DOI: 10.1002/cjoc.201201023

A Scalable Synthesis of 6,19-Dihydroxyandrostenedione†

Yubo Yan,[a] Ting Li,[b] Tao Liu,[b] Qingyu Dou,[b] Kai Ding,*[,c] and Weisheng Tian*[,a,c]

[a] *Laboratory of Resource Chemistry, Shanghai Normal University, 100 Guiling Road, Shanghai 200234, China*
[b] *Department of Chemistry, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China*
[c] *Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China*

Starting from the commercially available 19-hydroxyandrostenedione, a practical protocol for the preparation of 6,19-dihydroxyandrostenedione is reported. This compound is a key intermediate for the synthesis of cyclocitrinols. With the stereospecific epoxidation and following isomerization to allylic alcohol as key steps, a six-step procedure provided desired product in high yield. The sequence is easy to scale-up without the need of laborious chromatography.

Keywords 6,19-dihydroxyandrostenedione, allylic alcohol, epoxide, stereospecific, steroid

Introduction

Steroids bearing a 19-hydroxyl group are important raw materials for production of steroidal estrogens.[1] In the synthesis of estrogens, the 19-decarbonylation of these steroids converts the A ring to an aromatic ring. Although the process is widely used to prepare the 19-nor-steroids in industry, the easily occurring decarbonylation might become a significant side reaction in organic synthesis.

Cyclocitrinols are a series of usual C25 steroid with a bicyclo [4.4.1] system at rings A/B.[2] In their total syntheses, 6,19-dihydroxyandrostenedione is a key intermediate (Figure 1). There are a series of methods for γ-oxidation of α,β-unsaturated ketone, such as direct oxidation under strong basic condition[3a] or two-step transformation with dienol ether or ester as intermediates.[3b] Therefore, we attempted to prepare the key intermediate via γ-oxidation of enone from commercially available 19-hydroxyandrostenedione (**1**). However, conventional methods were proved to be inefficient due to the effect of 19-hydroxyl group. Herein, we describe a scalable synthesis of 6,19-dihydroxyandrostenedione from commercially available compound **1**. The six-step route features high yield, high stereoselectivity and simple operation.

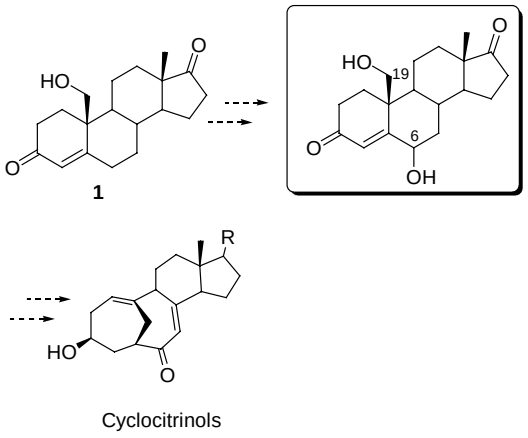


Figure 1 Key synthetic intermediate.

Experimental

General

All NMR experiments were recorded on VARIAN Mercury 300 MHz spectrometer or Bruker DPX400 spectrometer. Chemical shifts are reported in parts per million (ppm) on a δ scale, and referenced to the residual solvent peak (^{1}H δ 7.26, ^{13}C δ 77.0 for $CDCl_3$). Coupling constants (*J*) are reported in Hertz. Low- and high-resolution EI-MS were measured on a Finnigan MAT 900 XL-Trap mass spectrometer in positive ionization mode. Optical rotation was measured by JASCO P1030 polarimeter in the solvent indicated. Melting points were measured by WRS-1B digital melting-point apparatus.

The six-step synthesis of 19-acetoxy-androst-4-ene-3,17-dione (7)

The mixture of 0.27 g of DMAP and 27.2 g (90.0 mmol) of 19-hydroxyandrostenedione in 90 mL of ace-

* E-mail: dingkai@mail.sioc.ac.cn, wstian@mail.sioc.ac.cn
Received October 20, 2012; accepted November 22, 2012; published online December 27, 2012.
† Dedicated to the Memory of Professor Weishan Zhou.

 © 2013 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

tic anhydride was stirred at room temperature for 1 h. The excess of acetic anhydride was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine. The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo* to provide **2** (31 g) as a yellow oil.

