: $M^+$, 344.1998. $C_{21}H_{28}O_4$ requires M, 344.1987.

### *16-Dimethoxymethyl-3,17β-dihydroxyestra-1,3,5(10)-triene (4)*

To a suspension of 16-dimethoxymethylestrone **(3)** (0.15 g) in methanol (25 ml) was added sodium borohydride (45 mg) in methanol (20 ml). This was stirred at room temperature and the progress of the reaction monitored on TLC until all the starting material had disappeared (~ 1 hour). The reaction mixture was diluted with water and extracted with $CHCl_3$ (three times). The combined $CHCl_3$ extracts were washed with brine, dried, and evaporated. Crystallization of the oily product from ethanol gave the pure sample (0.12 g, 80%); mp 232–234 C $(\alpha)_D$ + 67.5° (c, 0.77%, THF); IR $\nu_{max}$ (mull) 3,300 (OH, broad), 1,600 (C=C) and 1,510 $cm^{-1}$ (C=C); $^1$H NMR δ 0.82 (s, 3H, 18-Me), 3.38 and 3.42 (s, 6H, $CH(OMe)_2$), 3.80 and 3.90 (d, J ~ 3 Hz, 1H, $CH(OMe)_2$), 4.6 (d, J ~ 8 Hz, 1H, 17-H), 6.6 (m, 2H, 4-H and 2-H), 7.1 (d, J ~ 9 Hz, 1H, 1-H). Found: $M^+$, 346.2143. $C_{21}H_{30}O_4$ requires M, 346.2144.

### *16-Formylestra-1,3,5(10),16-tetraen-3-ol (5a)*

To the 16-butylthiomethylene estradiol **(11a)** (0.5 g) in a mixture of acetonitrile (50 ml) and water (25 ml) were added mercuric chloride (0.25 g) and $CdCO_3$ (0.1 g). The resulting reaction mixture was heated under reflux and the progress of the reaction monitored on TLC. After 24 hours it was diluted with water (50 ml) and extracted with $CHCl_3$ (three times). The $CHCl_3$ extracts were washed with water and brine, dried, and evaporated. Chromatographic purification of the crude product [diethyl ether/petroleum ether (bp 40-60 C), 2 : 1] gave the product **5a** (0.2 g, 45%).

Alternatively, the deprotection was performed with $TiCl_4$ in acetonitrile. Thus, the 16-butylthiomethylenestradiol (0.25 g) was dissolved in acetonitrile (25 ml) and $TiCl_4$ (0.5 ml) added. The mixture was stirred for 20 minutes, during which time it turned deep red. Water (10 ml) was added and the reaction mixture stirred for a further 4 hours. It was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and evaporated. Chromatographic separation of the crude product, followed by recrystallization from methanol or acetone/petroleum ether (bp 40-60 C), gave pure **5a** (0.1 g, 52%; mp 253–255 C, $(\alpha)_D$ + 88° (c, 5%, THF); IR $\nu_{max}$. (KBr) 3,310 (broad, OH), 1,675 (C=O), aldehyde), 1,610 and 1,585 $cm^{-1}$, (C=C); $^1$H NMR δ 0.92 (s, 3H, 18-Me), 6.65 (m, 2H,4-H and 2-H), 7.05 (br s, 1H, 17-H), 7.18 (d, J ~ 10 Hz, 1H, 1-H), 9.78 (s, 1H, CHO). Found: $M^+$ 282.1625. $C_{19}H_{22}O_2$ requires M, 282.1620.

### *3-Acetoxy-16-formylestra-1,3,5(10),16-tetraene (5b)*

A mixture of 16-formylestra-1,3,5(10),16-tetraen-3-ol **(5a)** (0.1 g) and acetic anhydride (0.5 ml) in pyridine (5 ml) was stirred together overnight. It was poured onto ice-water and extracted with $CH_2Cl_2$ (three times). The combined $CH_2Cl_2$ extracts were washed with brine, dried, and evaporated. Recrystallization from ethanol gave pure sample (90 mg, 78%); mp 148–150 C, $(\alpha)_D$ + 48° (c, 0.5%, $CHCl_3$); IR $\nu_{max}$ (film) 1,730 (C=O, 3-OAc) 1,675 (C=O), aldehyde) and 1,600 $cm^{-1}$ (C=C); $^1$H NMR δ 0.92 (s, 3H, 18-Me), 2.3 (s, 3H, 3-OAc), 6.85 (m, 2H, 4-H and 2-H), 7.0 (br s, 1H, 17-H), 7.3 (d, J ~ 10 Hz, 1H, 1-H), 9.78 (s, 1H, CHO). Found: C, 77.9; H, 7.6%; $M^+$, 324.1724. $C_{21}H_{24}O_3$ requires C, 77.75; H, 7.40%; M, 324.1724.

