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SYNTHESIS OF 7α-SUBSTITUTED ANDROSTENEDIONES BY A 1,4-CONJUGATE ADDITION APPROACH

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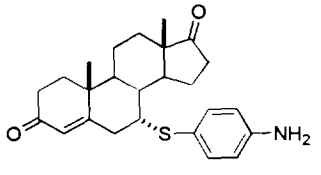
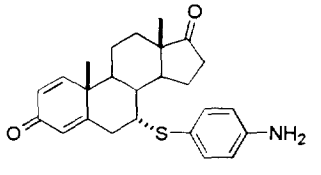
Abstract: Oxidation of enol lactone **9** with $Pd(OAc)_2$ gave enone **8**, which underwent stereoselective 1,4-conjugate addition with a series of cuprates affording the 7α-ketones **10-12** in excellent yield. Subsequent saponification and cyclization gave enol lactones **13-15**, which can be transformed into the testosterone derivatives by treatment with 2.1 eq of $LiCH_2P(O)(OMe)_2$.

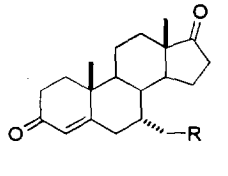
Inhibitors of aromatase, the enzyme which converts androgens to estrogens, have been shown to be useful in the treatment of estrogen dependent diseases, such as breast cancer.[1] While both non-steroidal and steroidal aromatase inhibitors have been reported, our interest has been in the latter class.[2] We have reported on the synthesis, *in vitro* and *in vivo* activity of a number of 7α-thiosubstituted androstenediones, such as **1** and **2**.[3] Although these 7α-substituted steroids are potent inhibitors of aromatase with apparent K_i's of 18 nM and 10 nM, the presence of a thioether linkage was of some concern as it is a potential site for metabolism. Indeed, metabolism studies have shown that the sulfur atoms in **1** and **2** can be oxidized to the sulfoxide and sulfone *in vitro*.[4] These oxidized metabolites are liable to undergo a retro-Michael reaction, giving an inactive (against aromatase) steroid and hence reducing the overall effectiveness of **1** and **2**. Replacement of the thioether linkage with a carbon-carbon bond was seen as a potential solution to this problem, and thus compounds **3** and **4** were designed to prevent loss of the 7α-sidechain by metabolism, while hopefully retaining useful levels of activity as aromatase inhibitors.



