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Practical synthesis of androgen: The efficient transformation of 17-oxo group to 17α-hydroxy group

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The present report describes the improved transformation of the 17-oxo group in 3β-acetoxy-5α-androstan-17-one to a 17α-hydroxy group. A mixture of 17α-acetoxy and 16-ene compounds, which are usually produced by the standard synthetic route, were treated with peracetic acid (epoxidation of the 16-ene compound) and then sodium borohydride-sodium hydroxide (reduction-hydrolysis) to give the desired 17α-hydroxy compound in much better yield than that in previous reports. Recrystallization of the crude product with cyclohexane-methanol gave the pure compound in 54% yield (total yield from starting ketone). (*Steroids* **63**:630–632, 1998) *© 1998 by Elsevier Science Inc.*

Keywords: androgen; 5α-androstane-3β,17α-diol; epoxidation; reduction; steroid

Introduction

Musk is a substance secreted by the glands of male musk deer.[1] As is well-known, musk is not only used as the basis of numerous perfumes, but also as one of the most important Chinese drugs. Musk exhibits cardiovascular stimulation, male hormonal and anti-inflammatory activities, and also induces the potentiation of the β-adrenergic effect.[2] In 1975, more than 14 types of steroidal compounds, which contain 11 androgens, were isolated from musk by Do et al.[3] and some of these androgens play an important role in the use of musk as a drug.

Study of artificial musk has been carried out because natural raw materials are becoming insufficient, and synthesis of 11 androgens has also been begun in recent years. In the syntheses of these steroids, introduction of the 17α-hydroxy group has proved to be the most difficult.[4,5] Generally, 17β-hydroxy compounds were easily prepared by the reduction of 17-oxo compounds by $NaBH_4$, but the published reaction,[6] i.e., the Mitsunobu reaction, cannot be used to invert the configuration of the hydroxy group in the esterification. In a previous study,[5] the 17α-hydroxy compound **5b** could be prepared from the 17-oxo substrate **1** by reduction, tosylation, substitution, and then hydrolysis (scheme 1). However, the selectivity of the substitution on the tosyl group by acetate in a S_N2 fashion was low because of the competition with elimination, and this low selectivity made the purification of **5b** difficult. In other words, the substitution gave a mixture of **4**, **5a**, and several olefinic products shown in Scheme 1,[5] and column chromatography was required for further purification of **4** and **5a** from the reaction mixture. Therefore, the reported yield of **5b** from **1** via **4** was as low as 4%.[5] Some interesting results for obtaining 17α-hydroxy compounds have been reported so far. Henbest and Jackson[7] claimed that 17α-acetoxy-3-oxoandrost-4-ene was obtained from the reaction of the 17β-*p*-toluenesulfonyloxy-3-oxoandrost-4-ene with tetrabutylammonium acetate in *N*-methylpyrrolidone at 160°C in 34% yield, followed by the elimination product in 57% yield. Göndös and Orr[8] reported reduction of the 17-oxo group in estrone methyl ether to a 17α-hydroxy group in 36% yield, employing a chiral reducing agent (diphenylsilane–Rh–(−)-diop) accompanied with the 17β-hydroxy compound in 26% yield. In these cases, the yields of the 17α-hydroxy compounds were moderate, but the selectivities were not satisfactory.

In our study of the efficient syntheses of steroids,[9] we have found an improved method for introducing the 17α-hydroxy group, and this will be described in the present

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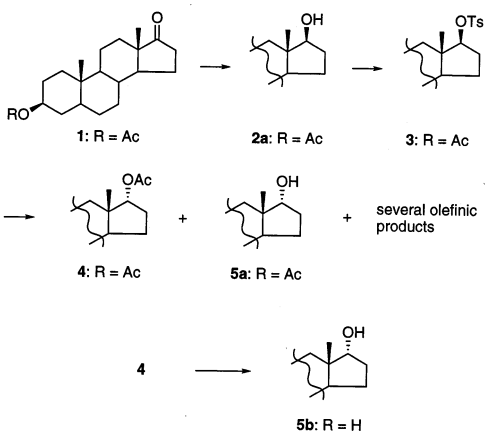


Scheme 1 Published route for the synthesis of 5α-androstane-3β,17α-diol (**5b**).

report. In our procedure, the by-product **6**, which was formed by the 16,17-elimination during the substitution, was converted into the final product **5b** by epoxidation and reduction-hydrolysis without separation from the reaction mixture (Scheme 2).

