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Remote C–H bond functionalization of androstane C-ring: C12-amination

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ABSTRACT

A new functionalization method for the C-ring of the androstane framework has been established. The key feature is a remote C–H amination, which enables the preparation of the C12-amino, oxo, hydoxy, and C11,12-dehydro derivatives of epiandrosterone.

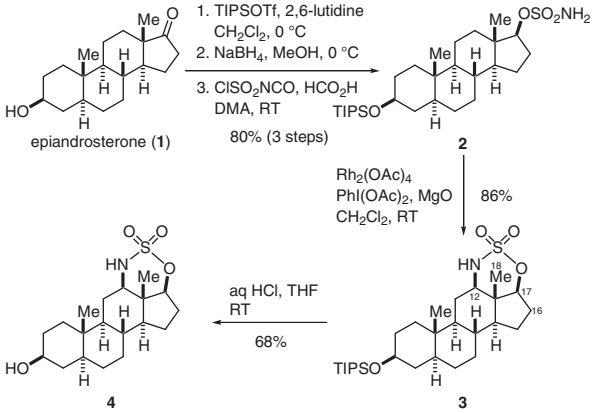
Chemical derivatization of steroids is an effective tool for natural product synthesis[1] and can provide important bioactive agents.[2,3] However, only a few functionalizations of the non-activated C-ring of the androstanes have been reported. In 2003, Shönecker and co-workers developed a copper-mediated remote hydroxylation of the C12 position.[4–6] This method enabled Giannis and Shair to accomplish the elegant total syntheses of cyclopamine[7] and cephalostatin,[8] respectively. We describe here a new method to functionalize the androstane C-ring through a remote C–H amination.

Functionalization of the C-ring was investigated using epiandrosterone (**1**, Scheme 1). Protection of the secondary alcohol of **1**, stereoselective reduction of the ketone, and subsequent treatment with chlorosulfonyl isocyanate and formic acid[9] afforded sulfamate **2** in 80% overall yield. Rhodium-catalyzed C–H bond amination of **2** according to the Du Bois method[10] successfully provided the C12,17-oxathiazinane **3** in 86% yield. It is noteworthy that the C16- and C18-aminated products were not detected. This exclusive chemoselectivity is attributed to the long S–O and S–N bonds and the obtuse N–S–O angle of the sulfamate, as well as the difference in reactivity between the primary and secondary C–H bonds.[10] The structure of **3** was unambiguously confirmed by X-ray crystallographic analysis of the corresponding alcohol **4** (Fig. 1).[11]

We next examined the cleavage of the S–O and/or S–N bonds of oxathiazinane **3** (Table 1).[12] Birch reduction resulted in no reaction and the starting material was recovered (entry 1). Treatment of **3** with $LiAlH_4$ in THF afforded no products (entry 2),[13] whereas $LiAlH_4$ reduction in toluene followed by Boc-protection furnished carbamate **5** in 39% yield (entry 3). After careful screening of reagents and conditions, we found that refluxing with AlH_3 in toluene afforded amino alcohol **6** in 90% yield (entry 5).

Selective oxidation of the amino group was achieved by treatment of **6** with 3,5-di-*t*-butyl-1,2-benzoquinone **7** to give ketone **8** in 95% yield (Scheme 2).[14] Stereoselective reduction of ketone **8** was realized by treatment with sodium metal in the presence of isopropanol to give the C12β-hydroxy product **9** (77%). The C11,12-dehydro derivative **10** was also prepared under Shapiro's conditions in 63% overall yield.

In summary, we established a versatile method to install functionality to the non-activated C-ring of epiandrosterone.



Scheme 1. Remote amination of epiandrosterone C-ring.

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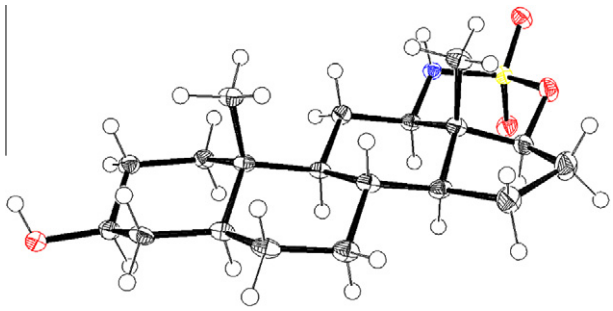
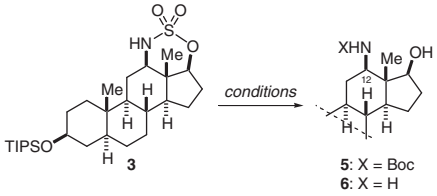
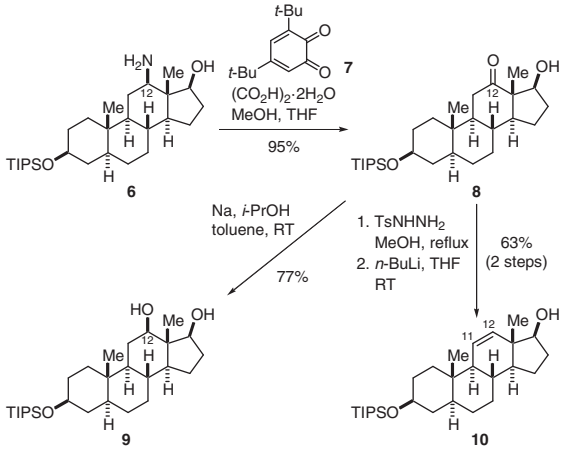


Figure 1. ORTEP drawing of **4**.

Table 1
Cleavage of oxathiazinane moiety



Entry	Conditions	Results
1	Na, EtOH, NH_3 −78 to −33 °C, 2 h	No reaction
2	$LiAlH_4$, THF, reflux, 12 h	No reaction
3	$LiAlH_4$, toluene, reflux, 24 h; $(Boc)_2O$, rt, 1 h	**5**: 39% **3**: 25%
4	Red-Al, toluene, reflux, 24 h; $(Boc)_2O$, rt, 1 h	**5**: 53%
5	AlH_3, toluene, reflux, 5 h	**6**: 90%



Scheme 2. Functionalization of the C-ring.

Rhodium-catalyzed remote C–H amination efficiently furnished the oxathiazinane, which was converted into the C12-amino, oxo, hydoxy, and C11,12-dehydro androstanes. Natural product syntheses using this strategy will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.103.

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