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Synthesis of Steroid Derivatives for in vitro Hormone Levels Diagnostics.

Kos, Martin
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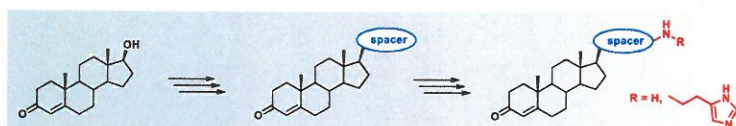
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Synthesis of Steroid Derivatives for *in vitro* Hormone Levels Diagnostics

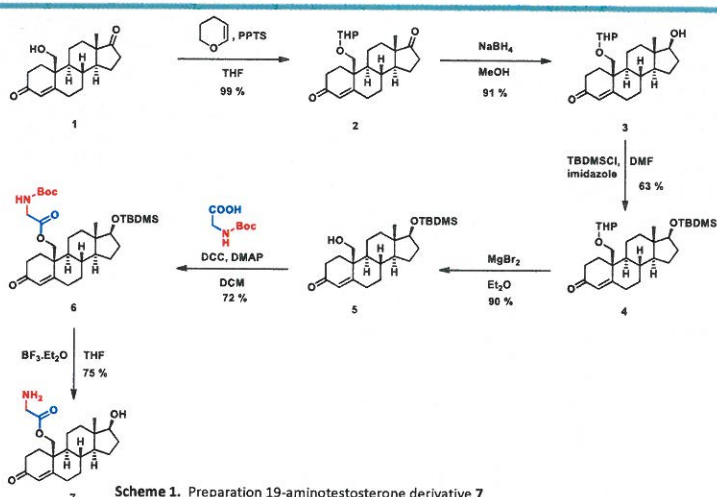
Martin Kos,¹ Lubomír Váňa,¹ Jaroslav Žádný,¹ Jan Storch,^{*1}

¹Institute of Chemical Process Fundamentals of the CAS, v. v. i., Rozvojová 1/135, Prague 6, 165 02, Czech Republic, e-mail: kos@icpf.cas.cz

Introduction. The determination of free steroid hormone levels (e.g., testosterone or progesterone) is very important in the diagnosis of a wide variety of diseases. For example, elevated levels of testosterone can occur in testicular tumors, adrenal tumors, ovarian and adrenal neoplasia, congenital adrenal hyperplasia, polycystic ovary syndrome, and female hirsutism. On the contrary, decreased levels might cause hypogonadism, insufficient testicular descent or ovarian failure. Both methods ELISA (Enzyme-Linked Immunosorbent Assay) and RIA (RadioImmunoAssay) have been using for determining serum hormone concentrations in medicine. RIA is based on mostly radioiodinated steroids, therefore these compounds must be attached to moieties, which can be easily iodinated (e.g., imidazole or phenol). On the other hand, ELISA applicable compounds must contain functional group, which can be easily attached to various enzymes (i.e., primary amine or carboxylic acid).

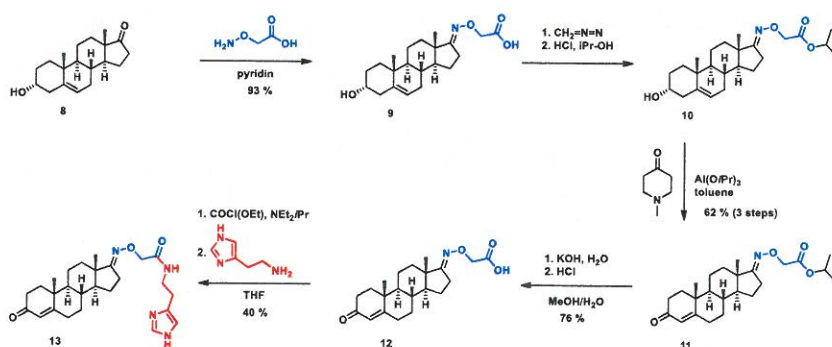


Synthesis of amino derivative^[1]. 9-Hydroxy group of commercially available androsten-3-17-dione **1** was firstly protected by reaction with dihydropyran. 17-Keto group of derivative **2** was reduced by sodium tetrahydridoborate to hydroxyl, which was subsequently protected by *t*-butyldimethylsilyl chloride. THP protecting group of **4** was selectively deprotected by reaction with magnesium bromide. Derivative **6** was formed by esterification of *N*-Boc-glycine with 19-hydroxysteroid **5**. Both Boc and TBDMS protecting groups were cleaved by reaction with boron trifluoride diethyl etherate in the final step. The overall yield of the above described synthesis was 28 %.

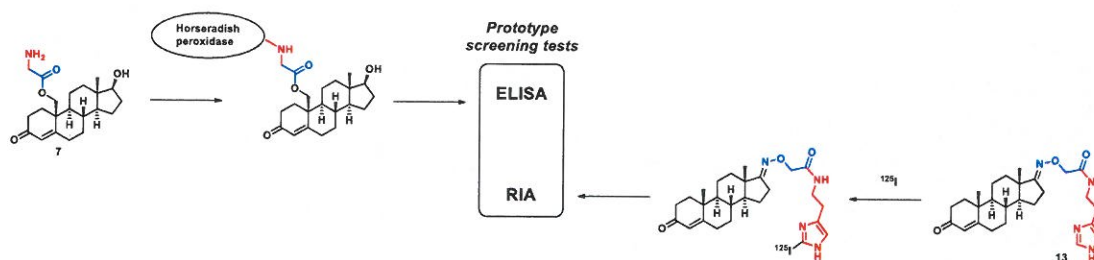


Scheme 1. Preparation 19-aminotestosterone derivative 7

Synthesis of histamine derivative^[2]. Commercially available starting material **8** was converted to carboxylic acid **9** by condensation with hydroxylamine-*O*-acetic acid. The isopropylester **10** was formed by methylation of acid **9** and subsequent transesterification of methylester intermediate with isopropyl alcohol. The oxidation of 3-hydroxy group was performed by Oppenauer oxidation. The oxidation was accompanied by isomerization of double bond to conjugation with 3-carbonyl group. After hydrolysis of ester **11**, the amide **13** was formed by mixed anhydride method. The overall yield of the above described synthesis was 17 %.



Scheme 2. Preparation of 17-histamine androstenedione derivative 13



Conclusion. The histamine derivative **13** was successfully prepared by five-step synthesis. This compound was radioiodinated and used to a development of RIA kit. The amino derivative **7** was successfully prepared in six steps. It was conjugated with horseradish peroxidase and used in an ELISA kit development.