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Synthesis of 6-Azacholesten-3-ones: Potent Inhibitors of 5α-Reductase.

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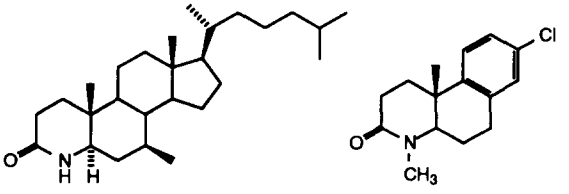
Abstract: *4-Cholesten-3-one was converted into 6-azacholesten-3-ones (**7, 14 and 15**). These compounds proved to be potent inhibitors of both type 1 and 2 human 5α-reductase.*

The enzyme 5α-reductase (5AR) catalyzes the conversion of testosterone (T) to the more potent androgen dihydrotestosterone (DHT)[1] and two isozymes of this enzyme have been discovered in humans.[2] DHT is believed to be involved in several androgen dependent diseases, i.e. benign prostatic hyperplasia, alopecia, acne and hirsuitism.[3] We were interested in finding a novel inhibitor of this enzyme which might be useful in the treatment of these diseases. Earlier work has shown that type 1 5AR is found predominately in the skin and liver.[4] Due to its localization in the skin a type 1 selective inhibitor could be useful in treating acne, alopecia and hirsuitism.

Recently, two series of compounds, 4-azasteroid **1**[5] and tricyclic lactam **2**,[6] were reported to selectively inhibit type 1 5AR. Earlier work from our laboratories showed that 6-azasteroids were potent dual inhibitors of 5α-reductase.[7] It was felt that incorporation of the cholesterol side chain at C17 along with the C7 methyl group, as seen in **1**, might provide a potent type 1 selective compound.

Figure 1.



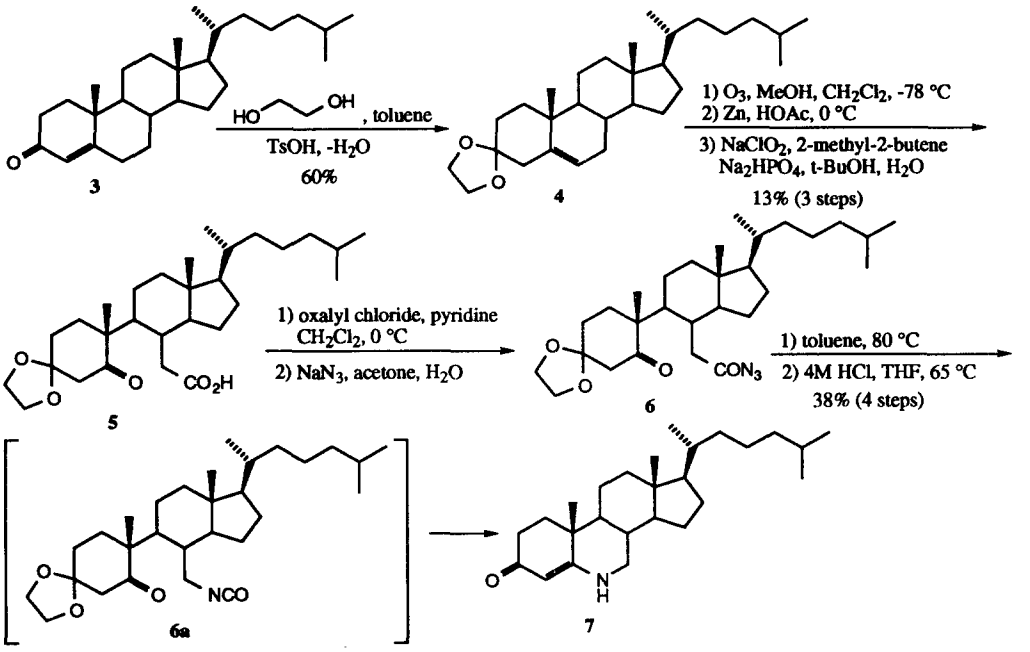
1 **2**

The synthetic route that was initially developed to construct the 6-azasteroid nucleus turned out to be very sensitive to the substituent at C17 when trying to cyclize the seco isocyanate **6a**[8] to reform the B-ring.[7b] Although a carboethoxy group at C17 allowed the cyclization to proceed smoothly, when the cholesterol side chain was incorporated the cyclization no longer worked. This sensitivity to the cyclization reaction was also observed when various carboxamides were introduced at C17 prior to B-ring closure.[7b]

Due to these difficulties with the cyclization an alternate synthetic route was devised to circumvent this problem. After examining several alternatives a synthetic route was finally developed to construct the desired 6-azacholesten-3-ones. Initially the non-C7 methylated 6-azasteroid was synthesized. The synthesis started

