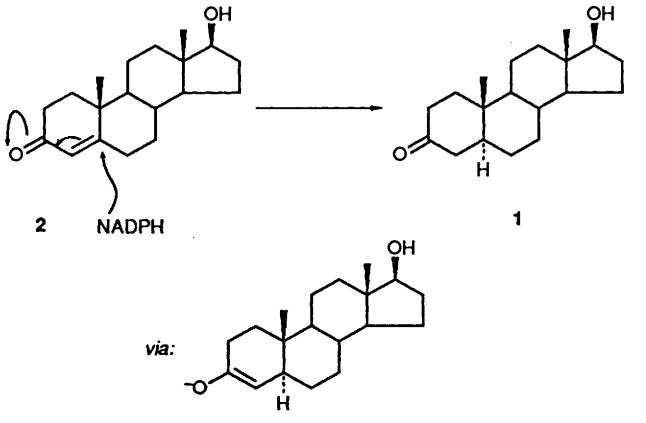
# The Synthesis of 4-Cyanoprogesterone: A Potent Inhibitor of the Enzyme 5-α-Reductase

**Margret Haase-Held, Maria Hatzis and John Mann**
*Department of Chemistry, Reading University, Whiteknights, Reading RG6 2AD, UK*

We describe a number of synthetic approaches to 4-cyanoprogresterone. This compound is a potent inhibitor, both *in vitro* and *in vivo* of the enzyme 5-alpha-reductase

A large percentage of males over the age of 50 suffer from benign prostatic hypertrophy (enlargement of the prostate gland), and a proportion of these (around 11 000 new cases per annum in the UK) eventually suffer from prostatic cancer. Both conditions are androgen-dependent and, in particular, the steroid dihydrotestosterone **1** is believed to be intimately involved in progression of these diseases, as well as a causative factor in such conditions as acne and male-pattern baldness.[1] Clearly drugs that inhibit the production of this metabolite are of interest both to the pharmaceutical and cosmetic industries.

Dihydrotestosterone is produced by the reduction of testosterone **2**, and this process is catalysed by the enzyme 5-α-

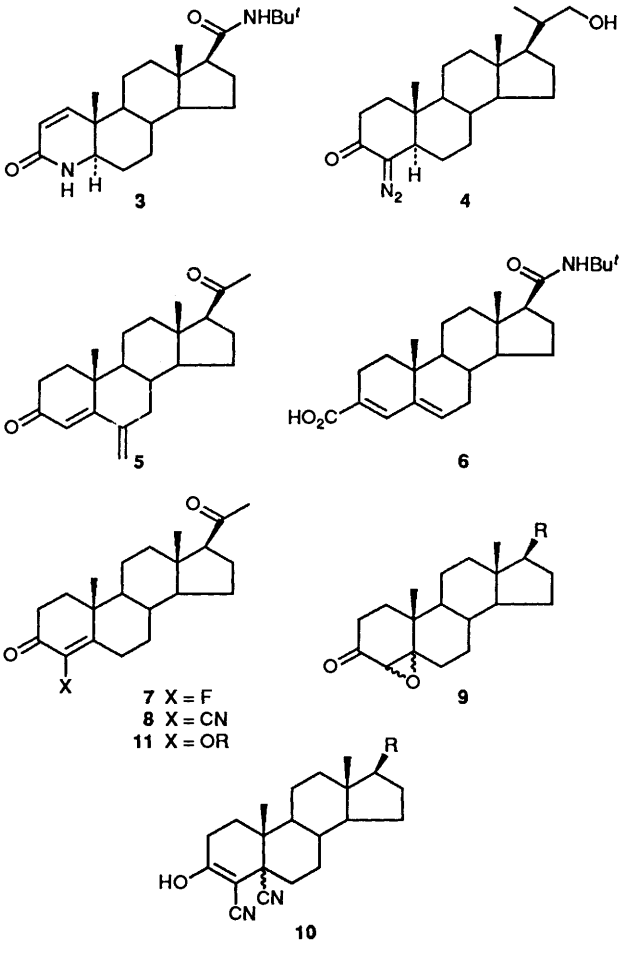



**Scheme 1**

reductase, probably *via* the mechanism shown in Scheme 1.[1] Stabilisation of the proposed enolate intermediate is thus an obvious strategy for the design of potential inhibitors, and a number of compounds that satisfy this requirement, have been produced. Of these, the compounds **3**,[2] **4**,[3] **5**[4] and **6**,[5] have proved to be the most potent, and compound **3** ($K_i$ 25 nm) has recently been introduced as a prescription drug for the treatment of prostatic hyperplasia in the UK and elsewhere.

