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DIASTEREOSELECTIVE ADDITION OF ORGANOMAGNESIUM REAGENTS TO 17β-TBDMS-DIHYDROTESTOSTERONE

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Abstract: Several alkylations of the C3-carbonyl of 17β-TBDMS-DHT (**1**) with Grignard reagents were performed to obtain a series of potential inhibitors of androgen formation. It has been found that, depending on the nucleophilicity of the Grignard reagent used, there was a difference in the diastereoselectivity. The stronger reagents proceeded preferentially through the equatorial attack, while the weaker ones proceeded through the axial attack.

It is well known that the active male hormones testosterone (T) and dihydrotestosterone (DHT) play an important role in the development of several androgen-sensitive diseases such as benign prostatic hyperplasia, acne, alopecia in men, hirsutism in women, male

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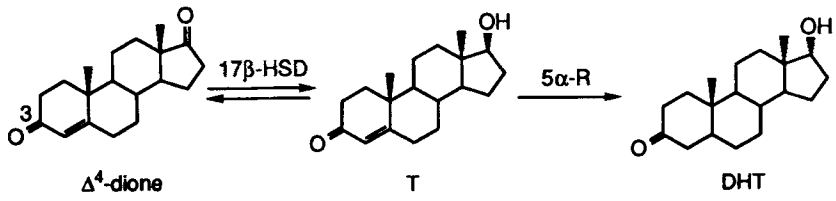
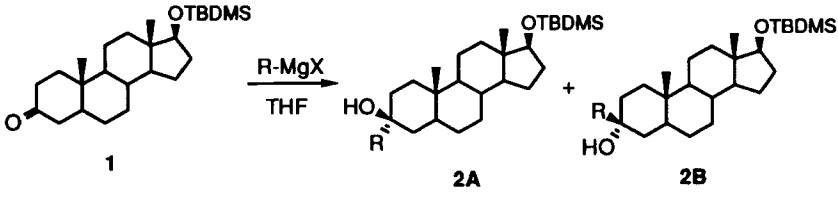
pattern baldness and prostatic carcinoma.[1] 5α-reductase (5α-R)[2] and 17β-hydroxysteroid dehydrogenase (17β-HSD)[3] are key enzymes involved in the production of these active androgen steroids. 17β-HSD catalyses specifically the stereoselective reduction of the C17-carbonyl of Δ^4-androstenedione (Δ^4-dione), leading to testosterone, while 5α-R catalyses the last step in the formation of dihydrotestosterone (Scheme 1). A therapeutic approach to treating these androgen-sensitive diseases is to stop the formation of the active androgens by inhibiting a target enzyme of steroidogenesis. During our studies on the synthesis of 17β-HSD inhibitors, we performed several alkylations of the C3-carbonyl of 17β-TBDMS-DHT (**1**), to obtain its 3β-alkylated derivatives directly. The alkylations were all done under similar reaction conditions with a Grignard reagent. Interestingly, our results were divided into two groups according to the nature of the Grignard reagent. We herein report and discuss the diastereoselectivity observed for a variety of Grignard reagents on the C3-carbonyl of 17β-TBDMS-DHT and our attempts to increase the equatorial attack.

Results and Discussion

DHT, with the 17β-hydroxyl protected as a *t*-butyldimethylsilyl ether (TBDMS-Cl, imidazole, DMF), was alkylated with a variety of Grignard reagents (Scheme 2). In all cases, a mixture of the two possible stereoisomers at position 3 (**2A** and **2B**) was obtained. The proportions varied with the nature of the alkylating group (Table). The stereochemical assignment was done using ^1H and ^{13}C NMR data, based on the known $C\underline{H}_3$-19 and $\underline{C}H$-3 chemical shifts (δ) of *epi*-



Scheme 1

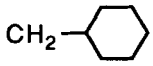
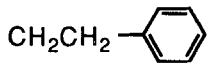
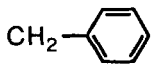


Scheme 2

androsterone and dihydro *epi*-androsterone (**2A**) (R = H, 17–C=O and 17β-OH, respectively), as well as androsterone and dihydro androsterone (**2B**) (R = H, 17-C=O and 17β-OH, respectively).[4a,b] In the **2A** series, these δ values were always higher (0.79 - 0.86 ppm for the C<u>H</u>$_3$-19 and 71.5 - 73.6 ppm for the <u>C</u>H-3) than corresponding data in the **2B** series (0.73 - 0.82 ppm and 69.8 - 72.3 ppm).[4c] For example, the C<u>H</u>$_3$-19 and the <u>C</u>H-3 chemical shifts of hexyl derivatives were 0.82 and 72.8 ppm for the **2A** stereoisomer, while these values were 0.73 and 71.5 ppm for the **2B** stereoisomer.

