DOI: 10.1002/cjoc.201201147

Stereospecific Synthesis of Drospirenone†

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A procedure for the stereospecific synthesis of drospirenone has been developed. The key steps included the stereospecific reduction of the C^7-tertiary alcohol with ZnI_2/Et_3SiH, a novel mild and stereospecific tertiary alcohol reduction system, and the tandem oxidation/cyclopropanation reactions.

Keywords drospirenone, stereospecific synthesis, ionic hydrogenation, Oppenauer oxidation, cyclopropanation

Introduction

Drospirenone (**1**) (Figure 1) is a unique progestogen derived from 17α-spirolactone, with a pharmacologic profile very similar to that of endogenous progesterone. In contrast with other available progestins, compound **1** is a progestogen with aldosterone receptor antagonism (PARA) through its affinity for the mineralocorticoid receptor. It is able to act on the renin-angiotensin-aldosterone system (RAAS), which prevents excessive sodium loss and regulates blood pressure.[1]

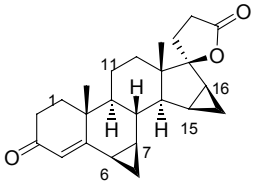
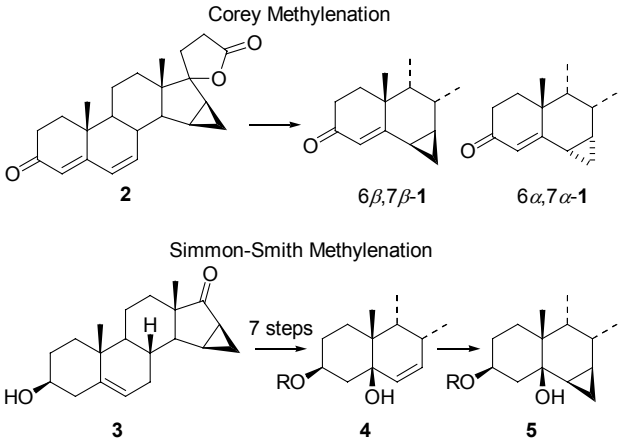


Figure 1 Structure of drospirenone (**1**)

The synthesis of **1** is quite complicated. Initially **1** was prepared by treatment of diene **2** with dimethylsulfoxonium methylide (Corey methylenation) in moderate yields as a mixture of 6β,7β- and 6α,7α-methylene (*ca*. 2∶1). The desired 6β,7β-dropirenone could be obtained only in low yield by tedious separation and purification of the mixture.[2] Wiechert *et al*.[3] reported the first stereoselective synthesis of **1** by applying the Wieland's procedure for prorenone synthesis[4] starting from androstenolone in 15 steps with 2.6% overall yields. Later Petzoldzt *et al*.[5] improved the synthesis by combining synthetic and microbiological processes in an overall yield of 9.5%. The key precursor 3β-hydroxy-15β,16β-methylene androst-5-ene-17-one (**3**) was stereoselectively transformed into the 5β-allylic alcohol **4**, which directed the Simmon-Smith methylenation (Zn-Cu/CH_2I_2) to stereospecifically deliver the 6β,7β-methylene compound **5** (Scheme 1). These transformations encountered with long steps, highly toxic and expensive reagents, which could eventually present a hazard to the environment. In order to prepare greater quantities of compound **1**, it is desirable to develop a greener method for the stereoselective introduction of the 6β,7β-methylene group.

Scheme 1 Reported synthetic methods for drospirenone (**1**)



Results and Discussion

As we recently reported an efficient and stereocontrolled access to the 6β,7β-methylene unit in steroid,[6]

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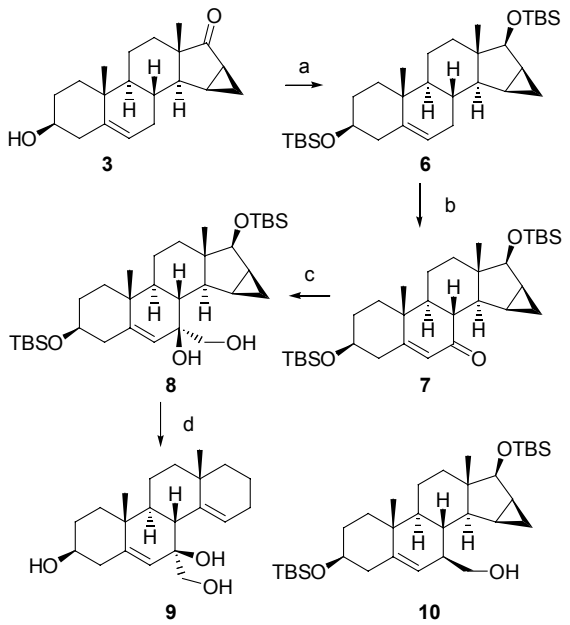
Received November 19, 2012; accepted December 21, 2012; published online January 8, 2013.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201201147 or from the author.

