# SYNTHESIS OF 5,17-DIHYDROXY-5α, 17α, -19-NORPREGN-20-YN-3-ONE, A MAJOR PHOTODEGRADATION PRODUCT OF NORETHINDRONE

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## ABSTRACT

A convenient synthesis of 5,17-dihydroxy-5α,17α-19-norpregn-20-yn-3-one in multigram quantities from norethindrone is reported. Confirmation of the structural assignment of this major photodegradation product of norethindrone is thus made.

## INTRODUCTION

The β-ketol 5,17-dihydroxy-5α,17α-19-norpregn-20-yn-3-one (**5**) has recently been identified as a major photodegradation product of norethindrone (**1**)(1,2). The structural assignment was based on elegant two-dimensional NMR analysis of ketol **5** isolated from a complex mixture of degradation products obtained by UV-B irradiation of norethindrone in an aqueous medium (3).

We had need for ketol **5** in gram quantities. We describe here a simple synthesis of this material, its full characterization, and thus confirmation of the structural assignment.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were measured on a Nicolet 5PC FT-IR spectrometer using KBr pellets. UV spectra were measured in methanol on a Hewlett-Packard 8450A spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in methanol. $^{1}H$ and $^{13}C$ NMR spectra were

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measured on a Bruker AM-500 spectrometer in deuteriochloroform unless otherwise stated. Chemical shifts are expressed in ppm downfield from internal TMS (tetramethylsilane). Elemental analyses were performed by the Analytical and Environmental Research group, Syntex Research. Norethindrone USP was obtained from Syntex Corporation.

**17α-19-Norpregn-4-en-20-yne-3β,17-diol** (**2**). Norethindrone, 30.0 g, was reduced with lithium aluminum tri-tert-butoxyhydride according to the method of Klimstra and Colton (4). The isolated product had mp 126-128 C. An analytical sample was recrystallized from acetone/water (mp 137-138 C) and acetone/hexanes (mp 139-140.5 C) (5).

**4ξ,5-Epoxy-5ξ,17α-19-norpregn-20-yne-3β,17-diol** (**3**). A solution of 28 g of 17α-19-norpregn-4-en-20-yne-3β,17-diol (**2**) in 320 mL methylene chloride was cooled to ice-bath temperature and treated with a solution of 22.7 g m-chloroperbenzoic acid (Aldrich 85%) in 320 mL methylene chloride. The mixture was allowed to stir and warm to room temperature overnight. After dilution with 1 L methylene chloride, the solution was washed with 10% w/v aqueous sodium sulfite, saturated sodium bicarbonate, and water. After drying over magnesium sulfate, the solvent was evaporated and the resulting solid recrystallized from methylene chloride/hexanes/ethyl acetate, giving 23.9 g of a crumbly white solid. This was used directly in the next step.

**4α,5-Epoxy-17-hydroxy-5α,17α-19-norpregn-20-yn-3-one** (**4**). A solution of 5.92 g dry DMSO (dimethylsulfoxide) in 38 mL dry methylene was cooled to dry ice/isopropanol-bath temperature and treated with 11.95 g trifluoroacetic anhydride in 13.3 mL dry methylene chloride, keeping the reaction temperature below -60 C. After stirring at bath temperature for 30 min, a solution of 12.0 g 4ξ,5-epoxy-5ξ,17α-19-norpregn-20-yne-3β,17-diol (**3**) in 40 mL dry methylene chloride was added over 20 min. After stirring for 30 min at bath temperature 11.0 g triethylamine was added over 4 min. The cold bath was removed after 15 min and when the reaction mixture reached 5 C (ca 40 min) it was poured into 435 mL water. Repeated extractions with ethyl acetate (5 x 100 mL) gradually extracted all the product. The combined extracts were washed with water, saturated sodium chloride, and dried briefly with sodium sulfate. Concentration gave a paste which was triturated with, and then recrystallized twice from, ethyl acetate, giving 2.76 g (23.1%) 4α,5-epoxy-17-hydroxy-5α,17α-19-norpregn-20-yn-3-one (**4**): mp 252-254 C; $[\alpha]_D$ -122.1° (c = 0.303); $\nu_{max}$ 3440 (hydroxy), 3266 (acetylene CH), 1709 (ketone); $^1$H NMR δ 3.02 (s, 1H, 4β-H), 2.59 (s, 1H, acetylene H), 0.90 (s, 3H, C-18 methyl); $^{13}$C NMR δ 206.08 (C-3), 87.29 (C-20), 79.78 (C-17), 74.18 (C-21), 64.75 (C-5), 61.78 (C-4), 49.05 (C-14), 46.89 (C-13), 46.04 (C-10), 41.08 (C-9), 40.54 (C-8), 38.80 (C-16), 36.39 (C-2), 33.07 (C-12), 32.46 (C-6), 27.95 (C-11), 26.08 (C-7), 22.92 (C-15), 20.77 (C-1), 12.66 (C-18).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 75.98; H, 8.54.