1



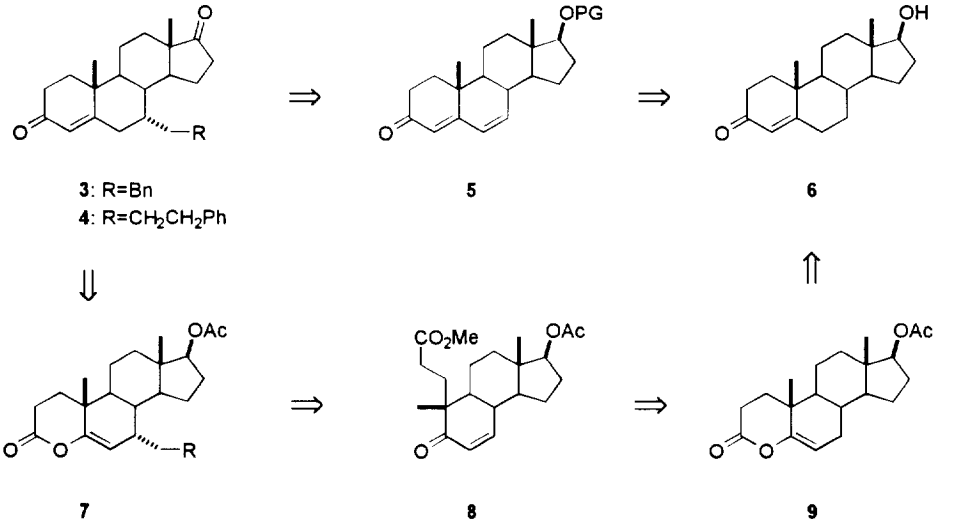
2



3: R=Bn
4: R=CH_2CH_2Ph

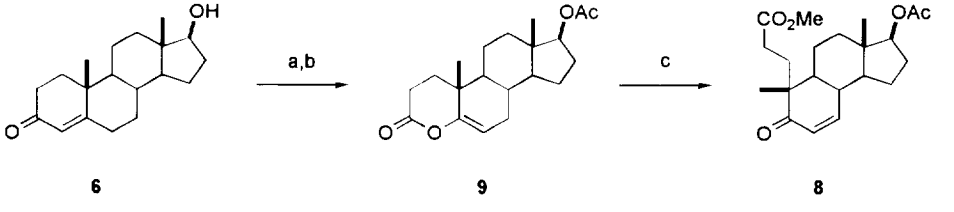
The most direct approach to these compounds was viewed to be 1,6-conjugate addition of the appropriate organocuprate to a Δ^6-testosterone derivative **5** (Scheme 1). While this approach works well for simple alkyl cuprates, severe difficulties were encountered when cuprates derived from phenethyl and phenpropyl halides were used.[5] Although these initial difficulties were subsequently overcome,[6] a second complementary approach to **3** and **4** was developed and is the subject of this *Letter*.

Scheme 1



Several methods are already available for the conversion of steroidal enol lactones into the α,β-unsaturated derivative (Scheme 1, **9**→**6**),[7] therefore it was thought that a 7-substituted enol lactone **7** could be converted into the desired targets in the same way (Scheme 1, **7**→**3** or **4**). A 7α-substituted enol lactone, such as **7**, could be prepared from the corresponding 7α-substituted *seco*-A ring ketone, which in turn would come from the *seco*-A ring enone **8** and the appropriate cuprate. The problem then reduced to devising a synthesis of enone **8** and the stereocontrolled 1,4-addition of cuprates to it.

Scheme 2[a]

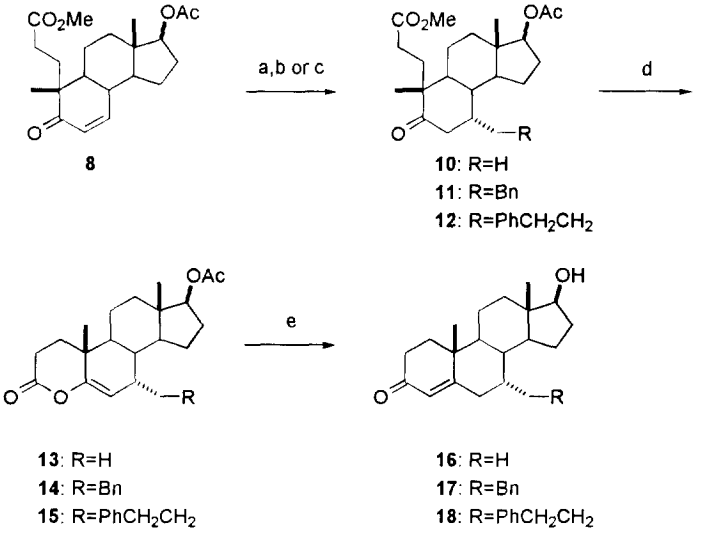


[a] Reagents and conditions: (a) $KMnO_4$, $NaIO_4$, Na_2CO_3, *t*-BuOH, H_2O, Δ; (b) Ac_2O, NaOAc, Δ, 60%; (c) $Pd(OAc)_2$, Bu_3SnOMe, allyl methyl carbonate, MeCN, Δ, 81%.

The first approach to **8** involved addition of NBS and MeOH to enol lactone **9**, followed by dehydrobromination of the resulting 6-bromoketoester with DBU in refluxing benzene. However, certain aspects of this two-step procedure were unsatisfactory and led us to seek an alternative.[8] It has long been established that enol acetates can be oxidized to the corresponding enone by $Pd(OAc)_2$.[9] **9** is simply an internal enol acetate, therefore it should undergo oxidation with $Pd(OAc)_2$ in the same way. Indeed, treatment of **9** with $Pd(OAc)_2$ in the presence of Bu_3SnOMe and allyl methyl carbonate in refluxing acetonitrile gave **8** in 81% yield (Scheme 2).