† Dedicated to the Memory of Professor Weishan Zhou.

we started the synthesis from commercially available 3β-hydorxy-15β,16β-methylene androst-5-ene-17-one (**3**) (Scheme 2). The 17-ketone in **3** was transferred into C-17 hydroxyl by reduction with $NaBH_4$ in methanol, and followed masking of both the C-3 and C-17 hydroxyl with TBSCl (*tert*-butyldimethylsilyl chloride)/imidazole gave **6** in quantitative yield. Using an improved allylic oxidation method,[7] a C-7 ketone group in steroidal frame was introduced by oxidation of **6** with *N*-hydroxyphthalimide/$Na_2Cr_2O_7$•$2H_2O$ in acetone at 40 ℃ in 78% yield. Treatment of α,β-unsaturated ketone **7** with (isopropoxydimethylsilyl)methyl Grignard reagent (Tamao's reagent),[8] followed by oxidative cleavage of the C—Si bond by H_2O_2 gave the 7α-hydroxylmethyl and tertiary alcohol **8** in 83% yield.[9]

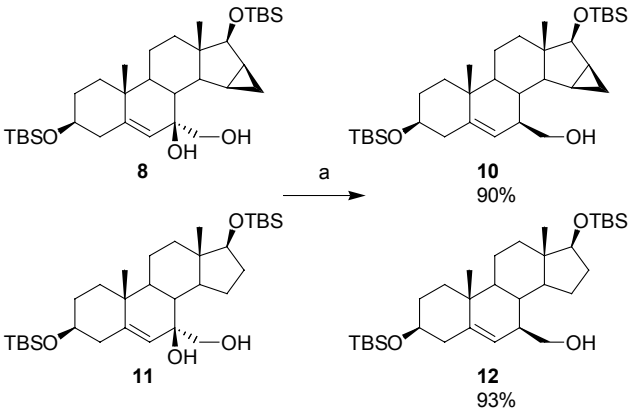
Scheme 2 Synthesis of compound **8**



Reagent and condition: (a) (1) $NaBH_4$, MeOH, 0 °C, 1 h, 99%; (2) TBSCl/imidazole, DMF, r.t., 5 h, 99%; (b) *N*-hydroxyphthalimide/$Na_2Cr_2O_7$•$2H_2O$, acetone, 40 °C 36 h, 78%; (c) Tamao's reagent, THF, 0 °C, 2 h, 81%; (d) BF_3•Et_2O/Et_3SiH, CH_2Cl_2, 0 °C, 10 min, 57%.

However, when ionic hydrogenation conditions (BF_3•Et_2O/Et_3SiH) were applied to remove the C-7 tertiary alcohol moiety in **8**,[6] the 15β,16β-methylene ring expansion compound **9** was isolated in 57% yield instead of the desired 7β-hydroxymethyl product **10**. This is reasoned for that the strong Lewis acid BF_3•Et_2O had caused the 15β,16β-methylene ring opening. Then we had to seek a mild Lewis acid for catalyzed reduction with Et_3SiH. After screening various Lewis acids, we found that ZnI_2 could promote the ionic hydrogenation efficiently in high yield.[10] When **8** was treated with 10 equiv. Et_3SiH and 2.5 equiv. ZnI_2, the reaction went smoothly at room temperature and gave **10** stereospecifically in 90% yield without ring opening (Scheme 3). Similarly, treatment of tertiary alcohol **11** with this novel ionic hydrogenation conditions provided 7β-hydroxymethyl compound **12** in 93% yield.

Scheme 3 Reduction of tertiary alcohol



Reagent and condition: (a) ZnI_2 (2.5 equiv.), 1,2-dichloroethane, Et_3SiH (10 equiv.), r.t., 2 h.

With successful entry to 7β-hydroxymethyl compound **10**, the synthesis of target drospirenone (**1**) was outlined in Scheme 4. Global removal of the TBS group in **10** with acetic acid/water (V∶V=4∶1) at 45 ℃ afforded triol **13**. We envisioned that the C-3 hydroxyl and C-7 methyl primary alcohol in **13** could be selectively protected with TBSCl due to the stereohindered environment of C-17 hydroxyl group. Indeed, the C-3 hydroxyl and C-7 methyl hydroxyl could be selectively masked with 2.5 equiv. of TBSCl/imidazole (89% yield). Then the 17-OH in **14** was affected by Oppenauer oxidation to afford 17-keone **15** in 85% yield. A C_3 side chain was introduced in **16** by the alkynylation of **15** with propargyl alcohol and *t*-BuOK in 96% yield. The 17α-spirolactone **18** was achieved smoothly by hydrogenation of the triple bond in **16** (10% Pd/C) and Oppenauer oxidation of the 17α-hydroxypropanyl **17**. Finally, the target drospirenone (**1**) was obtained through a three-step sequence involving silyl ether deprotection (TBAF, 99%), mesylation (MsCl, Et_3N, 89%), and tandem Oppenauer oxidation/cyclopropanation reactions (73%). The spectral data (^1H and ^{13}C NMR) of our synthetic drospirenone (**1**) matched exactly with those reported in the literature.[11]