### *16-Formyl-3,17β-dihydroxyestra-1,3,5(10)-triene (6a)*

The 16-dimethoxymethyl-3,17β-dihydroxyestra-1,3,5(10)-triene **(4)** (0.15 g) was dissolved in acetone (25 ml). To this was added 2 N HCl (5 ml), and the resulting reaction mixture was stirred at room temperature for 20–30 minutes while monitoring the progress of the reaction on TLC. The reaction mixture was diluted with water and extracted with $CHCl_3$ (three times). The combined $CHCl_3$ extracts were washed with brine, dried, and evaporated. Chromatographic purification of the crude product gave the aldehyde **(6a)**, which was crystallized from methanol/$H_2O$.

Similarly, the enol ether **(8)** (0.3 g) was deprotected with dilute HCl in acetone as above to give the same aldehyde **(6a)** (0.2 g, 70%); mp 203–206 C, $(\alpha)_D$ + 75° (c, 0.5%, THF); IR $\nu_{max}$ (KBr) 3,360 (OH, broad), 1,710 (C=O, aldehyde), and 1,610 $cm^{-1}$ (C=C); $^1$H NMR [dimethylsulfoxide (DMSO) $d_6$] δ 0.8 (s, 3H, 18-Me), 3.8 (d, 1H, J ~ 8 Hz, 17-H), 6.7 (m, 2 H, 4-H and 2-H), 7.15 (d, J ~ 9 Hz, 1 H, 1-H), 9.82 (d, 1H, J ~ 2 Hz, CHO). Found: $M^+$. 300.1738 $C_{19}H_{24}O_3$ requires M, 300.1725.

### *3,17β-Diacetoxy-16-formylestra-1,3,5(10)-triene (6b)*

The 16-formylestradiol **(6a)** (0.1 g) was acetylated by stirring with acetic anhydride (0.5 ml) in pyridine (2 ml) to give the 3,17β-diacetoxy-16-formylestra-1,3,5(10)-triene **(6b)**. Crystallization from ethanol gave pure sample (0.1 g, 94%); mp 128–130 C; IR $\nu_{max}$ (film) 1,740 (C=O, broad, 17-OAc, 3-OAc, and CHO) and 1,610 $cm^{-1}$ (C=C); $^1$H NMR δ 0.9 (s, 3H, 18-Me), 2.12 (s, 3H, 17-OAc), 2.32 (s, 3H, 3-OAc), 4.86 (d, J ~ 9 Hz, 1H, 17-H), 6.85 (m, 2H, 4-H, and 2-H), 7.3 (d, J ~ 9 Hz, 1H, 1-H), 9.84 (d, J ~ 2 Hz, 1H, CHO). Found: C, 71.7; H, 7.7%; $M^+$, 384.1937. $C_{23}H_{28}O_5$ requires C, 71.9; H, 7.3%; M, 384.1937.

### *16-Methoxymethylenestra-1,3,5(10)-trien-17-one (7)*

A mixture of hydroxymethylene estrone **(2)** (1 g), trimethyl orthoformate (2.5 g), and methanolic $CeCl_3$ solution (0.4 M, 20 ml) was stirred at room temperature overnight. It was diluted with water and extracted with $CHCl_3$ (three times). The combined $CHCl_3$ extracts were washed with water and brine, dried, and evaporated. Chromatographic purification of the crude product

