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Determination of a synthetic strategy for a new androstane analogue with potential antiandrogenic activity

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Continuing our design and synthesis of antiandrogenic compounds as possible drugs for the treatment of androgen related diseases, as prostate cancer, we developed two synthetic strategies starting from 16-dehydropregnelonone acetate (16-DPA). Our goal was to obtain the new analogue 6-oxo-17β-cyclohexylcarbamoylandrosta-4,16-diene-3β-hexanoate (6). In the first route, the double bond in C_5 of 16-DPA was submitted to selective epoxidation with m-chloroperbenzoic acid in chloroform to afford the 5,6-epoxy derivative (1). This was treated with chromium trioxide in acetone-water to obtain a hydroxycarbonyl derivative (2). Elimination of the hydroxyl group on C5 of 2 with thionyl chloride ($SOCl_2$) yielded the conjugated ketone 3β-acetoxypregna-4, 16-diene-6, 20-dione (3) from which by the bromoform reaction (Br_2/NaOH) on its methyl ketone in C20 was expected to obtain compound 4 which has carboxylic acid en C_{17} and an alcohol in C_3. Esterification of the free hydroxyl group on C_3 of 4 with hexanoic acid (HA), 4-(dimethylamino) pyridine (DMAP) and N,N'-dicyclohexylcarbodiimide (DCC) yieldedthehexanoate (5) fromwhichwasobtained6having a cyclohexylamideon C_{17}byitstreatmentwith$SOCl_2$ and cyclohexyl amine.

In the alternative route, 16-DPA was submitted to the bromoform reaction to yield 3β-hydroxyandrost-5-en-17-carboxylic acid (7). Esterification of the free hydroxyl group on C3 of 7(HA, DMAP and DCC)yielded its hexanoate (8). 5-en moiety of 8 was submitted to selective epoxidation (m-chloroperbenzoic acid) to afford the 5,6-epoxy derivative (9). This compound was oxidated (CrO_3) to obtain its hydroxycarbonyl derivative (10). Elimination of the hydroxyl group on C_5 of 10 and the formation of the cyclohexylamideon C_{17}in order to obtain the final compound 6 was achieved by the treatment of 10 with $SOCl_2$ and cyclohexyl amine. In both cases, reaction intermediates as well as final products were spectroscopically chacarterized.

Comparing to the yield obtained with both strategies to obtain 6, we found that the second one allowed higher yields because in case of the first route this allowed obtaining the carboxylic acid 4 with very low yield (ca. 10%).

Biography

Diego Rodríguez-Soacha has graduated as Pharmaceutical Chemist from National University of Colombia at age of 22, and currently is undergoing his master's degree in Pharmaceutical Sciences. He has completed post degree studies in pharmacotherapy and modified release drug systems. He is part of a national research group in medicinal chemistry, which develops research on synthesis of new and rogenic analogues. He is presently the technical Director at a traumatology specialized clinic.

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