Conclusions

In summary, we have demonstrated a novel stereospecific synthesis of drospirenone in 19% overall yield starting from the commercially available **3**. The key steps involved a novel mild reduction of tertiary alcohol with ZnI_2/Et_3SiH to stereoselectively prepare the 7β-hydroxyl methyl steroid and a tandem oxidation/

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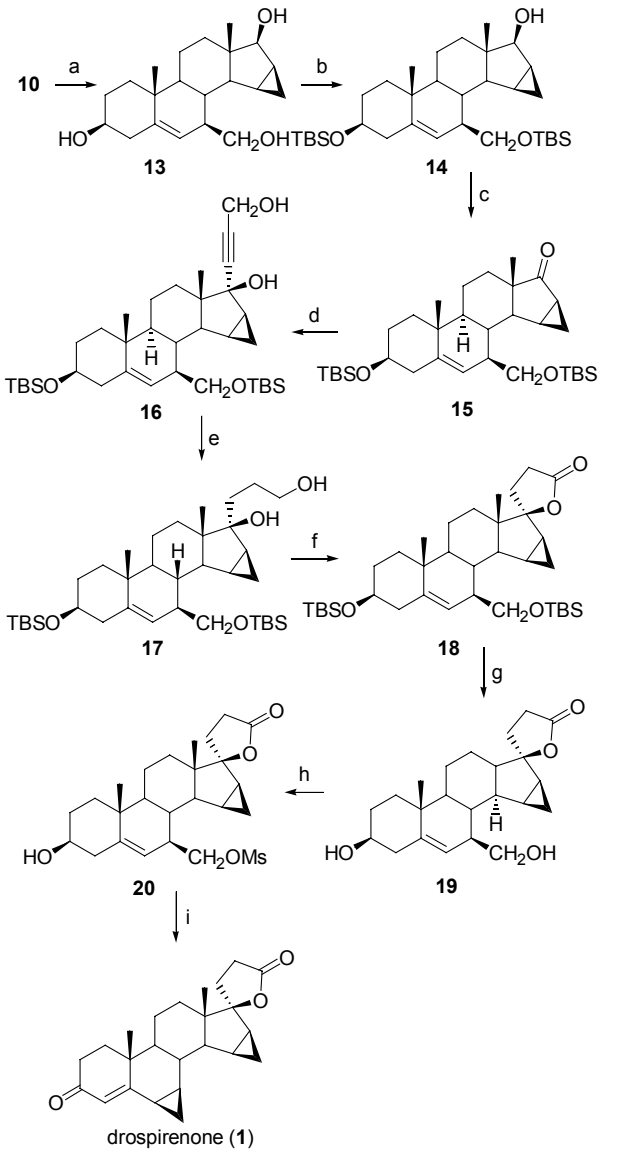
Scheme 4 Synthesis of drospirenone (**1**)



Reagent and condition: (a) AcOH/H_2O (V : V=4 : 1), 40 °C, 6 h, 99%; (b) TBSCl (2.5 equiv.), imidazole, DMF, 10 h, 90%; (c) Al(OPr-*i*)$_3$, cyclohexanone, refluxe, 1 h, 85%; (d) propargyl alcohol, *t*-BuOK, THF, 0 ℃ to r.t., 2 h, 96%; (e) 10% Pd/C, H_2, MeOH, r.t., 2 h, 90%; (f) Al(OPr-*i*)$_3$, cyclohexanone, refluxe, 1 h, 80%; (g) TBAF, THF, 40 ℃, 1 h, 99%; (h) MsCl, TEA, THF, 0 °C, 89%; (i) Al(OPr-*i*)$_3$, cyclohexanone, toluene, 1 h, 73%.

cyclopropanation method for the stereospecific construction of the 6β,7β-methylene ring. Besides, all the reactions proceed under mild conditions with benign reagents. The new ionic hydrogenation condition is useful for the reduction of tertiary alcohol compounds bearing sensitive functional groups to strong Lewis acids.

Acknowledgement

This research was financially supported in part by the China Postdoctoral Science Foundation and the National Basic Research Program of China (Nos. 2010CB833200, 2010CB833300), the National Natural Science Foundation of China (Nos. 20832007, 21102167), the Science and Technology Commission of Shanghai Municipality (No. 12DZ1930902) and the Knowledge Innovation Program of Chinese Academy of Sciences. We thank Zhejiangshenzhou Pharmaceutical Co., Ltd for providing starting materials.

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