

Synthesis of 4-Chloro-17 α -hydroxymethyl-17 β -methyl-18-nor-androsta-4,13-dien-3 β -ol

A 0.05 M solution of 4-chloro-androst-4-ene-3,17-dione in dry Et₂O under argon atmosphere has been treated with 1.1 eq of K-selectride (1 M) by dropwise addition to the stirring solution. After 1.5 h the reaction mixture was diluted with water and extracted three times with Et₂O. The combined organic phases were washed with brine and dried with Na₂SO₄. Evaporation at reduced pressure gave the crude compound as a yellow solid.

The reduced substance was dissolved in dry DMF (0.1 M) then 2.5 eq of imidazole and 1.5 eq of TBSCl have been added at room temperature. After 48 h of stirring the solvent was evaporated. The crude solid has been solubilized in EtOAc/H₂O and transferred in a separatory funnel. The obtained organic phases have been washed with brine and dried with Na₂SO₄. After evaporation the product was obtained as a yellow oil.

A solution of Nysted reagent (20 % wt., 5 eq) diluted in half volume of dry THF was cooled to 0 °C and subsequently treated with 2.2 eq of TiCl₄. After stirring for 15 minutes at 0 °C the solution was allowed to warm to room temperature. Next, a solution of starting material dissolved in dry THF was added dropwise to the reaction flask to give a violet mixture. After overnight reaction at room temperature the reaction was quenched with HCl_{aq} (1 M) at 0 °C. Following dilution with water and the mixture was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over Na₂SO₄. Evaporation at reduced pressure gave the crude compound as a yellow solid.

To a 0.1 M solution of the olefin in DCM, 3 eq of KHCO₃ and 1.2 eq of m-CPBA have been added at room temperature. After 3 hours, the solution was diluted with water and extracted with DCM in a separatory funnel. The combined organic phases were washed with brine and dried with Na₂SO₄, then evaporated to give the crude compound as a yellow solid.

To a solution 0.04 M of DCM under argon atmosphere at -78 °C, 2.2 eq of 2,6-lutidine and 2 eq of TMSOTf have been added dropwise. After five minutes the compound has been solubilized in DCM and subsequently added dropwise to the reagent's solution at -78 °C. After one hour the reaction mixture has been quenched by the addition of HCl_{aq} 2 M (10 eq) and let stir for 30 minutes at room temperature. Then, the solution was diluted with water and extracted with DCM in a separatory funnel. The combined organic phases were washed with brine and dried with Na₂SO₄, then evaporated to give yellow mixture.

To a solution 0.04 M of epoxide in MeOH, 5 eq of aqueous HCl have been added dropwise. After 1 hour the Wagner-Meerwein rearrangement and deprotection was already accomplished. The mixture was let react overnight at room temperature. Then it has been quenched by addition of water and diluted in TBME and extracted in a separatory funnel. The combined organic phases were washed with brine and dried with Na₂SO₄ then evaporated to give the crude final product as a yellow oil.