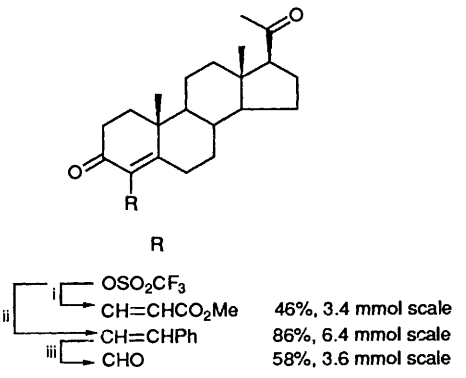
Our involvement in this programme arose from our work on inhibitors of the enzyme aromatase (for the treatment of breast cancer),[6] and the discovery that 4-fluoroprogresterone **7** was an inhibitor of both aromatase and 5-α-reductase at the micromolar level. Reasoning that the fluorine was probably acting as an electron-withdrawing group, we determined to prepare other 4-substituted progesterones in order to assess if these compounds would have improved biological potency. Our attempts (now successful) to prepare 4-cyanoprogresterone **8**, are the subject of this communication.

The only literature route to 4-cyanosteroids[7] involved addition of an excess of cyanide to steroidal 4,5-epoxides **9** to produce 4,5-dicyano products **10**, which were then pyrolysed to yield the desired 4-cyano steroids. Although progresterone could be epoxidized in good yield (30% $H_2O_2$, NaOH;




essentially quant.) to produce a mixture of epoxides **9** (R = Ac) (β:α ratio typically 4:1), the formation of the dicyanide **10** (R = Ac) was irreproducible (between experiments), and its pyrolysis gave only polymeric material. In consequence, we attempted to emulate the success of Piers and Fleming[8] in their palladium-catalysed reactions of cyanide with enol triflates. Reaction of the epoxide mixture **9** (R = Ac) with formic acid[6a] provided 4-hydroxyprogesterone **11** (R = H) in poor yield (*ca.* 40%), though the triflate **11** (R = $SO_2CF_3$) could then be produced in *ca.* 70% yield using trifluoromethanesulfonic anhydride and pyridine in dichloromethane. Reaction of this with LiCN in the presence of tetrakis(triphenylphosphine)palladium(0) and 12-crown-4 (typical ratios of 2:5:0.2:0.3) in dry benzene at room temperature, led to complete consumption of the triflate and production of an intractable mixture of products. Varying the reactant ratios, solvent, and reaction temperature, produced no improvement. It is worth noting that the triflate **11** (R = $SO_2CF_3$) proved to be a highly useful substrate for other

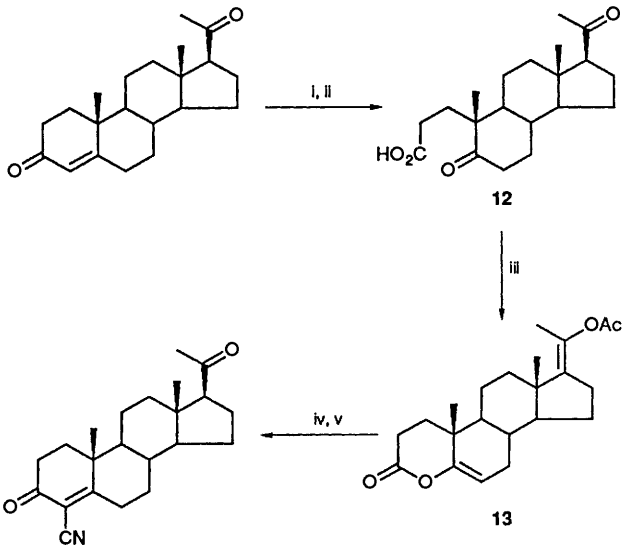
palladium-catalysed reactions, and a whole range of 4-alkylated derivatives of progresterone have been produced by this means (Scheme 2).




