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ALCOHOL INVERSION OF 17β–STEROIDS

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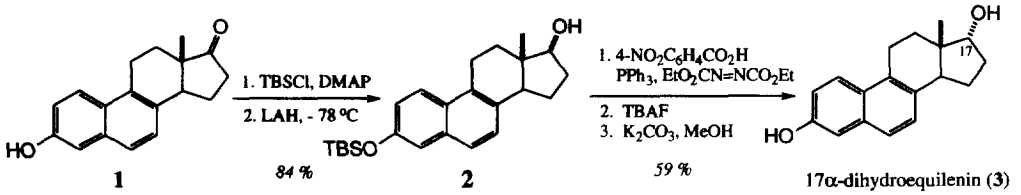
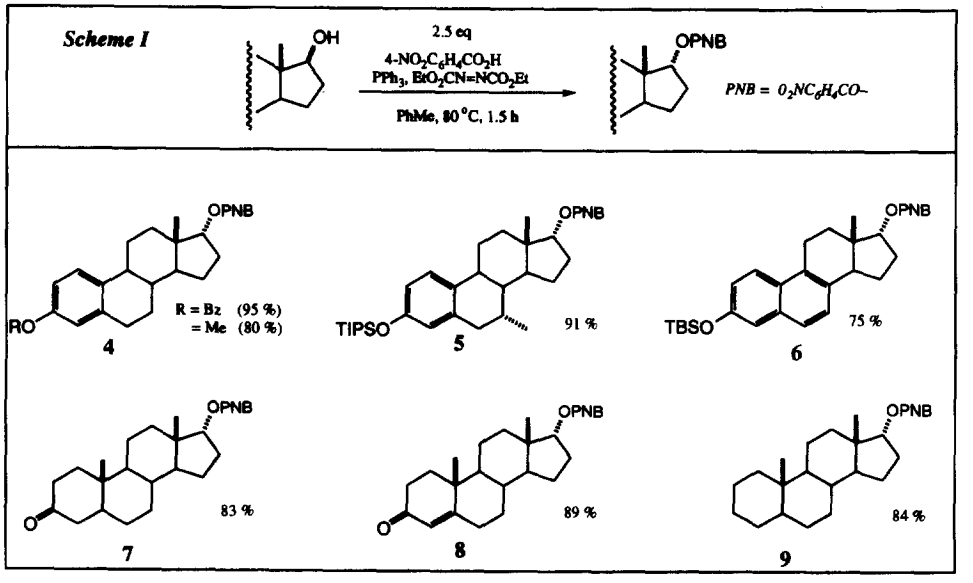
Abstract: Inversion of 17β-steroids has been accomplished using a modified Mitsunobu protocol in which 4-nitrobenzoic acid is employed as the acidic component. Excellent yields of inverted product were obtained for a number of representative steroid families including estrogens, equilenins, and androgens. Application of this methodology to the synthesis of 17α-dihydroequilenin is described.

The stereochemistry at the 17-position of sex steroids plays a key role in dictating the molecular interactions between a given hormone and its receptor. For example, 17α–estradiol binds with an order of magnitude less affinity to the estrogen receptor than its 17β-counterpart (see steroid numbering system in **3**).[1] Interestingly, one consequence of this phenomenon is a time-dependent mixed agonism-antagonism of the physiological functions of 17β–estradiol.[2] From a structure-activity standpoint, while 17β-steroidal alcohols are readily accessible via selective reduction of the corresponding ketones,[3] preparation of 17α-alcohols has proven somewhat problematic.[4] This is particularly true when Mitsunobu inversion conditions[5] (diethylazodicarboxylate, PPh_3, RCO_2H) are employed.[6] Significantly, only a limited number of reports employing this mild, essentially neutral, protocol have been documented and in each of these cases, poor[7] to negligible yields[4] of 17α-inverted product are observed. To address this issue, we have investigated the use of a modified Mitsunobu protocol to efficaciously prepare 17α-steroids.

Our interest in this area stemmed from the need for multigram quantities of 17α-dihydroequilenin (a non-uterotrophic component of Premarin[8]) for pharmacological evaluation in our animal models. The prohibitive ($3000/g) cost of **3** prompted us to examine Mitsunobu inversion of **2**, readily available from (+)-equilenin (**1**). Since the introduction of the Mitsunobu reaction in 1967,[1] numerous variants of the standard reagent protocol have been reported including changes in the azodicarboxylate,[9] phosphine,[10] and acidic components.[11,12] Work from our own laboratories[13] has indicated sterically encumbered alcohols can be easily inverted employing relatively acidic carboxylic acids such as 4-nitrobenzoic acid. Thus, it seemed likely use of this modification would provide access to the requisite D-ring α stereochemistry. Gratifyingly, when **2** was subjected to these modified Mitsunobu conditions (2.5 eq. 4-nitrobenzoic acid, PPh_3, and DEAD, respectively) followed by heating the reaction mixture to 80 °C for 1.5 h in toluene, the desired *p*-nitrobenzoate ester was isolated in 75 % yield. Removal of the silyl protecting group and saponification of the ester provided the





desired product (**3**) which was identical in all respects with an authentic sample. In an effort to generalize this methodology, a variety of steroidal frameworks were subsequently examined (Scheme I).[14] In all cases, efficacious inversion of the 17β-position was observed regardless of steroid class, i.e., estrogens (**4**, **5**), equilenins (**6**), and androgens (**7**–**9**), all proved amenable to the protocol employed. In addition, a variety of protecting groups including silyl (TBDMS, TBDPS), ester (acetate, benzoate), and ether (Me) functionality were well-tolerated.

In summary, modified Mitsunobu reaction conditions employing 4-nitrobenzoic acid as the coupling partner allow for efficacious alcohol inversion of the 17β-position in the steroid nucleus. These conditions appear general to various families of steroid hormones and represent a substantial improvement in current synthetic technology.

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