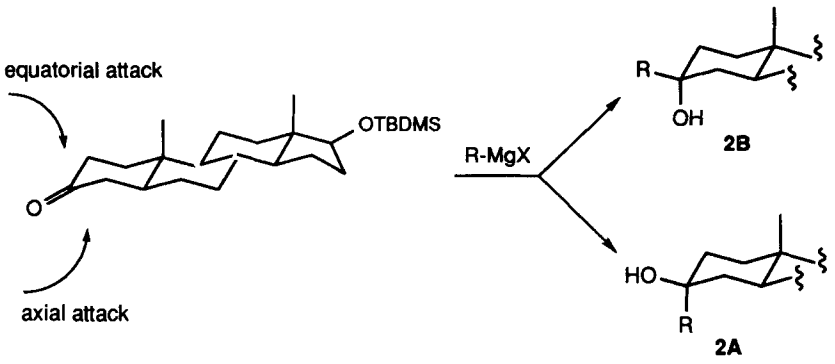
The carbonyl to be alkylated (C3) presents an equatorial side, less hindered than the axial side, due to the axial hydrogens at positions 1 and 5. Therefore, there are two possible pathways of addition for the

Table : Proportions of the axial (**2A**) and equatorial (**2B**) alkylation of 17β-TBDMS-DHT (**1**).

Entry	R	**2A/2B** (%)	Yield of **2A/2B** (%)[a,b]	Starting material (%)
1	CH_3	35/65	60	18
2	$(CH_2)_2CH_3$	31/69	65	13
3	$(CH_2)_5CH_3$	26/74	73	10
4	$(CH_2)_{11}CH_3$	25/75	51	5
5[c]		13/87	37	8
6[c]		34/66	58	30
7	$CH{=}CH_2$	58/42	56	22
8	$CH_2CH{=}CH_2$	58/42	66	10
9		57/43	88	0
10		60/40	61	18

a) Isolated yield after chromatography.
b) For the first group of the reagents (entries 1 to 6), a 10 to 20% of reduction products was isolated also.
c) Grignard reagent generated *in situ*.

reagent: an axial path of attack, leading to the 3α-alkylated compound (**2A**), and an equatorial one, leading to the 3β-alkylated compound (**2B**) (Scheme 3). In our studies, Grignard reagents with a saturated alkyl group proceeded preferentially through the equatorial attack (entries 1 to 5). Ethylbenzene magnesium bromide also proceeded through this attack (entry 6). On the other hand, the vinyl, allyl, phenyl and benzyl magnesium bromide proceeded preferentially through the axial attack (entries 7-10).



Scheme 3

We observed that the first group of reagents is constituted of stronger nucleophiles (entries 1 to 6), whereas we find stabilized weaker nucleophiles in the second group (entries 7 to 10). A systematic study was done by Chérest and Felkin,[5] on 4-*t*-butyl-cyclohexanone, using first *n*-propyl and than allyl magnesium bromide. The stereoselectivity of the addition is the same as the one we obtained with 17β-TBDMS-DHT. In fact, the two substrates are very similar, as the A-ring of the steroid is locked in the chair conformation.

Theories concerning the stereoselective addition on cyclic ketones are generally based on electronic and steric effects.[6] The results we obtained are in accordance with the theory developed by Cieplak and coworkers: the more the electronic density of the molecular orbitals implied in the transition state is low, the more the axial attack is promoted.[6b] This explains the predominant axial attack observed within the second group of our Grignard reagents, in which electronic density was diluted because of delocalisation (entries 7 to 10). For the first group, the equatorial attack was predominant and the

stereoselectivity increased with the size of the reagent (entries 1 to 6). This can be explained by the steric factors.[6a]

