Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3291–3294

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

EFFICIENT CONSTRUCTION OF 6-AZASTEROIDS: DUAL INHIBITORS OF STEROIDAL 5α-REDUCTASE

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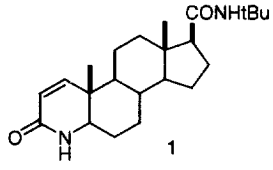
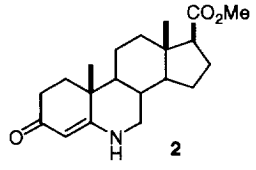
Received 4 August 1998; accepted 6 October 1998

Abstract: A new route to 17β-substituted-6-azaandrost-4-en-3-ones, potent dual inhibitors of type 1 and 2 steroidal 5 α-reductase, is described.

The use of steroidal 5α-reductase (5AR) inhibitors for the treatment of certain androgen dependent conditions, such as benign prostatic hyperplasia (BPH), acne, male pattern baldness, and female hirsutism is now a well developed hypothesis.[1] In humans two isozymes of 5α-reductase, types 1 and 2, catalyze the transformation of testosterone to dihydrotestosterone and are predominantly found in the skin and prostate, respectively.[2] Finasteride (**1**), a 4-azasteroid, was recently introduced as a type 2 selective 5AR inhibitor for the treatment of BPH.[3] In a search for potent dual inhibitors of 5AR, 6-azasteroids were recently reported by researchers at Glaxo Wellcome.[4] The prototypical compound in this series is the 17β-carbomethoxy-6-azaandrost-4-en-3-one **2**[5] shown below.



1



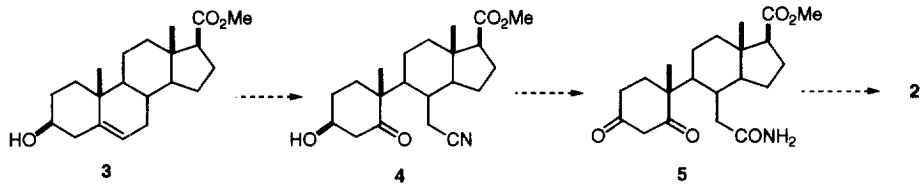
2

In order to fully evaluate the clinical potential of 6-azasteroids, such as **2**, a manufacturing route to these compounds was required. The previously reported synthesis of 17β-substituted-6-azaandrost-4-en-3-ones[4] starting from 3β-hydroxyetienic acid methyl ester[6] (**3**) followed the strategy reported by Lettre for 6-azacholesterol.[7] A significant drawback to this route in terms of safe large-scale production was the use of a Curtius rearrangement to introduce the nitrogen atom. Other mitigating circumstances included the use of several protecting groups and a number of chromium based oxidants. Finally, an oxidative cleavage of the C.5-C.6 olefin using ozone limited the throughput of the process. Because of problems associated with scale-up of the synthetic route described above it became necessary to explore a new route to 6-azasteroids and particularly to **2**.[8]

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00611-8

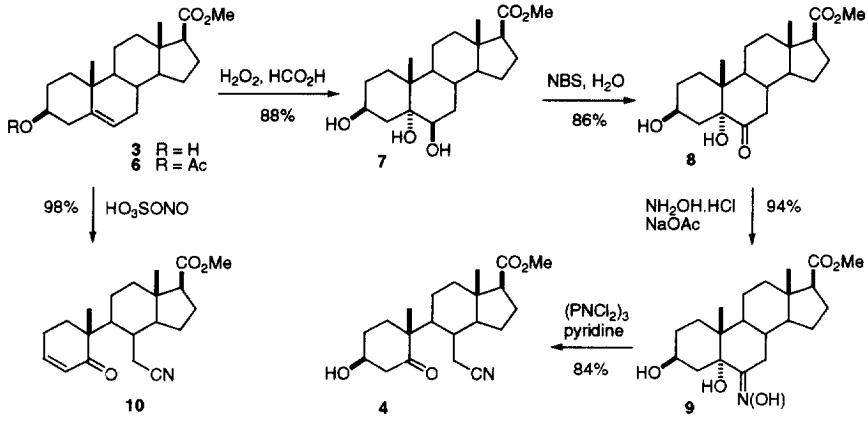
The synthetic plan for the preparation of **2** is set forth in Scheme 1. The starting material would continue to be derived from pregnenolone. A second-order Beckmann rearrangement was selected for cleavage of the C.5-C.6 bond.[9,10] Oxidation to a 1,3-diketone, hydrolysis of the nitrile to the corresponding amide, and Hofmann rearrangement[11] followed by cyclization would complete the synthesis of the 6-azasteroid. Herein is reported the successful realization of these goals and a synthesis of **2**.