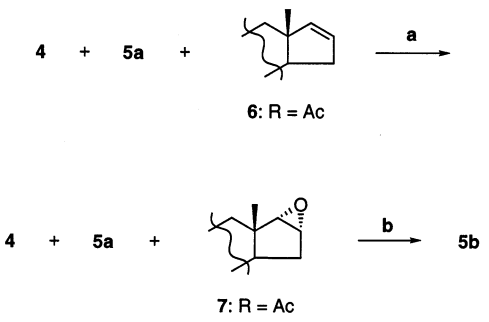
Experimental

General

^{1}H NMR (400 MHz) spectra were recorded on a JEOL A-400 (^{1}H 400 MHz) spectrometer with a TMS internal reference. Optical rotations were measured on a Horiba SEPA-200. All melting points were determined with a Yanako MP-500D melting point apparatus and were not corrected. Analytical thin layer chromatography was performed on M. Nagel silica gel 60 F-254 precoated plates. All compounds were used as purchased from Aldrich, Nacalai Tesque, and Wako Pure Chemical Industries.

*3β-Acetoxy-5α-androstan-17β-ol (**2a**)*

3β-Acetoxy-5α-androstan-17-one (**1**) (10.0 g, 30.1 mmol) was added to ethanol (99.5%, 100 cm^3) containing calcium chloride (1.7 g, 15.3 mmol), and then a solution of sodium borohydride (0.7 g, 18.5 mmol) in water (5 cm^3) was added dropwise over 1 min to the reaction mixture at room temperature. After stirring further for 1 h at room temperature, the mixture was neutralized by acetic acid to pH 5 (indicator paper), concentrated, put into 200 cm^3 of water, and allowed to stand for 3 h. The solid materials formed were collected by filtration, washed with water, and dried at 70°C to give 3β-acetoxy-5α-androstan-17β-ol (**2a**) as white crystals (10.0 g, 99%); mp. 106.8–107.4°C (lit.[5] 111–112°C).



Scheme 2 Epoxidation and reduction-hydrolysis pathway. (a) CH_3CO_3H in CH_3CO_2H. (b) $NaBH_4$-NaOH.

*5α-Androstane-3β,17β-diol (**2b**)*

The ester **2a** (1.0 g, 3.0 mmol) was hydrolyzed by a solution of sodium hydroxide (0.3 g, 7.5 mmol) in methanol (15 cm^3) and the crude product obtained by a standard procedure was recrystallized from ethyl acetate to give **2b** (0.75 g). Yield: 85% from **1**; mp. 166.8–169.2°C (lit.[10] 167–168°C, lit.[11] 168°C), $[\alpha]_D^{25}$ + 4.2 (*c* 1.0, dioxane) (lit.[12] $[\alpha]_D^{20}$ + 4.2, lit.[13] $[\alpha]_D$ + 4, lit.[10] [ϕ] + 16 [chloroform]).

*3β-Acetoxy-17β-p-toluenesulfonyloxy-5α-androstan (**3**)*

p-Toluenesulfonyl chloride (6.7 g, 35 mmol) was added to a solution of **2a** (5.0 g, 15 mmol) in pyridine (17.5 cm^3). After stirring at room temperature for 20 h, the mixture was poured into ice water. The crystals formed were filtered, washed with water, and dried in vacuo to give **3** (7.54 g). This product was used for the next reaction without further purification.

*5α-Androstane-3β,17α-diol (**5b**)*

A mixture of **3** (7.0 g, 14 mmol), potassium acetate (35.0 g, 357 mmol), and acetic acid (2.1 cm^3, 37 mmol) in *N,N*-dimethylformamide (DMF) (84 cm^3) was stirred at reflux temperature for 6 h. After cooling, the mixture was poured into water (800 mL) and extracted three times with chloroform (200 mL × 3). The combined organic layer was washed with water.

Peracetic acid (16%) in acetic acid (35.0 cm^3, 73.6 mmol of peracetic acid) was added to the above solution in chloroform, and the mixture was stirred for 24 h at room temperature. The resulting mixture was treated twice with 10% ferrous sulfate aqueous solution (44 cm^3), twice with an aqueous solution of sodium bicarbonate (13 cm^3), and twice with water. The recovered organic layer was concentrated and diluted with methanol (70 cm^3).

