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Synthesis of *ent*-19-nortestosterone from its naturally occurring antipode

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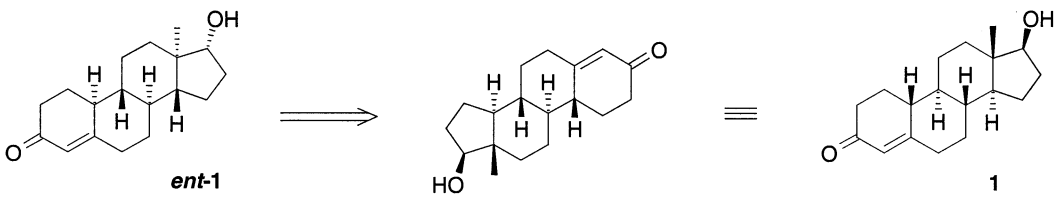
Abstract—The synthesis of *ent*-19-nortestosterone from natural 19-nortestosterone is described. The synthetic sequence takes advantage of the 'near symmetry' properties of the steroid; removal/introduction of a methyl group and conversion of the A- into the D-ring and vice versa eventually results in overall inversion of the stereochemistry. © 2001 Elsevier Science Ltd. All rights reserved.

Steroids play an extremely important role in biological processes. While their properties have been widely studied in a broad range of applications, their enantiomers, the so-called *ent*-steroids, in comparison have received only very little attention.[1] Nevertheless, information about the interaction of *ent*-steroids with hormonal receptors might lead to new valuable insights in receptor binding. Obtaining *ent*-steroids on the other hand is a far from trivial issue. In the quest for attaining the unnatural enantiomers of steroids, a number of groups used a classical resolution of a racemic intermediate or product. In more recent syntheses, the required chirality was introduced at some point via an enantioselective transformation of an achiral precursor.[2] Although both methods in principle may give the desired products in very high enantiomeric excess, they do not afford the enantiomer in absolute (100%) purity. With the goal of studying the hormonal properties of *ent*-steroids, it is necessary to have these compounds enantiomerically pure, since minute traces of the extremely potent natural enantiomers may mask the weak activities of the *ent*-steroids.

Therefore, we devised a strategy for the synthesis of *ent*-steroids which utilizes naturally occurring steroids as the starting material. Logically, such an approach affords *ent*-steroids with the same enantiomeric purity as their natural counterparts, which is believed to be complete. This strategy was applied to the synthesis of *ent*-19-nortestosterone *ent*-**1**, starting from its natural enantiomer, 19-nortestosterone **1**. Our strategy takes advantage of the near-symmetrical properties of the steroid skeleton. A 180° rotation of the molecule of 19-nortestosterone **1** about the axis perpendicular to the skeleton shows that the rotated structure is enantiomeric to the original with respect to the ring junctions. In fact, the only differences between the two skeletons are the different sizes of the A- and D-rings and the angular methyl group. *Therefore, 'correction' of these two differences will result in overall conversion of the 19-nortestosterone skeleton into its enantiomer!* The forward synthesis is outlined in Scheme 1.

19-Nortestosterone (**1**) was epoxidized with H_2O_2 and NaOH to afford selectively the β-epoxyketone **2** in quantitative yield.[3] Hydrazone formation with tosylhydrazine in acetic acid led to fragmentation of the A-ring to give the acetylenic ketone **3a**.[4] The radical cyclization of this compound under the influence of sodium naphthalenide in THF proceeded smoothly, but separation