[petroleum ether (bp 40-60 C)/acetone, 2 : 1], followed by crystallization from acetone/petroleum ether afforded pure 16-methoxymethylenestra-1,3,5(10)-trien-17-one **(7)** (0.9 g, 86%); mp 255–257 C, $(\alpha)_D$ + 104° (c, 1%, $CHCl_3$); IR $\nu_{max}$ (KBr) 3,250 (OH), 1,690 (C=O), and 1,615 $cm^{-1}$ (C=C); $^1H$ NMR δ: 0.9 (s, 3H, 18-Me), 3.91 (s, 3H, OMe), 6.65 (m, 2H, 4-H, and 2-H), 7.15 (d, J ~ 9 Hz, 1H, 1-H), 7.25 (br s, 1H, CHOMe). Found: C, 77.0; H, 8.0%; $M^+$, 312.1726. $C_{20}H_{24}O_3$ requires C, 76.89; H, 7.4%; M, 312.1725.

## *16-Methoxymethylene-3,17β-dihydroxyestra-1,3,5(10)-triene (8)*

The 16-methoxymethylene estrone **(7)** (0.8 g) was suspended in methanol (50 ml) and cooled in an ice-bath. $CeCl_3$ (0.4 g) was added to the suspension and stirred for 2–3 minutes before adding sodium borohydride (0.2 g).

The resulting mixture was stirred for about 45 minutes. It was extracted with $CHCl_3$ (100 ml), washed with brine, dried, and evaporated. The crude product was subjected to preparative TLC [petroleum ether (bp 40-60 C)/acetone, 2 : 1] to give an oily solid that could not be crystallized. IR $\nu_{max}$ (film) 3,300 (OH, broad) and 1,610 $cm^{-1}$ (C=C); $^1H$ NMR δ 0.7 (s, 3H, 18-Me), 3.63 (s, 3H, OMe), 4.15 (br s, 1H, 17-H), 6.16 (br s, CHOMe), 6.62 (m, 2H, 4-H and 2-H), 7.15 (d, J ~ 10 Hz, 1H, 1-H). Found: $M^+$, 314.1887. $C_{20}H_{26}O_3$ requires M, 314.1882.

## *3,17β-Diacetoxy-16-methoxymethylenestra-1,3,5(10)-triene (9)*

The above product **(8)** was acetylated by stirring 100 mg of it in pyridine (5 ml) and acetic anhydride (0.5 ml) at room temperature overnight. After the usual work-up, it was crystallized from methanol to give the 3,17β-diacetoxy-16-methoxymethylenestra-1,3,5(10)-triene **(9)** (90 mg, 82%); mp 159–160 C, IR $\nu_{max}$ (mull) 1,770 (C=O, 3-OAc), 1730 (C=O, 17-OAc), and 1,610 $cm^{-1}$ (C=C); $^1H$ NMR δ 0.82 (s, 3H, 18-Me), 2.16 (s, 3H, 17-OAc), 2.30 (s, 3H, 3-OAc), 3.65 (s, 3H, OMe), 5.38 (br s, 1H, 17-H), 6.0 (s, 1H, CHOMe), 6.85 (m, 2H, 4-H, and 2-H), 7.35 (d, J ~ 10 Hz, 1H, 1-H). Found: C, 72.39; H, 7.8%. $C_{24}H_{30}O_5$ requires C, 72.33; H, 7.59%.

## *16-Butylthiomethylene-3-hydroxyestra-1,3,5(10)-trien-17-one (10)*

16-Hydroxymethylene estrone **(2)** (1 g) was dissolved in dry dimethoxyethane (50 ml), $MgSO_4$; pTSA (50 mg) and n-butane thiol (5 ml) were added. The resulting reaction mixture was stirred and warmed to 60 C in an oil bath overnight. It was diluted with water and extracted with $CHCl_3$ (three times). The combined $CHCl_3$ extracts were washed with brine, dried, and evaporated. Some dry toluene was added and removed in vacuo to ensure total removal of the thiol. The crude product was subjected to preparative TLC [petroleum ether (bp 40-60 C)/acetone, 2 : 1] to give the product **(10)** (1.1 g, 89%). Recrystallization from methanol gave pure **10** (1.0 g, 81%); mp 177–178 C, $(\alpha)_D$ + 128° (c, 0.5%; $CHCl_3$), IR $\nu_{max}$ (mull) 3,308 (broad, OH), 1,690 (C=O), 1,610, and 1,590 $cm^{-1}$ (C=C); $^1H$ NMR δ 0.9 (s, 3H, 18-$CH_3$), 6.58 (m, 2H, 4-H, and 2-H), 7.12 (d, J ~ 10 Hz, 1H, 1-H), 7.4 (br s, 1H, $CHSC_4H_9$). Found: C, 74.6; H, 8.4; S, 8.7%; $M^+$, 370.1966. $C_{23}H_{30}O_2S$ requires C, 74.56; H, 8.16; S, 8.64%; M, 370.1966.