**Scheme 2** *Reagents and conditions:* i, $CH_2{=}CHCO_2Me$, $Et_3N/Pd(OAc)_2/DMF$, 60 °C, 2 h; ii, $CH_2{=}CHPh$, $Et_3N/Pd(OAc)_2/DMF$, 60 °C, 1.5 h; iii, ozonolysis

Our third attempted route, however, proved successful, and this is shown in Scheme 3. Ozonolysis of progesterone followed by oxidative work-up ($H_2O_2$–NaOH) produced the diketo acid **12** (80–90% yield), and this could be converted into the enol lactone **13** through reaction with a mixture of acetic anhydride and acetyl chloride (49–45%). Finally, addition of the anion of acetonitrile, followed by treatment of the crude reaction mixture with base (KOBu$^t$ in Bu$^t$OH) provided the desired 4-cyanoprogesterone **8** (40–45%).* Although the overall (unoptimised) yield of this three-stage process was only *ca.* 20%, it is operationally very simple, and has allowed the production of multigram quantities of **8**.

Biological evaluation of compound **8**† established that it possessed marked activity as an inhibitor of 5-α-reductase. *In vitro*, it caused a 50% inhibition of rat enzyme at 0.045 μmolar, and of the human enzyme at 0.05 μmolar. *In vivo*, there was a significant reduction in the weights of mouse prostate (*ca.* 15%), and seminal vesicles (*ca.* 40%) (when compared with controls) at a dose rate of 0.5 mmol $kg^{-1}$ of animal/day. These results will be described in full elsewhere, but clearly the synthesis of other derivatives of progesterone with electron-withdrawing substituents at C-4, is worthwhile. Such work is underway.




**Scheme 3** *Reagents and conditions:* i, ozonolysis; ii, $H_2O_2$/NaOH (overall 80–90%); ii, $Ac_2O$–AcCl, reflux 28 h (45%); iv, MeCN/BuLi/THF; v, Bu$^t$OH/$K^+$Bu$^t$O$^-$ (overall 40–45%)

## Acknowledgements

We thank the Cancer Research Campaign for very generous financial support.

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*Paper* 2/04963E
*Received* 16*th September* 1992
*Accepted* 21*st September* 1992

* A solution of acetonitrile (4 mmol) in THF (5 $cm^3$) was cooled to −78 °C, and BuLi (4 mmol) was added dropwise to it. The solution was stirred for 30 min prior to the addition of the enol lactone **13** (2 mmol). After 1 h at −78 °C and 2 h at room temp., *tert*-butyl alcohol (10 $cm^3$) containing potassium *tert*-butoxide (6 mmol) was added to the solution which was then stirred for 16 h at room temp. The products were extracted into $CH_2Cl_2$, and purified by silica chromatography eluting with $Et_2O$–light petroleum (9:1). 4-Cyanoprogesterone was recrystallised from $Me_2CO$–$Et_2O$ (4:1), and exhibited the following physical and spectral characteristics: m.p. 210–12 °C; $\delta_H(CDCl_3$, 400 MHz) 0.70 (s, 18-Me), 1.27 (s, 19-Me), 2.14 (s, 21-Me), 3.07 (dm, *J* 15.3, 6β-H); $\delta_C(CDCl_3$, 90 MHz) 208.8 (20-C), 192.0 (3-C), 183.4 (5-C), 113.9 (4-C) and 112.3 (CN) (Found: C, 77.6; H, 8.85; N, 4.2. $C_{22}H_{29}NO_2$ requires C, 77.84; H, 8.61; N, 4.13%).

† Biological experiments were carried out at the Institute of Cancer Research, Sutton, Surrey, using enzyme preparations from rat and human prostate, and measurements of the fall in plasma dihydrotestosterone levels following a single dose of 4-cyanoprogesterone. We thank Michael Jarman, Martin Rowlands and Elaine Barrie for these investigations.