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Synthesis of a B-Homo 6-Azaandrost-4-ene-3-one as a Novel Steroidal 5α-Reductase Inhibitor

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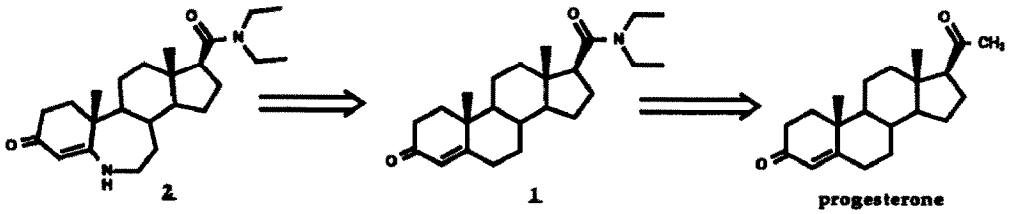
Abstract: *The preparation of a B-ring homologated analog of 17β-N,N-diethylcarboxy-6-azaandrost-4-ene-3-one, a potent inhibitor of type 2 steroidal 5α-reductase, is described.*

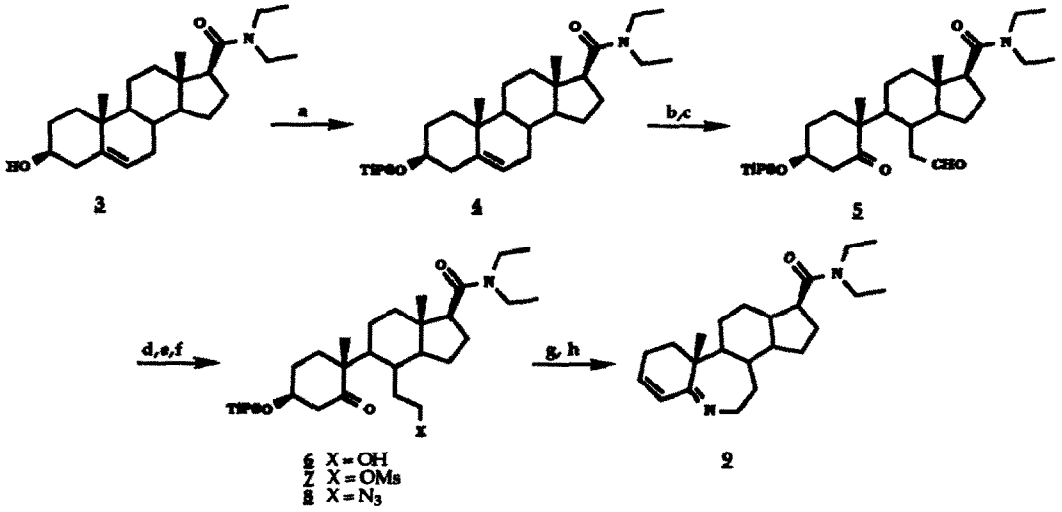
As males age, urinary complications are likely to develop as a result of an enlargement of the prostate known as benign prostatic hyperplasia (BPH). Although the cause of BPH is unclear, the permissive role of dihydrotestosterone (DHT) in the hyperplastic growth of the prostate is well established.[1,2] It has been shown that inhibition of 5α-reductase (5AR), the enzyme responsible for conversion of testosterone to DHT, decreases intraprostatic levels of DHT and causes a reduction in prostate size.[3]

In our research we have discovered an active series of 5AR inhibitors in the 6-azasteroids.[4] In an effort to investigate the structure activity relationship of this novel series it was decided that the B-ring homolog should be prepared and tested. This was accomplished from the C-17 diethyl amide analog **1**, which is easily accessible from progesterone.[5]



The planned synthetic route is shown in Scheme 1. Our previous work in the area made available the pregnenolone adduct[4] **3** which was protected as the triisopropylsilyl ether **4**. The B-ring was oxidatively cleaved with ozone followed by a zinc reduction[6] to afford the seco-aldehyde **5**. Selective reduction of the aldehyde in the presence of the ketone with lithium tris(t-butyloxy)aluminohydride[7] to provide alcohol **6**, activation as the mesylate **7** and reaction with azide provided **8**. Attempts to reduce this azide caused extensive beta-elimination[8] of the silyloxy component to produce the aza-diene **9**. From this point on it was clear that an alternative protecting group that was resistant to elimination was necessary.