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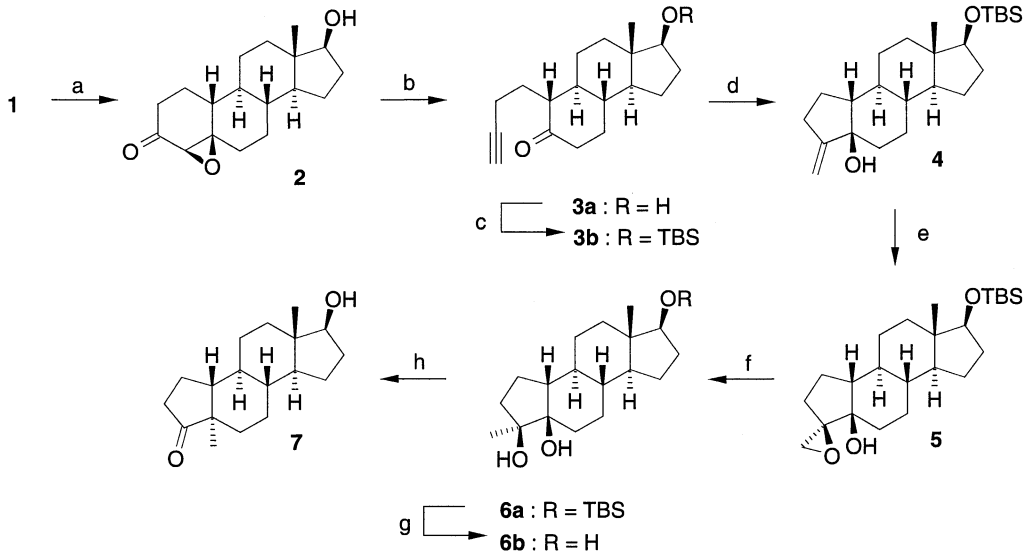
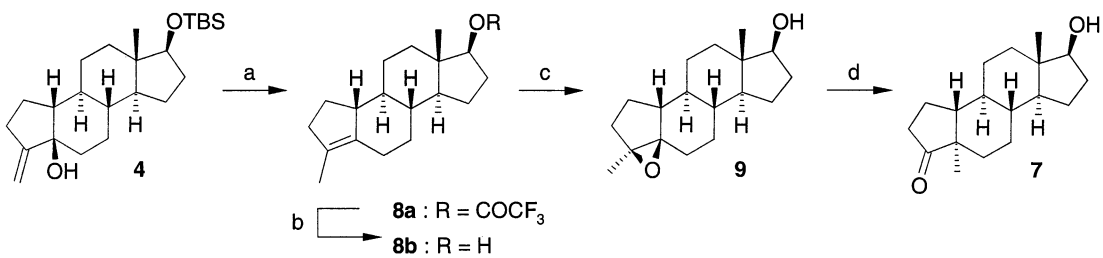


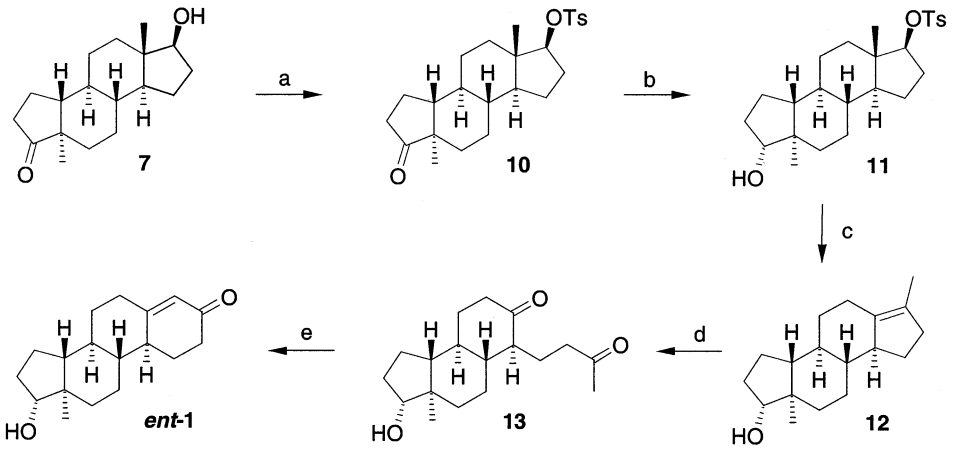
Scheme 1. *Reagents and conditions*: (a) H_2O_2, NaOH, MeOH, 0°C, 2 h, 99%; (b) $TsNHNH_2$, AcOH, −18°C→rt, 18 h, 73%; (c) TBSCl, imidazole, DMF, 0°C, 3 h, quant.; (d) Na, naphthalene, THF, rt, 63%; (e) *m*-CPBA, CH_2Cl_2, 0°C, 2 h, 75%; (f) $LiAlH_4$, ether, rt, 30 min, 95%; (g) TBAF, THF, reflux, 18 h, 87%; (h) conc. HCl, MeOH, reflux, 2 h, 20%.