## *16-Butylthiomethylene-3,17β-dihydroxyestra-1,3,5(10)-triene (11a)*

The butylthiomethylene estrone **(10)** (1 g) was suspended in methanol (100 ml). This was cooled to 0 C in an ice bath before adding sodium borohydride (0.5 g). The reaction mixture was stirred for ~ 2 hours while monitoring the progress of the reaction on TLC. It was diluted with water and extracted with $CHCl_3$ (four times). The $CHCl_3$ extracts were washed with water and brine, dried, and evaporated to give the crude product. Recrystallization from ethanol gave pure sample of **11a** (0.8 g, 80%); mp 85–88 C, $(\alpha)_D$ −39.4 C (c, 1%, $CHCl_3$); IR $\nu_{max}$ (mull) 3,340 (broad OH), 1,610, and 1,590 $cm^{-1}$ (C=C); $^1H$ NMR δ 0.7 (s, 3H, 18-Me), 4.06 (br s, 1H, 17-H), 6.1 (br s, 1H, $CHSC_4H_9$), 6.6 (m, 2H, 4-H, and 2-H), 7.15 (d, J ~ 9 Hz, 1H, 1-H). Found: $M^+$, 372.2114, $C_{23}H_{32}O_2S$ requires M, 372.2123.

## *16-Butylthiomethylene-3,17β-diacetoxyestra-1,3,5(10)-triene (11b)*

The dihydroxy product **(11a)** (0.2 g) was acetylated by stirring in pyridine (5 ml) with acetic anhydride (1 ml) to give 16-butylthiomethylene-3,17β-diacetoxyestra-1,3,5(10)-triene **(11b)**, which was recrystallized from ethanol after the usual work-up (0.18 g, 73%); mp 142–144 C, $(\alpha)_D$ + 3.7° (c, 1.1%; $CHCl_3$), IR $\nu_{max}$ (mull) 1,760 (C=O, 3-OAc), 1,740 (C=O, 17-OAc), 1,640 (C=C), 1,610 $cm^{-1}$ (C=C); $^1H$ NMR δ 0.76 (s, 3H, 18-Me), 2.18 (s, 3H, 17-OAc), 2.3 (s, 3H, 3-OAc), 5.34 (br s, 1H, 17-H), 5.86 (br s, 1H, $CHSC_4H_9$), 6.83 (m, 2H, 4-H, and 2-H), 7.3 (d, J ~ 10 Hz, 1H, 1-H). Found: C, 71.1; H, 8.3; S, 7.1%; $M^+$, 456.2333. $C_{27}H_{36}SO_4$ requires C, 71.02; H, 7.95; S, 7.0%; M, 456.2334).

## *4-(3-Hydroxyestra-1,3,5(10)-tetraen-16-yl)-2-methylene-4-butanolide (12)*

Activated zinc (0.15 g), dry THF (75 ml), ethyl or methyl α-(bromomethyl) acrylate (0.2 g), and the aldehyde **(5a)** (0.6 g) were heated under reflux with stirring under nitrogen. A pinch of *p*-dihydroquinone was added to the reaction mixture to reduce the extensive polymerization of the acrylate. After ~5 hours, more acrylate (0.1 g) was added to the reaction mixture. It was then left under reflux overnight, cooled, and poured onto ice/dilute HCl. The mixture was extracted with $CHCl_3$ (four times). The crude product was subjected to preparative TLC and crystallized from acetone/petroleum ether (bp 40-60 C) to give pure sample of the lactone **(12)** (0.3 g, 40%); mp 226–228 C, $(\alpha)_D$ + 71° (c, 0.5%, THF); IR $\nu_{max}$ (KBr) 3,400 (OH), 1,755 (C=O, lactone), 1,670 (C=C, lactone) $cm^{-1}$; $^1H$ NMR (DMSO $d_6$) δ 0.8 (s, 3H, 18-Me), 5.15 (t, J ~ 7 Hz, 1H, CHOCO, lactone), 5.7 (m, 1H, C=$CH_2$), 5.98 (br s, 1H, 17-H), 6.3 (m, 1H, C=$CH_2$), 6.65 (m, 2H, 4-H, and 2-H), 7.15 (d, J ~ 10 Hz, 1H, 1-H). Found: C, 78.63; H, 7.8%; $M^+$, 350.1891. $C_{23}H_{26}O_3$ requires C, 78.82; H, 7.48%; M, 350.1882.

