

TOTAL SYNTHESIS OF HUMAN PHASE I STEROID METABOLITES

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In doping control analysis, athletes' urine samples are examined for the presence of banned substances or their metabolites. Almost half of all adverse analytical findings reported by the World Anti-Doping Agency (WADA) originate from abuse of anabolic androgenic steroids (AAS)^[1]. Since 2006 a number of long-term metabolites (detection window > 2 weeks), including 1-6, with a 17-hydroxymethyl-17-methyl-18-nor fragment have been identified. A synthesis of the compounds 1-6 depicted in Figure 1 was carried out in our laboratories^[2,3] in order to corroborate the proposed structure and, if possible, secure the identities of the target Phase I metabolites.

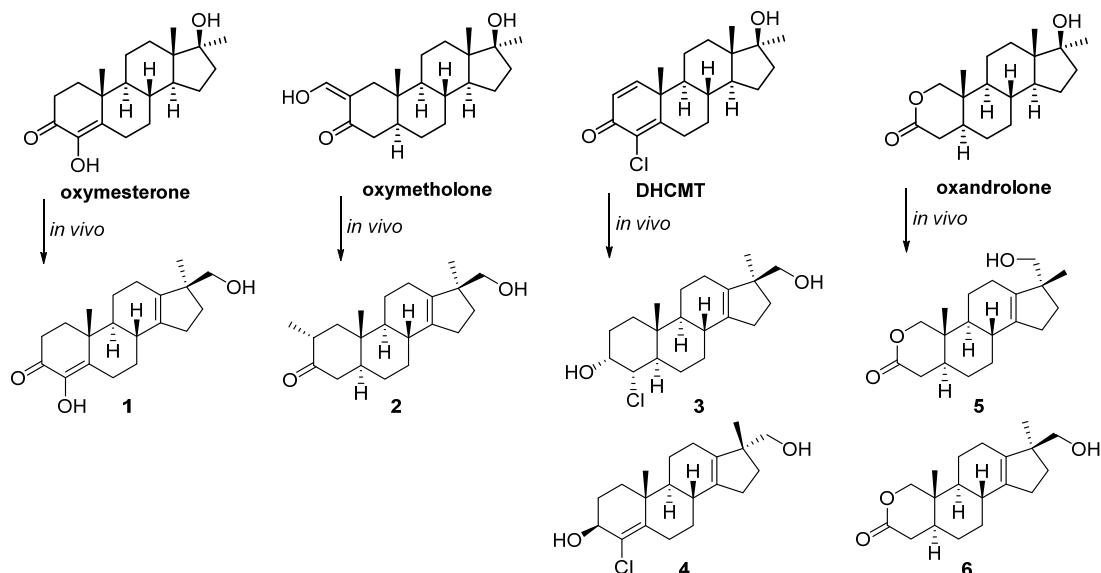
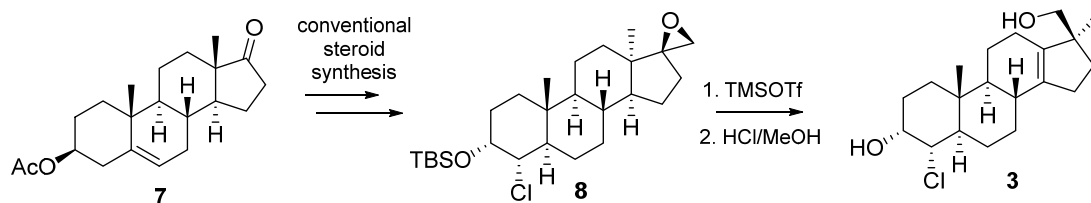


Figure 1 Target structures

The uncommon residues on the D-ring were introduced by a Wagner-Meerwein rearrangement, initiated by opening of a spiroepoxide (Scheme 1). Generally, the elaboration of the A-ring (starting from DHEA acetate 7) was carried out first with an appropriate handle on the 17-position (olefin, epoxide, ketone) to allow for rearrangement at the end of the synthesis.



Scheme 2 Key step of the syntheses

[1] <https://www.wada-ama.org/en/what-we-do/anti-doping-statistics> (accessed 25.04.2019)

[2] N. Kratena, B. Stöger, M. Weil, V. S. Enev, P. Gärtner, *Tetrahedron Lett.*, **2017**, 58, 1316.

[3] N. Kratena, S. M. Pilz, M. Weil, G. Gmeiner, V. S. Enev, P. Gärtner, *Org. Biomol. Chem.*, **2018**, 16, 2508.