It is possible to increase the axial attack of the carbonyl by using an aluminium complex, which chelates the carbonyl on the less hindered side in a stable conformation, making this side too hindered so that the addition takes place on the opposite axial side.[7] When methylaluminium bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD) was used with 17β-TBDMS-DHT (**1**) and allyl Grignard reagent, the proportions of **2A:2B** increased from 58:42 to 91:9 in the case of the allyl Grignard reagents. In our biological study, however, we were interested in obtaining mostly the 3β-alkylated stereoisomer, particularly in the second group (entries 7 to 10). We therefore looked for a way to increase the equatorial attack. We tried the use of a bulky quaternary ammonium salt, as reported by Chastrette and Amouroux on 4-*t*-butyl-cyclohexanone.[8] As suggested by these authors, the effect of this salt is to increase the size of the Grignard reagent by complexation, thus disadvantaging the axial attack because of the steric hindrance. Bu_4NCl as well as Me_4NCl were used on our steroid substrate without success. Based on the theory developed by Cieplak,[6b] used here to explain the predominant axial attack of our weaker stabilized nucleophiles (entries 7 to 10), we tried a reaction solvent susceptible of bringing more electrons to the transition state. Switching from THF to diethyl ether resulted in a small increase of the equatorial attack (from 58:42 to 55:45) in the case of the allyl Grignard reagent, while a mix of THF and HMPA in proportions 1:2 resulted in equal equatorial and axial attacks (**2A**:**2B**, 50:50). The use of HMPA alone as a solvent reaction did not provide any increase of the equatorial attack.

All of these attempts were made because we were interested in a direct method of obtaining the 3β-alkylated derivatives. Recently, an indirect way to obtain 3β-alkylated derivatives exclusively was described by Hogenkamp and co-workers.[9] The carbonyl was first transformed to the oxirane, 3α-oxirane being the major product, and then the latter was opened by the appropriate nucleophile, leading exclusively to the 3β-alkylated compound. However, this indirect method adds one methylene group to the substituent.

In summary, the work reported here focused on the alkylation of a C3-steroid ketone by a series of Grignard reagents divided into two groups depending on their nucleophilicity. These results contribute further data to the previously reported work on the addition of organomagnesium compounds to cyclic ketones[6a] and can be rationalized with the Cieplak model based on the concept of transition state stabilisation.[6b,c] Thus, a predominant axial attack was observed for the less nucleophilic Grignard reagents (vinyl, allyl, phenyl, benzyl), while a predominent equatorial attack was observed for the more nucleophilic reagents.

Experimental Section

General: Dry argon was routinely used as atmosphere in all reactions. All glassware was baked at 80-100°C for a minimum of 2 h prior to use. The THF used in anhydrous conditions was distilled from sodium benzophenone ketyl. Diethyl ether, 99.8% anhydrous grade, and chemical reagents were purchased from Aldrich Chemical Company (Milwaukee, WI). DHT was obtained from Steraloids (Wilton, NH).

Solvents were purchased from BDH Chemicals (Montreal, Canada) or Fisher Chemicals (Montreal Canada). Thin layer chromatography (TLC) was performed on 0.20 mm silica gel 60 F_{254} plates (E. Merck) and 230-400 mesh ASTM silica gel 60 (E. Merck) was used for flash chromatography. NMR spectra were recorded at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C with a Brucker AC/F 300 spectrometer and IR spectra were obtained on a Perkin-Elmer 1600 (FT-IR series) spectrophotometer. High-resolution electronic impact mass spectra were provided by the Centre Régional de Spectrométrie de Masse, Université de Montréal, Canada. All the spectral data were in accordance with the assigned structure.

Typical experiment: To a solution of 17β-TBDMS-DHT (500 mg, 1.23 mmol) in dry THF (100 mL) at 0°C was added dropwise 3 eq. of commercially available Grignard reagent, in dry THF or dry diethyl ether. The mixture was allowed to react for 3 h at 0°C, then left over night at room temperature. A solution of saturated NH_4Cl was added and the crude product was extracted with EtOAc. The organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$ and evaporated under reduced pressure. The two stereoisomers **2A** and **2B** were easily separated by flash chromatography on silica gel, using a mixture of hexane and ethyl acetate as eluent. When the Grignard reagent was generated *in situ*, 5 eq. was prepared, using a well-known procedure described by Smith,[10] and the alkylation was done in dry diethyl ether. The steroid was then dissolved in dry diethyl ether and added dropwise to the solution of reagent. When a quaternary ammonium salt was used, the Grignard reagent was allowed to react with the salt for 30 min at room temperature. Thereafter, the steroid in

dry solvant (THF or diethyl ether) was added dropwise, according to the procedure previously described in the literature.[8]

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