## *4-(3,17β-Dihydroxyestra-1,3,5(10)-trien-16-yl)-2-methylene-4-butanolide (13)*

Activated zinc (0.15 g), dry THF (100 ml), methyl α-(bromomethyl) acrylate (0.2 g), and the aldehyde **(8)** (0.5 g) were heated under reflux while stirring under nitrogen with a magnetic stirrer; some crystals of *p*-dihydroquinone were also added. After ~8 hours, more acrylate (0.15 g) was added to the mixture, which was left to reflux overnight. It was cooled, poured onto ice/dilute HCl and extracted with $CHCl_3$ (four times). The combined $CHCl_3$ extracts were washed with brine, dried, and evaporated. Chromatographic purification, followed by crystallization from acetone/petroleum ether (bp 40-60 C) gave the lactone **(13a)** (0.18 g, 30%); mp 252–255 C; $(\alpha)_D$ + 24° (c, 0.25%, THF); IR $\nu_{max}$ (KBr), 1,610 (C=C) 1,665 (C=C, lactone), 1,750 (C=O, lactone), 3,350 (OH, broad). NMR (DMSO $d_6$) δ 0.88 (s, 3H, 18-Me), 3.6 (m, 1H, 17-H), 4.6 (m, 1H, CHOCO, lactone), 5.7 (br s, 1H, C=$CH_2$), 6.7 (m, 2H, 4-H, and 2-H), 7.2 (d, J ~ 10 Hz,

1H, 1-H). Found: C, 74.4; H, 7.6%; $M^+$, 368.1991. $C_{33}H_{28}O_4$ requires C, 74.97; H, 7.66%; M, 368.1987.

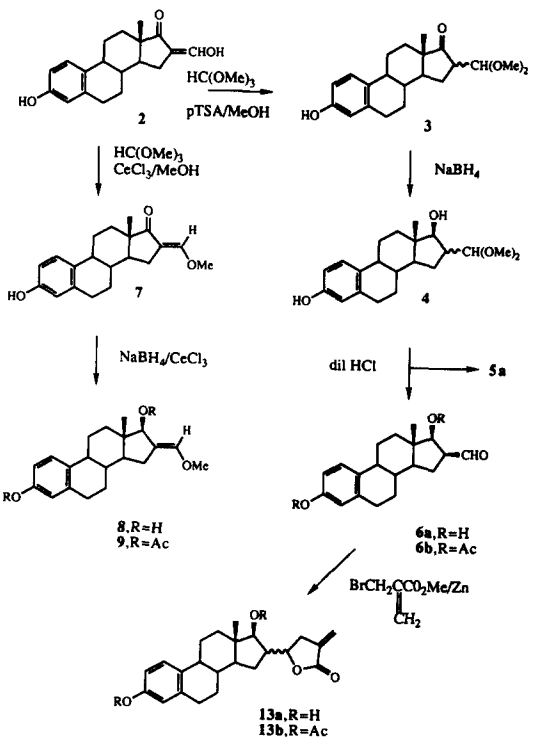
Acetylation of the lactone **(13a)** (0.1 g) with acetic anhydride (1 ml) in pyridine (2 ml) gave the acetylated lactone **(13b)** (80 mg, 74%). IR $\nu_{max}$ (film) 1,740 $cm^{-1}$ (broad 17-OAc, 3-OAc, C=O, lactone) 'H NMR δ 0.9 (s, 3H, 18-Me), 4.65 (m, 2H, CHOCO lactone and 17-H), 5.75 (m, s, 1H, $C=CH_2$), and 6.38 (m, 1H, $C=CH_2$).