Scheme 1



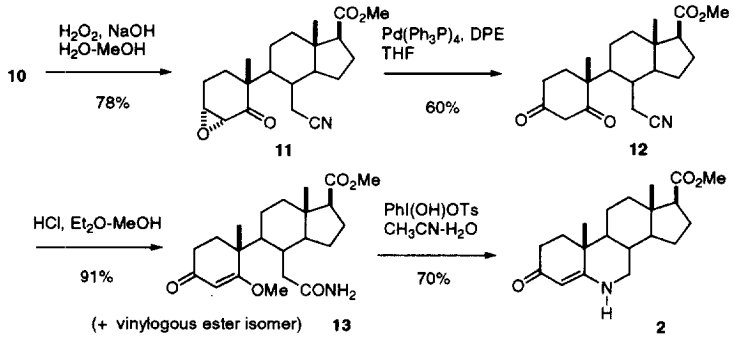
The first sub-goal, preparation of the α-hydroxyoxime **9**, was realized in a straightforward fashion as outlined in Scheme 2. Oxidation of the $\Delta^{5,6}$ olefin of 3β-hydroxyetienic acid methyl ester (**3**) to the corresponding hydroxyketone **8** was accomplished using the two step sequence developed by Fieser.[12] Thus, **3** was treated with 96% formic acid and 30% hydrogen peroxide followed by hydrolysis with NaOH to afford the 3β,5α,6β-triol **7** in 88% yield. Regioselective oxidation of the 6β-hydroxyl group with NBS in dioxane-H_2O gave hydroxyketone **8** in 85% yield. Conversion to the corresponding α-hydroxyoxime **9** was accomplished by heating **8** with hydroxylamine hydrochloride and sodium acetate in ethanol. The crystalline product **9** was isolated in 94% yield by filtration. The Beckman fragmentation of α-hydroxyoxime **9** was first attempted using thionyl chloride as the activating agent. Under these conditions a 1:1 mixture of the 3-hydroxy 5,6-seconitrile **4** and the corresponding β-elimination product, enone **10** was obtained. Suppression of this side reaction was accomplished using milder activation conditions. Thus treatment of **9** with phosphonitrilic chloride trimer[13] in pyridine-THF afforded the 3-hydroxy 5,6-seconitrile **4** as the sole product in 84% yield. Overall, the 3-hydroxy 5,6-seconitrile **4** had been prepared in four steps and 60% yield overall from 3β-hydroxyetienic acid methyl ester (**3**).

Scheme 2



A survey of the literature suggested a potentially more concise conversion of **3** to **4** by directly subjecting the C.5-C.6 olefin to nitrosation conditions.[14] In the event, treatment of 3β-hydroxyetienic acid methyl ester (**3**) with nitrosylsulfuric acid (2 equiv) in diethyl ether produced the enone 5,6-seconitrile **10** in 44% yield. Presumably the anticipated α-hydroxyoxime **9** was formed as an intermediate that underwent the Beckmann fragmentation and a subsequent β-elimination to generate the observed product **10**. Repeating these conditions on the acetylated substrate **6** generated the enone 5,6-seconitrile **10** in 98% yield.[15] In view of the efficiency of this oxidative fragmentation process, we decided to investigate the plausibility of enone **10** as a precursor to the desired β-diketone moiety. Towards this end, the enone was subjected to epoxidation conditions (hydrogen peroxide, sodium hydroxide, methanol) as shown in Scheme 3. The α-epoxide **11** crystallized directly from the reaction mixture in 78% yield[16] (ca. 10% of the β-epoxide remained in the filtrate). Rearrangement of the α-epoxy-ketone **11** to the 1,3-diketone **12** was accomplished using the protocol of Noyori.[17] Thus, treatment of **11** with catalytic tetrakis(triphenylphosphine)palladium (0) and 1,2-bis(diphenylphosphino)ethane in refluxing tetrahydrofuran provided the 1,3-diketone **12** in 60% yield. Interestingly the minor β-epoxide was inert to these palladium catalyzed rearrangement conditions. With the steroid A-ring now at the correct oxidation state, the next step was to convert the nitrile to the corresponding primary amide. This hydrolysis was best performed by treating **12** with anhydrous HCl in Et_2O/MeOH 3/1 at 0 °C followed by basic work-up. This reaction afforded the primary amide **13**, in which the 1,3-diketone had concurrently been transformed to a mixture of vinylogous methyl ester, in 91% yield.[18] With the primary amide in hand, the feasibility of the tandem Hofmann rearrangement/cyclocondensation reaction could be tested. This transformation was best accomplished using the conditions of Koser.[19] Thus treatment of the primary amide mixture **13** with 1.05 equiv of hydroxy(tosyloxy)iodobenzene in refluxing CH_3CN/H_2O 1/1 afforded the 6-azasteroid **2** in 70% yield.

Scheme 3



In summary, an efficient conversion of the readily available steroid **3** to 6-azasteroids such as the potent dual 5AR inhibitor **2** has been established (6 steps, 29% overall yield). Amongst the key features of this route are a one-step oxidative fragmentation of the C.5-C.6 double bond, (ii) a useful stereodependant application of the Noyori rearrangement to allow conversion of the enone to a 1,3-diketone, (iii) a tandem Hofmann rearrangement/cyclocondensation reaction to generate the 6-azasteroid skeleton. Furthermore, the above transformations avoid the use of ozone, protecting groups, heavy metal oxidants, and potentially hazardous azides.

Acknowledgements: We thank Dr. Peter White (Chemistry Department, University of North Carolina at Chapel Hill, Single Crystal X-ray Facility) for collection and interpretation of the X-ray data.

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