Preliminary conjugate addition experiments were performed with Me_2CuLi as they would lead to a known 7-substituted testosterone derivative, for which both the 7α- and 7β-derivatives had been prepared and characterized.[5a] Addition of 2.2 eq. of Me_2CuLi to **8** gave a single, diastereomerically homogeneous, conjugate addition product in 87% yield. Although the stereochemical sense of the addition product **10** was not determined directly, it was later shown by conversion to a known compound to have occurred exclusively from the α-surface. The esters in **10** were saponified with aqueous KOH and the resulting hydroxy ketoacid was cyclized to the enol lactone **13** with Ac_2O and AcONa. Utilizing Aristoff's procedure, **13** was transformed to the known testosterone derivative **16** in 75% yield by treatment with 2.1 eq. of $LiCH_2P(O)(OMe)_2$, then 1.0 eq of acetic acid followed by K_2CO_3 in aqueous methanol.[5a,7]

Scheme 3[a]



[a] Reagents and conditions: (a) Me_2CuLi, Et_2O, -42 °C, 87%; (b) $PhCH_2CH_2Li$, CuI, PBu_3, Et_2O, -42 °C, 93%; (c) $PhCH_2CH_2CH_2Li$, CuI, PBu_3, Et_2O, -42 °C, 77%; (d) (i) KOH, MeOH, H_2O, (ii) Ac_2O, AcONa, Δ, **10**→**13**, 75%, **11**→**14**, 71%, **12**→**15**, 66%; (e) (i) $LiCH_2P(O)(OMe)_2$, THF, -78 °C, (ii) AcOH, -78 °C→Δ, (iii) K_2CO_3, MeOH, H_2O RT, **13**→**16**, 75%, **14**→**17**, 88%, **15**→**18**, 67%.

Enone **8** also underwent stereoselective addition with cuprates derived from $PhCH_2CH_2Li$ and $PhCH_2CH_2CH_2Li$ in the presence of PBu_3 to give ketones **11** (93%, α/β, 7.5:1) and **12** (77%, α/β, 6.7:1) from which the α-epimer was isolated by MPLC. The stereochemistry of the conjugate addition products **11** and **12** was determined by their conversion into the known testosterone derivatives **17** and **18**. The pure 7α-ketones were converted by saponification and cyclization into the 7α-substituted enol lactones **14** and **15** in 71% and 66% yield respectively, (Scheme 3). **14** and **15** were readily transformed into the known testosterone derivatives using the same method as described above, affording **17** (88%) and **18** (67%).[10] The 7α-substituted testosterones can then be converted to the androstenedione derivatives by oxidation with PCC in quantitative yield.[6]

In summary, we have developed an alternative protocol for the stereoselective substitution of steroids in the 7-position by A-ring cleavage, 1,4-conjugate addition and recyclization. The pivotal step in this sequence is the application of Tsuji's procedure for oxidation of enol acetates to enones to the conversion enol lactone **9** to enone **8**.[9] Preliminary *in vitro* studies have demonstrated that **3** and **4** are effective inhibitors of aromatase with apparent K_i's of 13.1 nM and 16.5 nM, respectively.[6]

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References and Notes:

1. For an overview of aromatase see Brodie, A. M. H.; Santen, R. J., Eds. *Breast Cancer Research and Treatment* **1994**, *30*, 1.
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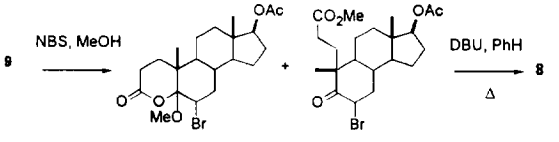
8. In addition to the desired product **i**, significant quantities of **ii** were formed, requiring a tedious chromatographic separation.



9. Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.
10. Testosterones **17** and **18** exhibited identical physical properties (mp, TLC, NMR) to those previously reported.[6]

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