## Results and discussion

The route sought to the 16-formyl derivative was through the estrone that has an activated 16-H. Thus, estrone **(1)** was converted to the 16-hydroxymethylene estrone **(2)** by reaction with NaH/ethyl formate. This β-ketoenol **(2)** needed to be protected before selectively reducing the 17-ketone function.

A survey of the literature showed various possible ways of protecting β-ketoaldehydes, including acetalization[10] and enol ether formation.[11–14] When enol ethers are used, reduction of the β-keto function is reported to proceed beyond the desired product, the olefinic C=C bond being reduced as well.[10,13] The acetalization approach was therefore investigated. Wenkert and Godwin[10] reported the use of trimethyl orthoformate and methanol in the presence of an acid catalyst (pTSA) for the protection of aldehyde function of a β-ketoaldehyde. Reaction of **2** with trimethyl orthoformate and methanol in the presence of a catalytic amount of pTSA afforded 16-dimethoxymethylestrone (**3**) in 10% yield, after chromatographic separation. Reduction of **3** with $NaBH_4$ in methanol gave 16-dimethoxymethylestradiol **(4)** in 65% yield. The presence of two doublets in the 'H NMR spectrum at δ 3.80 and 3.90 assigned to the acetal $CH(OMe)_2$ suggested that **4** was a mixture of 16-epimers. This was confirmed by the presence of two singlets for the $CH(OMe)_2$ protons at δ 3.38 and 3.42. Deprotection of **4** with dilute HCl in acetone gave the products, identified as the 16-formylestradiol **(6a)** (50%) and the tetraen-3-ol **(5a)** (10%) from spectroscopic data and after chromatographic separation. Although the IR spectrum of **6a** showed the peaks for the OH (3,360 $cm^{-1}$) and the aldehyde (1,710 $cm^{-1}$), that of **5a** showed only the aldehyde peak of an α,β-unsaturated carbonyl (1,675 $cm^{-1}$). The 'H NMR spectrum of **6a** showed a doublet at δ 9.82 (J ~ 2 Hz) for the aldehydic proton. Another doublet at δ 3.8 (J ~ 8 Hz) was assigned to the 17-H. Using the Karplus equation, the vicinal coupling of 17α-H and 16-H was estimated to be about 7 Hz for 16α-H (i.e., 16β-formyl) and 3 Hz for 16β-H (i.e., 16α-formyl). Because the observed coupling constant is 8 Hz, it is most likely that the aldehyde has a β-configuration. Acetylation of **6a** gave **6b**, confirming the presence of two OH groups (Scheme 1).

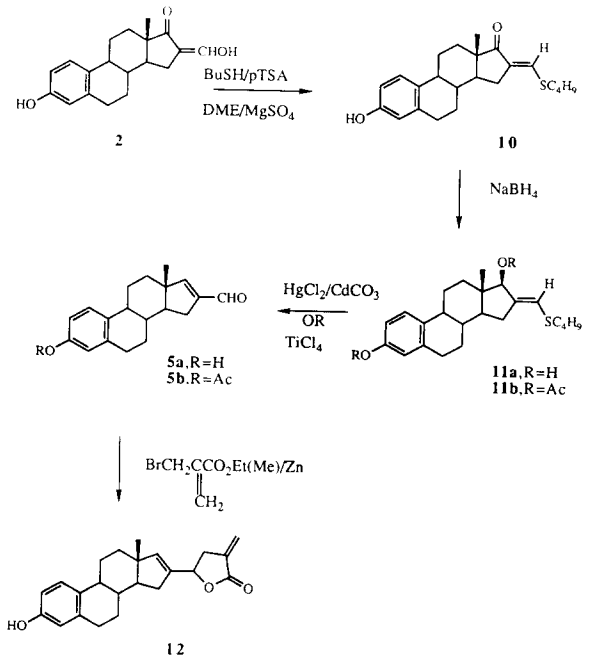
Another approach used to obtain the 16-formylestradiol **(6)** in better yield than the acetalization method involves the use of rare earth chlorides as reported by Luche and Gemal[15] in an efficient synthesis of acetals. In particular $CeCl_3 \cdot 6H_2O$ has been used to convert ketones and aldehydes to acetals, and some selective reactions with the aldehyde function of ketoaldehyde




