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Total synthesis of new steroids having an aromatic A ring with a 3-OH

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Abstract—A new strategy for introducing an hydroxy group at the position 3 of an aromatic A ring in a steroid, which is a key position for biological purposes, is described. This procedure has required a judicious choice of a *t*-butyl ether as protective group at the beginning of the synthesis, and its deprotection can be achieved in high yield in the final step.

Estrogens are active hormonal steroids possessing an aromatic A ring. It has been well established that estrogens act as important endocrine growth factors for at least a third of breast cancers.[1]

So we were interested in developing new molecules which might be used for the treatment of estrogen-dependent diseases. The A ring of those steroids is in general a phenol with an hydroxy group at the 3-position, required for the binding to the estrogen receptor and for inhibiting the 17-β hydroxysteroid dehydrogenase.[2]

In previous papers,[3] we reported a novel strategy for the preparation of a wide variety of steroids, which involved the addition of 1,8-bis(trimethylsilyl)-2,6-octadiene (BISTRO) to various electrophilic reagents.[4]

All the steroids previously described in our synthetic work possess an aromatic A ring substituted by a methoxy group at the 2- and/or 3-position. Nevertheless, all attempts realized for the final demethylation to obtain the required hydroxy group failed using different conditions (BBr_3 in CH_2Cl_2,[5] DIBALH in toluene,[6] CH_3SO_3H).

So we now settle this problem by using a *t*-butyl ether as a protective group, easier to remove than the precedent methyl ether.[7]

The required precursor steroids were prepared in the same way we used in our previous work (Scheme 1).[3]

First, using a procedure analogous to that described by Kametani[8] and Honda,[9] we efficiently prepared the 1-iodo-4-*tert*-butoxybenzocyclobutene **1**. The condensation of the activated spirolactone **2**[10] with **1**, using K_2CO_3 in acetone, led to the benzocyclobutene **3** in 72% yield. Compound **3** was then submitted to a decarbomethoxylation according to the Krapcho procedure (NaCN/DMSO).[11] Heating the new benzocyclobutene intermediates **4** afforded a mixture of two cycloadducts **5a** and **5b** in 68% yield and a 2:1 ratio. The two steroids **5a** and **5b** were separable by chromatography over silica gel and have, respectively, a *trans–anti–cis* and a *trans–anti–trans* ring fusion.[12] Much to our surprise and in contrast with the results previously observed for the steroids possessing a 3-methoxy group, the main product **5a** matches here the *trans–anti–cis* ring fusion of non-natural products.

The Wacker-type oxidation[13] of the vinyl group of **5b** gave the corresponding ketone **6** and the aldehyde **7** resulting from an anti-Markovnikov hydroxypalladation in a 10:1 ratio and a 56% overall yield (Scheme 2). The formation of the minor product has been rationalized by an intramolecular coordination of the palladium with the oxygen of the lactone moiety.[14]

The final step of our work, which constituted a key step, was the deprotection of the 3-OH. Preliminary experiments were carried out on compound **5b** and removal of the *tert*-butyl protective group could be achieved under mild conditions TFA:CH_2Cl_2 1:1,[7b,15] to afford **8** in 66% yield (Scheme 3).

Keywords: intramolecular Diels–Alder; Wacker-type oxidation; protective group.

