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Reduction of a Δ^4-Steroid with Diborane.

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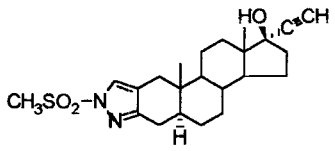
Key Words: 5β-steroids, boron rearrangement, synthesis, molecular mechanics.

Abstract. Reported here is a boron process equivalent to stereoselective olefin reduction and concomitant protecting group cleavage.

In connection with our work about antiandrogens and during the course of analog preparation of **1**[1] for structure-activity relationships, we discovered the anomalous reaction of a double bond with B_2H_6/THF.

We were interested in preparing the fluorinated steroidal derivative **2**. The aim was to prepare the 4-fluoro compound **3** which upon further manipulations would provide the desired compound.



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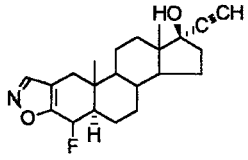

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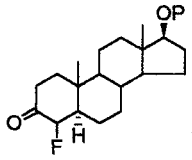
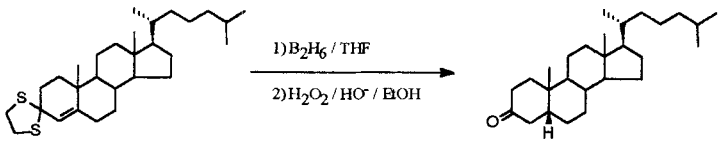


P = Protective group

3

In a previous analysis directed toward the functionalization at the C-4 position of a steroid, we selected the anti Markovnikov addition of water to a Δ^4-steroid. In order to optimize the reaction conditions, we decided to use a cholesterol derivative with an unfunctionalized side-chain. Considering that we needed a 3-keto function for further transformations, we prepared the dithioketal **4** known to be a convenient protecting group to avoid the isomerization of the double bond.

Interestingly, when we attempted the hydroboration-oxidation of compound **4** only **5** was isolated in 85 % yield (Scheme 1).



4 5

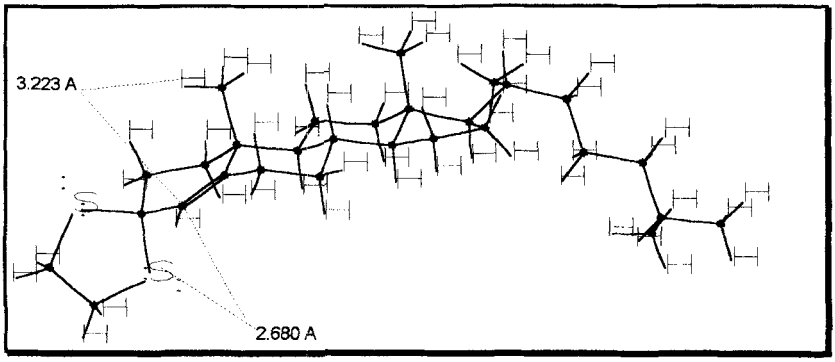
Scheme 1

This reaction was made with an excess of borane at 0°C, and all attempts using one equivalent of borane, dilute solutions, or lower temperatures only reduced the yield of the same compound. The absolute configuration at C-5 was unequivocally established by ^1H and ^{13}C-NMR where the spectral characteristics of **5** were in full agreement with those found previously.[2]

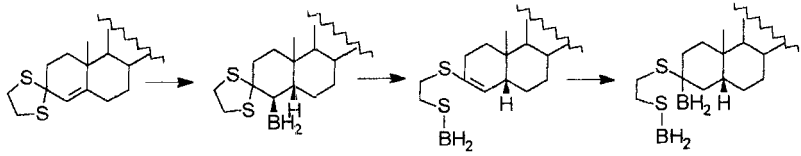
A survey of the literature on this subject revealed that mixtures of 5α/5β steroids were obtained by hydrogenation of Δ^4-3-keto-systems.[3] Variations in the reaction conditions caused large changes in the 5α/5β ratio, and 5β-steroids predominated from hydrogenations conducted in a strongly basic medium.[4] In dilute or weak base only slight excess of the 5β product was formed. Ravasio and Rossi reported recently that Cu/Al_2O_3 is an effective catalyst for stereoselective hydrogenations to give 5β-derivatives, but some steroids gave low yields of the 5β isomer.[5]

Presumably, this anomalous hydroboration reaction is controlled by a combination of steric and electronic factors. Although the α-attack would be expected to be favored because of C-19 methyl group, the increased steric bulkiness of the protecting group dominates the α-face and improved the β-stereoselectivity. Figure 1 shows the lower energy conformation which was obtained by molecular mechanics calculations (PCMODEL-386, v 4.0, Serena Software, 1990).[6]

Comparing the distances between C-4 and the hydrogens of C-19 (4.331 Å, 3.930 Å and 3.223 Å) with the distance between C-4 and the pseudoaxial sulfur atom (2.680 Å), it can be noted that the sulfur atom is closer to C-4 than the hydrogens of the methyl group. Taking this into account, it is possible to predict that the steric factor drives the stereochemical outcome.



The mechanism of the reaction has not been established, however the formation of the product has led us to postulate the mechanism depicted in Scheme 2.



Scheme 2

It is possible that conversion of **4** into **5** occurs by a series of steps that first involves the addition of borane to the olefin (Scheme 2). Furthermore, considering that no detectable amounts of secondary alcohol were found, boron migration must occur. Boron affinity for sulfur compounds is well known considering, for example, commercially available complex like BH_3-Me_2S. Taking into account recent studies about reductive cleavage of allylic ethers, this migration is presumably assisted by sulfur atom with protecting group fragmentation.[7] In the last step, re-addition of borane and subsequent oxidation leads to the ketone.

In summary, a stereocontrolled synthesis of a 5β-steroid was carried out in a highly efficient manner. We are currently exploring further synthetic possibilities of this reaction for non-steroidal systems like sesquiterpenes in order to obtain *cis*-fused products.

EXPERIMENTAL

General procedure: 1.5 ml of a solution of B_2H_6 / THF (2.4 M) was added to 107 mg (0.23 mmoles) of **2**. The solution was stirred under nitrogen at 0° C for 5 hours. After that, water was slowly added until no more hydrogen developed. The mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in 3 ml of a mixture of ethanol-THF (1:4) and 250 µl of a saturated solution of KOH in water were added. The solution was stirred at 0° C and 0.5 ml of H_2O_2 30% was added. After stirring for 5 minutes, the product extracted with ethyl acetate.

NOTES AND REFERENCES

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6. The force field used in PCMODEL is called MMX and is derived from the MM2(QCPE-395, 1977) force field of N.L. Allinger, with the pi-VESCF routines taken from MMP1(QCPE-318), also by N.L. Allinger.
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