of the product from the remaining starting material was troublesome. Therefore, prior to the cyclization the hydroxyl group was protected as a TBDMS-ether to afford **3b**. Treatment of **3b** with sodium naphthalenide in THF resulted in completely diastereoselective cyclization to the allylic alcohol **4** in 63% yield after recrystallization.[5] Having the five-membered ring in place, introduction of the methyl-substituent was in order. Thus, directed epoxidation of the double bond with *m*-CPBA provided **5**, which was reduced using lithium aluminum hydride to afford diol **6a** in 70% yield (two steps). Initially, we anticipated that formation of ketone **7** could be achieved using a pinacol rearrangement so that **6a** was refluxed in HCl/MeOH for 2 h.[6] Unfortunately, only a trace of the desired rearranged product was obtained, whereas the major part of the product turned out to be a complex mixture of elimination and desilylation products. Interestingly, application of identical conditions after removal of the TBDMS group (TBAF, THF, reflux) led to the desired ketone **7** in 20% yield. The use of different acids, e.g. acetic acid and tosic acid, did not significantly improve the yield of the rearrangement. Since we considered such a low yielding step not very practical for this multistep sequence, an alternative route to arrive at ketone **7** was investigated (Scheme 2).

This alternative pathway proceeded via the tetra-substituted olefin **8b**, which in line with literature precedent[6] was considered a useful intermediate to arrive at ketone **7**. Alkene **8a** was obtained from **4** via TFA/TFAA-mediated generation of the corresponding allylic cation, followed by in situ reduction with Et_3SiH from the less hindered site to give the desired olefin. Subsequent cleavage of the trifluoroacetate with potassium carbonate then gave **8b** in 50% yield over two steps. In the next step, the double bond had to be selectively epoxidized to the corresponding β-epoxide **9**. Studies on similar systems revealed that treatment with *m*-CPBA leads to the α-isomer, whereas reaction with *t*-BuOOH and $Mo(CO)_6$ favors formation of the β-epoxide.[7] Indeed, applying the latter conditions led to the desired epoxide **9** as the sole product, which in a Lewis acid-mediated rearrangement was converted into the desired ketone **7** in 46% yield. Unfortunately, although the rearrangement itself proceeded in a higher yield than in the earlier described route, the overall yield was not significantly improved. The final part of the synthesis involved transformation of the hydroxy-substituted five-membered ring into a six-membered ring enone system. To this end, a well-known method for this type of transformation was used (Scheme 3).



Scheme 2. *Reagents and conditions*: (a) CF_3CO_2H, $(CF_3CO)_2O$, Et_3SiH, CH_2Cl_2, rt, 2.5 h, 72%; (b) K_2CO_3, MeOH/heptane, rt, 15 min, 69%; (c) *t*-BuOOH, $Mo(CO)_6$, toluene, 80°C, 3 h, 68%; (d) $BF_3{\cdot}OEt_2$, toluene, 0°C, 45 min, 46%.



Scheme 3. *Reagents and conditions*: (a) Ts_2O, pyridine, 0°C, 2 h, 92%; (b) $NaBH_4$, MeOH, 0°C, 1.5 h, 92%; (c) EtMgBr, benzene, reflux, 1 h, quant.; (d) $KMnO_4$, $NaIO_4$, $NaHCO_3$, *t*-BuOH, reflux, 45 min, 42%; (e) KOH, MeOH, rt, 2 h, 74%.

First, the hydroxyl group was reacted with *p*-toluenesulfonic anhydride to afford tosylate **10**. Since the projected rearrangement involved reaction with ethylmagnesium bromide, the carbonyl group first had to be protected as the alcohol **11** via reduction with $NaBH_4$ in methanol. Then, reaction with ethylmagnesium bromide in refluxing benzene afforded alkene **12**,[8] which in the next step was oxidatively cleaved using a mixture of potassium permanganate and sodium periodate to give **13** in reasonable overall yield. Finally, a classical Robinson annulation under the influence of KOH in methanol afforded the desired enantiomer of 19-nortestosterone in 74% yield.[9]

In summary, we have clearly demonstrated the viability of the principle that steroids can be converted into the corresponding *ent*-steroids. In this case, we started form 19-nortestosterone, which in 13 steps was converted into its enantiomer in 1.9% overall yield. The interaction of this compound with different steroid receptors is currently under investigation.

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