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THE PREPARATION AND EVALUATION OF (+/-)-*TRANS*-1-DIAZO-8-METHOXY-4a-METHYL-1,2,3,4,4a,9,10,10a-OCTAHYDRO-PHENANTHREN-2-ONE AS AN INHIBITOR OF HUMAN TYPE-1 STEROID 5α-REDUCTASE

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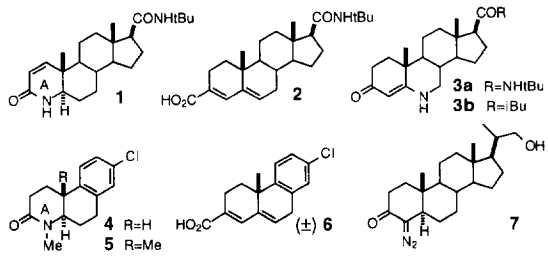
Abstract: (+/-)-*trans*-1-Diazo-8-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-2-one has been prepared and evaluated *in vitro* as an inhibitor of type-1 ($K_{i,app}$ 120 nM) and type-2 ($K_{i,app}$ 2000 nM) human recombinant steroid 5α-reductases. Copyright © 1996 Elsevier Science Ltd

The inhibition of steroid 5α-reductase (SR) has been proposed as a means of treating disorders associated with an elevated level of dihydrotestosterone (DHT), the product of SR action on testosterone (T).[1] These disorders include benign prostatic hyperplasia (BPH), prostatic cancer, and conditions of the skin such as acne, androgenic alopecia, and hirsutism.[1] The recent identification[2] of two isoenzymes of SR (types-1 and -2) has focussed attention to the identification and potential development of inhibitors of both isozymes (a dual inhibitor), as well as those which are isozyme selective.

Steroid-based, transition-state analogs have traditionally found wide application as inhibitors of SR, examples include finasteride **1**[1,3] (currently marketed world-wide for the treatment of BPH), epristeride **2**[1,4] and the 6-azasteroids **3**.[1,5] Non-steroidal compounds have also been indentified as potent inhibitors of SR, examples include benzophenone carboxylic acids,[6] indole carboxylic acids,[6] and benzoquinolinones of the type **4** and **5**.[7] Compounds **4** and **5** bear a structural resemblance to the 4-azasteroid inhibitors such as **1**.[7,8] Other tricyclic non-steroidal inhibitors of SR (e.g., **6**,[9] 9,10-dihydrophenanthrene-2-carboxylic acids[8] and phenanthridin-3-ones[10]) have been synthesized based on this apparent similarity. In this paper we would like to report the synthesis and testing of the diazoketone **11**, a novel and potent, non-steroidal inhibitor of type-1 SR. This compound was designed to incorporated the structural features of **7**,[11] a previously reported diazoketone, steroid-based time-dependent inhibitor of rat prostatic SR (K_i = 35 nM), and the tricyclic skeleton common to **4**, **5**, **6**, and several classes of non-steroidal SR inhibitors.[7-10]



Chemistry.[12] The diazoketone **11** was prepared from **8**,[13] by an analogous route to that used in the preparation of **7**[11] (Scheme 1). The enone **8** was reduced with lithium in ammonia and the resulting enolate trapped with TMSCl to give **9**, which was purified by flash silica chromatography. The relative configuration of **9** was assigned as shown on the basis that H_1 appeared as a broad singlet in the 250 MHz ^{1}H NMR spectrum of **9**. Acylation, of the regenerated enolate of **9**, with benzoyl chloride, gave the diketone **10**. Purification by preparative silica chromatography followed by treatment with sodium hydride and tosyl azide gave **11**. A diaxial coupling constant of 12.3 Hz for H_1-H_{10a} of **10** was consistent with the assigned relative configuration.

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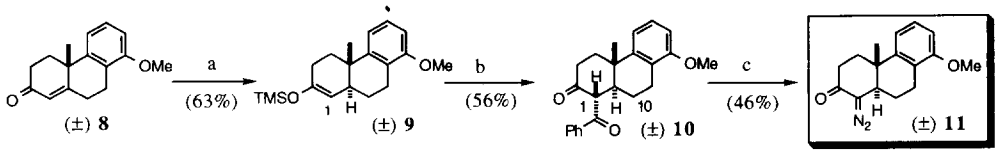

Scheme 1. (a) aniline/THF/Li in NH_3/-78 °C 2 h then isoprene then TMSCl/Et_3N (b) MeLi/ether/-78 °C 2 h then PhCOCl/ether/-78 °C to 18 °C (c) NaH/THF then tosyl azide/18 °C 45 min.

Enzyme Inhibition. The potencies for inhibition of types 1 and 2 SR with **11** were estimated in the form of apparent inhibition constants ($K_{i,app}$); these values were determined using recombinant human enzymes expressed in CHO cells as has been described in detail.[14] The diazoketone **11** proved to be a potent inhibitor of type-1 SR (type-1 $K_{i,app}$ = 120 nM) with approximately 18-fold selectivity over the type-2 enzyme ($K_{i,app}$ = 2000 nM), in spite of the fact that a 7-methoxy substituent may not be an optimal substituent for promoting maximal inhibitory properties.[7-10] With the exception of compound **6**, which is selective for type-2 SR, all other reported tricyclic non-steroidal inhibitors of SR, such as **4** and **5**, show greater potency for the type-1 isoenzyme.[7-10] In a separate set of experiments, compound **11** did not demonstrate any time-dependent inhibition of either type-1 or type-2 human recombinant SR. In constrast, the steroid-based diazoketone **7** has been reported to be a time-dependent inhibitor of rat prostatic SR, a characteristic that is consistent with a mechanism-based, irreverisble mode of enzyme inactivation.[11] A significant amount of work has been reported on species differences in SR's.[1,15] This work has, however, not been applied to compounds of the type **7**. In summary, compound **11** represents a novel addition to an important and growing class of tricyclic, non-steroidal, inhibitors of the SR isoenzymes.

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