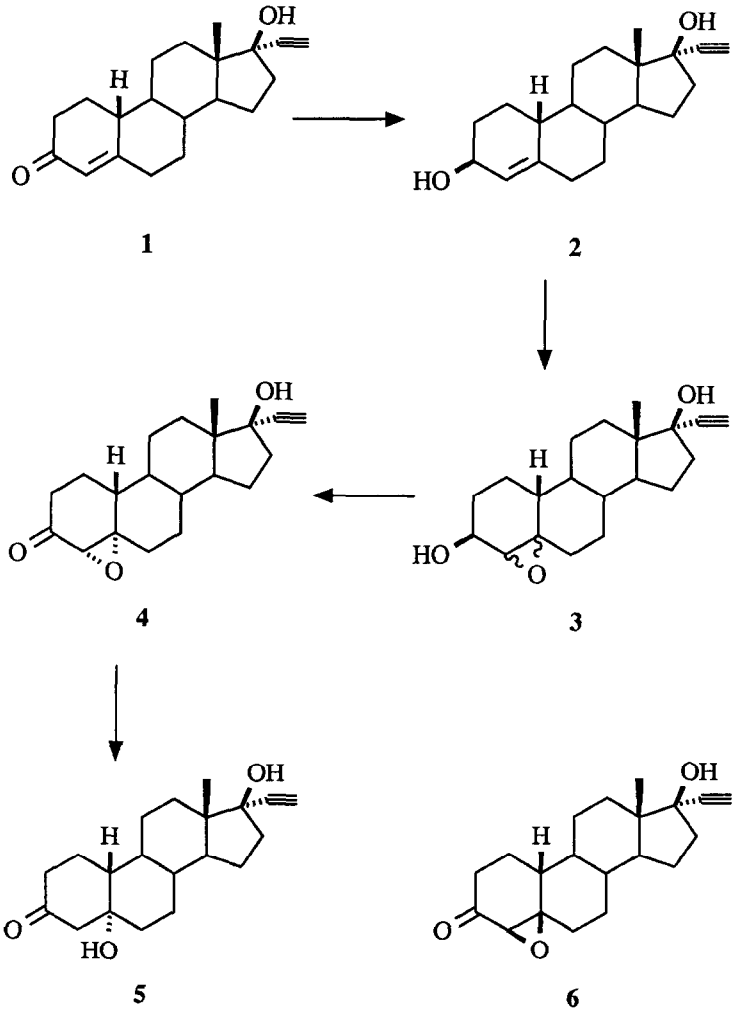
**5,17-Dihydroxy-5α,17α-19-norpregn-20-yn-3-one** (**5**). A solution of