Sodium borohydride (0.7 g, 19 mmol) and sodium hydroxide (1.8 g, 44 mmol) were subsequently added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was neutralized with acetic acid, concentrated, and recrystallized with cyclohexane-methanol to give **5b** (2.25 g, 7.69 mmol).[a] Compound **5b**: yield 55% from **3**, mp. 218–219.5°C (lit.[4] 218–220°C, lit.[10] 221–222°C), $[\alpha]_D^{25}$ − 5.6 (*c* 1.0, dioxane) (lit.[4] $[\alpha]_D^{20}$ + 5.6, lit.[10] [ϕ] − 21 [chloroform]).[b]

Results and Discussion

First, reduction of the 17-oxo group to a 17α-hydroxy group was examined. Reduction of the 17-oxo group in **1** with

[a]Stereochemistry of these diols, 5α-androstan-3β,17β-diol (**2b**) and 5α-androstan-3β,17α-diol (**5b**) was confirmed by ^{1}H NMR analysis (NOESY). Optimized geometry by MO calculation (MOPAC in CAChe system) showed that the distances between 17H and protons on 18-CH_3 of 17α- and 17β-hydroxy compounds are 2.5 and 3.8 Å, respectively. On the other hand, NOESY analyses of the hydration product of **2b** and of **5b** revealed that the 17H of **5b** was close to the protons on 18-CH_3, but not in the case of **2b**.

[b]The sign of optical rotation of **5b** was negative and opposite to the value reported in Ref. 4. We thought that the sign of the reported value in Ref. 4 was incorrect because that of the molar rotation in Ref. 8 was negative, even though a different solvent was used.

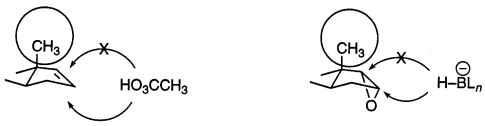
metalhydrides, such as $NaBH_4$, was known to give the 17β-hydroxy product **2a** because of steric hindrance from the 18-methyl group in **1**. There is only one example of the reduction of the 17-oxo group in estrone methyl ether to a 17α-hydroxy group by employing a chiral reducing agent (diphenylsilane-Rh-(−)-diop) (vide infra).[8] We wished to avoid steric hindrance from the 18-methyl group in **1** by using electron-transfer and protonation. Substrate **1** was allowed to react with a sodium-methanol system, but the same compound **2a** was obtained as the sole product. Thus, direct reduction of the 17-oxo group to a 17α-hydroxy group was not successful.

Next, nucleophilic inversion of stereochemistry at C-17 in **3** was carried out. Compound **2a** was prepared by the reduction of 17-oxo substrate **1** using $NaBH_4$ in almost quantitative yield and identified by the hydrolysis to 5α-androstane-3β,17β-diol (**2b**). Then *p*-toluenesulfonation of **2a** gave **3**. Substitution of the 17-*p*-toluenesulfonate group in **3** with acetate anion yielded a mixture of the desired 17α-acetate product and several by-products, results similar to those in the literature. We had been attempting to obtain **4** selectively, but could not achieve this.

Above substitution reaction afforded a mixture of **4**, **5a**, and **6** followed with small amounts of other compounds on thin-layer chromatography, so transformation of by-product **6** to **5b** was examined with epoxidation, reduction, and hydrolysis. The reactions proceeded smoothly to give the desired product **5b** in good yield. That is, a reaction mixture from substitution was exposed to epoxidation by peracetic acid, reduction with sodium borohydride, and hydrolysis with sodium hydroxide to yield the 17α-hydroxy compound **5b** in 55% yield after recrystallization from **3**. Overall yield of **5b** from **1** was 54%, the best among the reported values.

The method described in this report has some advantages: 1) isolation of the desired intermediate **4** from a reaction mixture by column chromatography is not needed because the crude mixture can be used for epoxidation and reduction without loss of **4**; 2) reduction and hydrolysis are performed at the same time by use of the combination of sodium borohydride and sodium hydroxide; and 3) after reduction-hydrolysis, simple recrystallization affords the desired product in pure form.

As shown in the Chart, the α stereochemistry of the



epoxide is expected because of steric hindrance to approach of the peracid by the 18-methyl group. The 17α-alcohol stereochemistry also results from steric hindrance by the 18-methyl group, which blocks hydride attack at C-17 in the epoxide.

In conclusion, the 17α-hydroxy product **5b** could be obtained through the epoxidation and reduction-hydrolysis of the mixture formed by the reaction of **3** with acetate anion without purification of the intermediate in good yield. Purification by recrystallization was improved with cyclohexane as well.

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