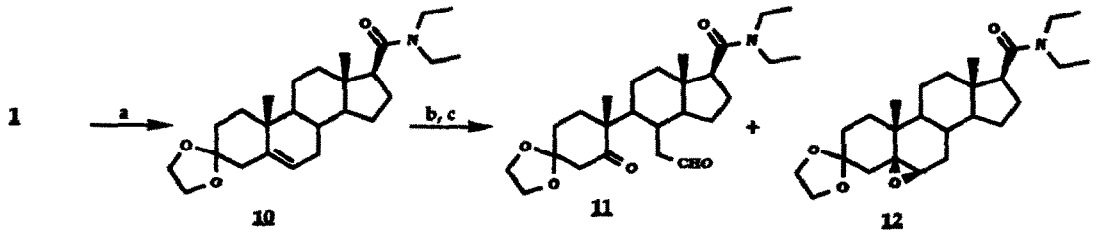
Scheme 1



Key: a, triisopropylsilyl chloride/TEA/CH_2Cl_2 (78%); b, O_3/MeOH/CH_2Cl_2; c, Zn/HOAc (95%); d, $LiAlH(OtBu)_3$ /THF (75%); e, MsCl/TEA/CH_2Cl_2 (99%); f, NaN_3/DMF,70°C(90%); g, $P(Ph)_3$/THF; h, 3N HCl/reflux (80%).

As shown in Scheme 2, the ethylene ketal was selected to protect the 3-oxo functionality of the previously described enone **1**. The protection provided a second benefit in that the double bond migrated to the adjacent ring preparing the B-ring to be oxidatively cleaved.[9] The olefin in **10** was then subjected to ozonolysis conditions in 30% methanol in dichloromethane followed by reduction with activated zinc powder and acetic acid. The resulting material was a 1:1 ratio of seco aldehyde **11** and β-epoxide[10] **12** which were separable by flash chromatography (30-70% EtOAc/hexane). This result was not surprising since a trace of a similar epoxide was observed in the sequence where

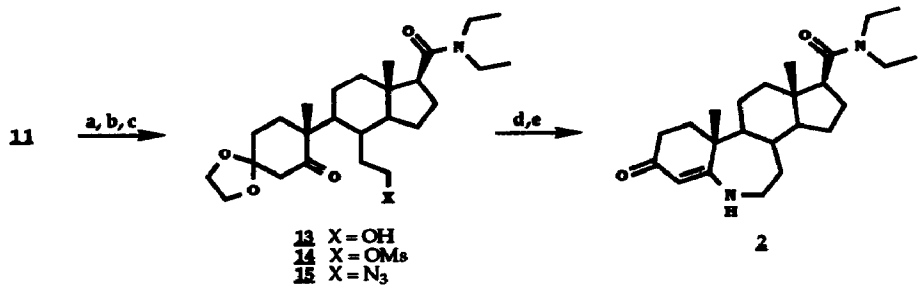
Scheme 2



Key: a, ethylene glycol/pTSA/toluene (55%); b, O_3/MeOH/CH_2Cl_2 (86%); c, Zn/HOAc (84%).

the triisopropylsilyl group was used to protect the 3-oxo functionality. We feel this occurs because generally the methyl at C-19 directs chemistry to occur on the α-face, but in the case of the ketal, reaction on the α-face is sterically limited due to the axial-down positioning at C-3 thus leading to the observed mixture of products.

Scheme 3



Key: a, $LiAlH(OtBu)_3$ /THF; b, MsCl/TEA/CH_2Cl_2; c, NaN_3/DMF,70°C; d, $P(Ph)_3$/THF; e, 3N HCl/ reflux (25%).

The synthesis was completed as indicated in Scheme 3, where the seco-aldehyde **11** was selectively reduced to give alcohol **13**. The alcohol was activated as the mesylate **14**, converted to the azide **15** and the reduction was then carried out with triphenylphosphine, presumably to form an aza-Wittig type adduct which was not isolated prior to cyclization.[11] Acidic deprotection was performed in the same pot to afford **2** which was characterized by high resolution MS, HPLC, ^1H and ^{13}C NMR .[12]

The IC_{50} of **2** was determined to be 3.8 nM toward human type 2 5α-reductase. With the addition of this novel steroidal homolog to the collection of potent 5α-reductase inhibitors, new advances in the therapeutic area are possible.

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10. A 2.3:1 mixture of α:β epoxides was prepared from treatment of **10** with 3-chloroperoxybenzoic acid and the ^1H NMR data for each was compared with that of **12**. The methine proton at C-6 demonstrated a coupling of J = 4.4 Hz (2.82 ppm:$CDCl_3$) for the α-epoxide and J = 1 Hz (3.07 ppm: $CDCl_3$) for the β-epoxide **12**.
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12. Spectral data for **2**: hi-res MS observed 387.3012, theoretical 387.3029; ^{13}C NMR (75.5MHz, $CDCl_3$) δ 196.4 (C=O), 176.7, 171.9 (C=C), 102.9 (C=O,amide), 56.0, 51.1, 46.2, 44.5, 44.2, 41.9, 40.5, 40.2, 39.5, 39.1, 37.0, 34.5, 32.0, 25.6, 25.5, 24.1, 19.8, 14.7, 13.9, 13.4.

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