3.72 g diphenyldiselenide in 75 mL ethanol was treated with solid sodium borohydride until a persistent lack of yellow color was noted. After 2 min of stirring, 0.239 g glacial acetic acid was injected, followed after 6 min by a slurry of 2.50 g 4α,5-epoxy-17-hydroxy-5α,17α-19-norpregn-20-yn-3-one (**4**) in 70 mL ethanol. The yellow color reappeared instantaneously and the remainder of the slurry was washed in with an additional 10 mL ethanol. After 1 h total reaction time, the homogeneous yellow solution was diluted with 600 mL ethyl acetate, washed with saturated aqueous sodium chloride, decanted, and treated with 25 g Merck silica gel G-60. The solvent was removed in vacuo at 35 C giving a dry yellow powder which was placed atop a bed of 220 g silica gel packed in 10% v/v ethyl acetate/hexanes in a 600 mL "C" sintered glass funnel. The bed was eluted with 1 L 10% v/v and then 2.5 L 30% v/v ethyl acetate/hexanes, followed by 2.5 L ethyl acetate while collecting 500 mL fractions. Fractions containing the desired product were concentrated to ca 5-10 mL in vacuo at 35 C and then cooled to ice-bath temperature for 1 h. Solvent was cannulated away and the solid residue triturated with hexanes at ice-bath temperature until the supernatant was colorless. Drying in vacuo at room temperature gave 2.1 g (83.3%) 5,17-dihydroxy-5α,17α-19-norpregn-20-yn-3-one (**5**): mp 133-135 C; $[\alpha]_D$ 9.29° (c = 0.269); $\nu_{max}$ 3387 (hydroxyl), $CD_3OD$ relative to internal TMS: δ 2.84 (s, 1H, acetylene H), 2.51 (d, J = 14 Hz, 1H, 4β-H), 0.865 (s, 3H, C-18 methyl); $^{13}C$ NMR in $CD_3OD$ relative to internal TMS: δ 214.03 (C-3), 88.78 (C-20), 80.41 (C-17), 75.54 (C-5), 74.65 (C-21), 56.10 (C-4), 50.50 (C-14), 48.19 (C-10), 48.13 (C-13), 43.32 (C-9), 43.12 (C-8), 41.82 (C-2), 40.15 (C-6), 39.84 (C-16), 33.97 (C-12), 27.00 (C-11), 26.58 (C-1), 26.58 (C-7), 23.84 (C-15), 13.30 (C-18).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.90; H, 8.98.

## RESULTS AND DISCUSSION

As shown in Scheme 1 the approach was to prepare the 4α,5α-epoxide of norethindrone (**4**) and reduce it to the desired product. Attempted preparation of epoxide **4** via the iodohydrin method of Cornforth and Green (6) gave a complex mixture of products including epoxides **4** and **6** (1). A slightly longer sequence, suggested by the work of LeQuesne and co-workers with 19-nortestosterone, readily gave pure epoxide **4** in multigram quantities (7). Norethindrone was reduced with lithium aluminum tri-tert-butoxyhydride in THF (tetrahydrofuran) to the 3β-alcohol **2** (4). Attempted inversion of the 3β-alcohol by the method of Walker and co-workers (8) gave a mixture of at least three products. Simple epoxidation of the 3β-alcohol with m-chloroperbenzoic acid in methylene




**SCHEME 1**

chloride gave a mixture of α- and β-epoxy alcohols which were not separable by TLC. Since it was known that the α- and β-epoxy ketones were separable chromatographically, oxidation of the mixture of hydroxy epoxides was studied. Chromium-based oxidants such as chromium trioxide/pyridine (7,9), chromium trioxide/3,5-dimethylpyrazole (10), and pyridinium dichromate (11) did give the desired mixture of epoxy ketones. It was found, however, that the α-epoxide was unstable to work up from these reactions.

Swern oxidation using trifluoroacetic anhydride/DMSO (12) proved to be a superior method, giving a mixture of the very insoluble epoxy ketones **4** and **6**. The desired α-epoxide proved to be much less soluble than the β-isomer and was isolated in pure form by crystallization from ethyl acetate in 23.1% yield. Analysis by TLC using a single development with diethyl ether/hexanes 7:3, which easily separates the isomeric epoxides (13), showed that no β-epoxide was present.

Conversion of epoxy ketone **4** to the desired β-ketol **5** was accomplished in good yield by the excellent method of Yoshikoshi and co-workers (14), using easily prepared sodium phenylselenide in ethanol.

The 500 MHz $^{1}H$ and 125.8 MHz $^{13}C$ NMR spectra of synthetic product **5** agree well with the values presented by Sedee and co-workers (1,15).

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NOTES AND REFERENCES

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