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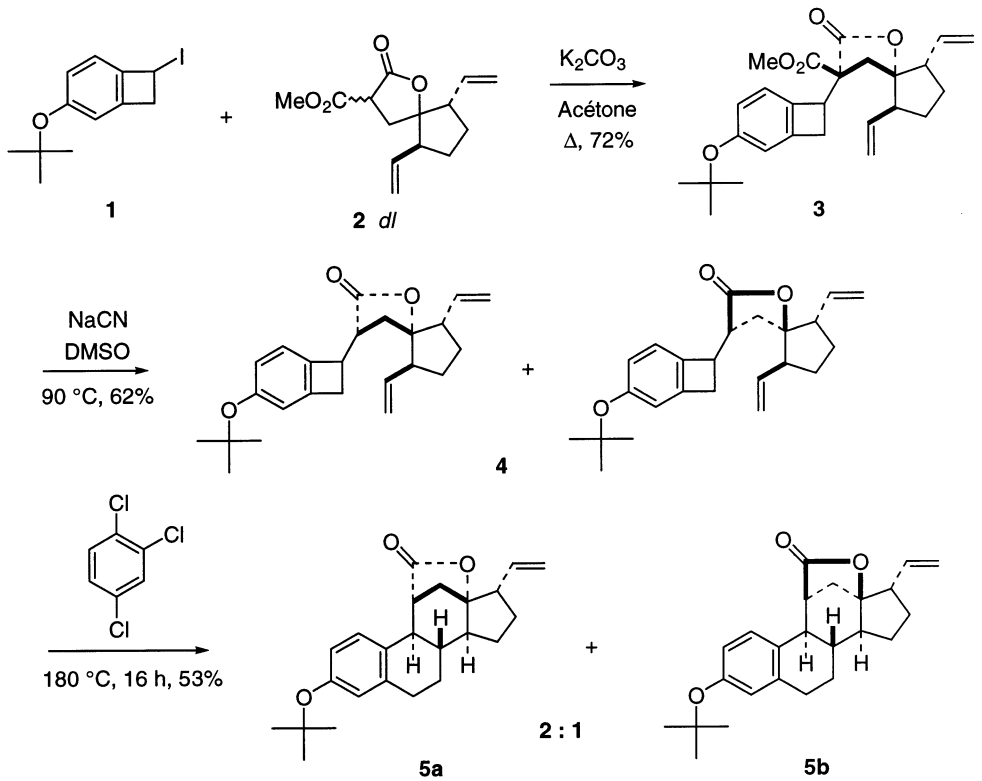
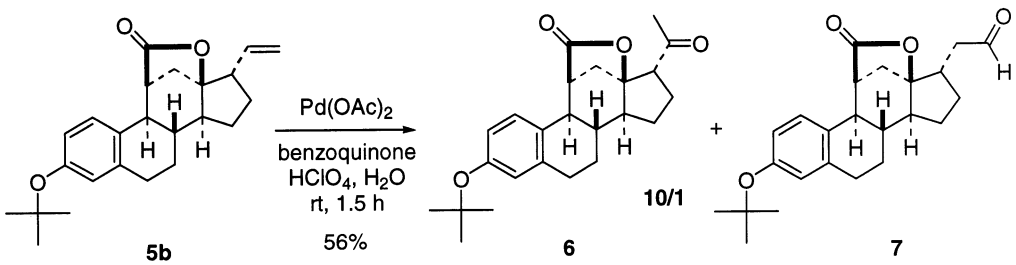
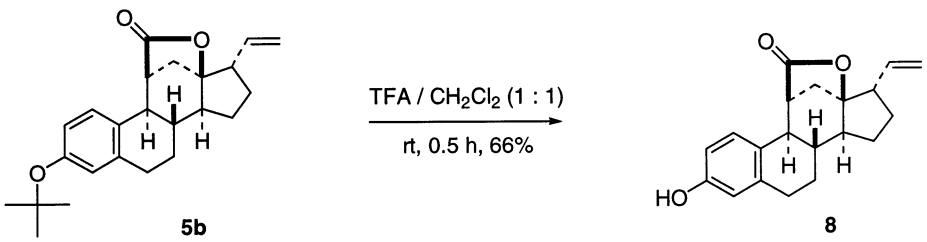


Scheme 1.



Scheme 2.



Scheme 3.

The same conditions applied to **6**, which possess the stereochemistry of the natural products, gave **9** in 83% yield (Scheme 4). This molecule can be considered as a good intermediate for preparing new compounds and examining their estrogenic properties.

Conclusion: We have shown herein that our strategy is compatible with the synthesis of a wide range of steroids and particularly steroids possessing an hydroxy group in a biologically important position in the aromatic A ring. We are currently pursuing our research towards more complex target systems.

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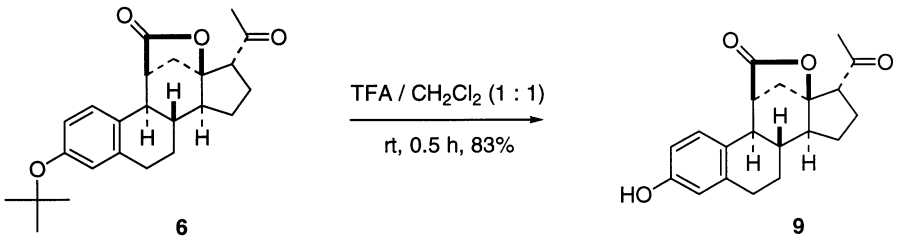

Scheme 4.

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