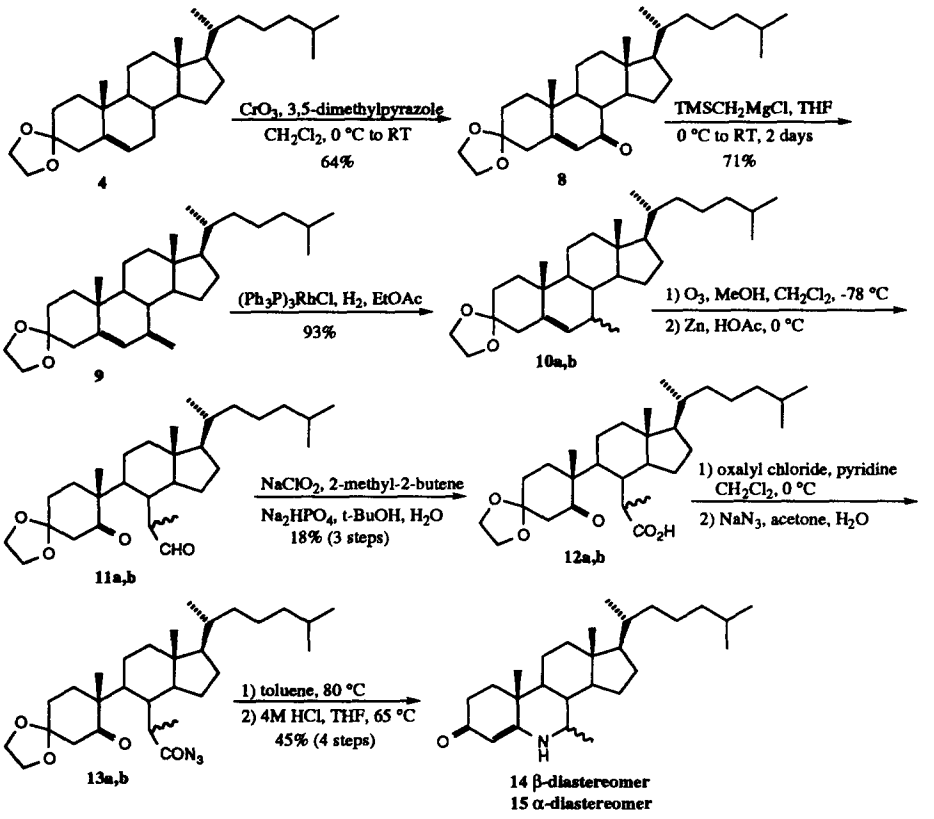
with 4-cholesten-3-one **3**. The first step involved ketalization to give **4** followed by ozonolysis and reductive workup generating the ketoaldehyde which was then directly oxidized affording ketoacid **5**. The acid was converted to the acid chloride followed by reaction with sodium azide to give acyl azide **6**. Heating **6** to 80 °C generated the isocycanate which was immediately treated with aqueous acid yielding the desired product **7**.

Scheme 1.



Incorporation of the methyl group at C7 required slight modifications of the above synthesis. Ketal **4** was oxidized at C7 using the Salmond[9] procedure to give enone **8**. The enone was converted to the 1,3-diene via the Peterson olefination[10] affording **9**. Selective hydrogenation of the diene with Wilkinson's catalyst gave the C7 methylated compounds **10a,b** as a 2.2:1 diastereomeric mixture.[11] The mixture was taken on into the ozonolysis reaction. Treatment of **10a,b** with ozone followed by reductive workup gave ketoaldehydes **11a,b**. Interestingly we had noticed in prior work that the ketal at C3 caused significant amounts (>50%) of the C5-C6 β-epoxide to be formed.[12] However, when a β-triisopropylsiloxy group was at C3 prior to ozonolysis very little epoxide was seen.[7b] Incorporation of the methyl group at C7 seemed to further enhance the epoxide formation accounting for the low yield of the desired ketoaldehyde. Ketoaldehyde **11a,b** was then oxidized as before generating ketoacid **12a,b**. The acid was transformed to acyl azide **13a,b**, heated to 80 °C and treated with aqueous acid affording 6-azacholesten-3-ones **14** and **15** as a 2.4:1 (β/α) mixture of diastereomers.[13]

Scheme 2.



The 6-azasteroids **7**, **14** and **15** were assayed against both type 1 and type 2 5AR. The results are reported in table 1. The results show that all three compounds are potent dual inhibitors of 5AR. Unlike the 4-azasteroids the cholesterol side chain imparts very little selectivity between type 1 and type 2 5AR.[5] The little selectivity seen favors the α-C7 methyl diastereomer **15** 7-fold toward type 1 5AR versus the β-diastereomer **14**.

In summary, a synthetic route was designed to construct 6-azacholesten-3-ones to elucidate whether a selective type 1 5AR inhibitor could be found in this framework. Incorporation of a C7α-methyl group in the cholesterol series resulted in 7-fold selective type 1 5AR inhibitor **15**.

Table 1. compound	type 1 5AR (K_i)	type 2 5AR (K_i)
7	1.0 nM	2.3 nM
14	1.0 nM	1.2 nM
15	0.8 nM	7.9 nM

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References and Notes

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13. All new compounds exhibited spectroscopic (IR and NMR) and analytical (combustion analysis and/or high resolution mass spectrum) data in accord with the assigned structure. Compounds **14** and **15** were separated via semiprep HPLC and their stereochemistry elucidated via a 2D NOE, COSY and homonuclear decoupling experiment.

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