**Scheme 1**

have been observed. Thus, the use of $CeCl_3$ in acetalization of 16-hydroxymethylene estrone was studied. When **2** was allowed to react with methanol in the presence of trimethyl orthoformate and $CeCl_3$, the desired acetal **(3)** was not obtained. Rather, the product isolated was the (E)-enol ether **(7)** in 90% yield. The 'H NMR spectrum of **7** showed a singlet at δ 3.91 (CHOMe) and a methine proton (brs, CHOMe) signal at δ 7.25. The enol ether **(7)** was successfully reduced to the hydroxyenol ether **(8)** (80%) by use of $NaBH_4$ in the presence of $CeCl_3$. This method has been reported to be successful in similar systems in which hydride reductions in absence of $CeCl_3$ reduced both the ketone and the double bond.[16] Acetylation of this estradiol enol ether **(8)** with acetic anhydride in pyridine afforded the 3,17β-diacetoxy enol ether **(9)**. The 'H NMR spectrum confirmed the presence of two acetate groups at δ 2.3 and 2.16 (3- and 17-OAc, respectively). Deprotection of **8** with dilute HCl in acetone afforded the 16-formylestradiol **(6a)**.

The use of thiols to form thioenol ethers has been reported by Ireland and Marshall[12] for the protection of hydroxymethylene groups while allowing the reduction of the β-keto functions. Using a modified form of the Bernstein method,[14] β-ketoaldehyde **(2)** was successfully converted to the (E)-16-butylthiomethylene estrone **(10)** in 90% yield. Reduction of **10** with $NaBH_4$ gave the 16-butylthiomethylene estradiol **(11)**. Deprotection of thioenol ethers has been extensively studied,[17,18] and $HgCl_2/CdCO_3$ has been reported to proceed smoothly. Attempted deprotection of **11a** with $HgCl_2$/




**Scheme 2**

$CdCO_3$ in acetonitrile/water gave the $\alpha,\beta$-unsaturated aldehyde **(5a)** and not the 16-formylestradiol **(6a)**. The formation of the $\alpha,\beta$-unsaturated aldehyde **(5a)** is presumed to involve dehydration of the expected $\beta$-hydroxyaldehyde **(6a)**. However, buffering the reaction mixture with $CaCO_3$ rather than $CdCO_3$, because of the greater solubility of the former, did not prevent the formation of **(5a)**. $TiCl_4$ was also used to deprotect **(11a)**, as has been reported for similar deprotections[19]; again **(5a)** was obtained (Scheme 2).

Reaction of the 16-formylestra-1,3,5(10), 16-tetraen-3-ol **(5a)** with ethyl $\alpha$-(bromomethyl) acrylate and activated zinc in THF (Drieding-Schmidt reaction) gave the expected $\alpha$-methylene lactone **(12)**, which contained polymer by-products. After flash chromatography and preparative TLC, followed by recrystallization, the $\alpha$-methylene lactone **(12)** was obtained in 40% yield. The 'H NMR spectrum confirmed the presence of the $\alpha$-methylene lactone moiety and showed important signals at $\delta$ 5.7 and 6.3 (m, $C{=}CH_2$), $\delta$ 5.15 (t, CHOCO), and 5.98 (brs, 17-H). The IR spectrum showed bands at 1,755 $cm^{-1}$ (C=O, lactone) and 1,670 $cm^{-1}$ (C=C, lactone).

Similarly, the 16-formylestradiol **(6)** was converted to the desired lactone **(13a)**. After purification of the crude product by flash chromatography and preparative TLC, a pure sample of **13a** was obtained that was highly insoluble in most solvents. Acetylation of **13a** with acetic anhydride in pyridine afforded the diacetoxy derivative **(13b)**, which was more soluble in solvents. The 'H NMR spectrum showed important signals at $\delta$ 4.65 (m, 17$\alpha$-H, and CHOCO) and 5.75 and 6.38 (m, $C{=}CH_2$).

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