Compound **2**: $C_{21}H_{38}O_4$; M_W 344.44; wax; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.9 (s, 1H), 4.66 (d, J=11.3 Hz, 1H), 4.16 (d, J=11.1 Hz, 1H), 1.99 (s, 3H), 0.88 (s, 3H).[4a]

The mixture of 31 g of crude **2**, 72 mL of triethyl orthoformate and 6 drops of concentrated sulfuric acid in 50 mL of THF was stirred at 60 ℃ for 6 h. The resulting dark solution was added to the mixture of 200 mL of water and 50 mL of saturated $NaHCO_3$, which was extracted with ethyl acetate (100 mL×2). The organic phase was washed with water (100 mL) and concentrated *in vacuo* to provide 43 g of crude ketal **3** as a brown oil.

Compound **3**: $C_{25}H_{36}O_6$; M_W 433.55; white solid; $[\alpha]_D$ 17.5 (1.00, $CHCl_3$); m.p.: 125−126 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.56 (m, 1H), 4.44 (d, J=11.9 Hz, 1H), 4.06−3.70 (m, 9H), 2.57 (dd, J=14.3, 2.3 Hz, 1H), 2.14 (d, J=14.3 Hz, 1H), 2.02 (s, 3H), 0.84 (s, 3H).[4b]

To a solution of 43 g of ketal **3** in 150 mL of methanol was added 54 g (390 mmol) of K_2CO_3. The suspension was heated under reflux for 4 h and was added to 1000 mL of water. The suspension was filtrated with Buchner funnel to provide a wet cake, which was solved with ethyl acetate (400 mL). The organic phase was washed with water and dried with Na_2SO_4, concentrated *in vacuo*. The resulting solid was recrystallized with ethyl acetate and hexane to furnish 27 g of pure **4** as a white solid (77%, 3 steps).

Compound **4**: $C_{23}H_{34}O_5$; M_W 390.51; white solid; $[\alpha]_D$ −31.7 (1.00, $CHCl_3$); m.p.: 205−206 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (s, 3H, 18-Me), 3.62 (dd, J= 11.4, 9.1 Hz, 1H, 19-H), 4.02−3.75 (m, 9H), 5.87−5.66 (m, 1H, 4-H).[4c]

To a solution of 5.85 g of pure **4** (15 mmol) in 50 mL of dichromethane was added *m*-CPBA (22.5 mmol) at room temperature. After stirring for 30 min, 10 mL of saturated Na_2SO_3 was added to remove the excess of oxidant. The mixture was stirred for 1 h. The organic phase was washed with saturated Na_2CO_3 (50 mL), water (50 mL) and dried with Na_2SO_4. The solution was concentrated under reduced pressure to provide crude epoxide **5**.

Compound **5**: $C_{23}H_{34}O_6$; M_W 406.51; white solid; $[\alpha]_D$ −5.7 (1.00, $CHCl_3$); m.p.: 119.5−120 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (s, 3H, 18-Me), 3.02 (s, 1H, 6-H), 3.55 (d, J=11.6 Hz, 1H), 3.98−3.76 (m, 8H), 4.07 (d, J=11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 119.3, 109.3, 66.8, 65.1, 64.5, 64.2, 64.1, 63.5, 60.8, 50.7, 47.9, 46.0, 41.5, 38.6, 34.0, 31.9, 31.3, 31.0, 30.7, 30.6, 22.4, 20.9, 14.3; HRMS calcd for $C_{23}H_{34}O_6$+Na^+: 429.2253, found 429.2251.

The mixture of crude **5**, 10 mL of acetic anhydride and 0.1 g of DMAP was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was solved into 100 mL of ethyl acetate. The solution was washed with saturated Na_2CO_3, water and brine. The solution was concentrated to provide epoxide **6** as a yellow solid.

Compound **6**: $C_{25}H_{36}O_7$; M_W 448.55; white solid; $[\alpha]_D$ −32.8 (1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.81 (s, 3H, 18-Me), 2.06 (s, 3H, 19-AcH), 2.95 (s, 1H, 6-H), 3.98−3.76 (m, 8H), 4.05 (d, J=11.3 Hz, 1H, 19-H), 4.34 (d, J=11.3 Hz, 1H, 19-H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.9, 119.2, 109.3, 66.2, 65.1, 64.5, 64.2, 64.0, 60.8, 60.7, 50.3, 47.6, 45.6, 42.5, 38.2, 34.0, 31.4, 31.3, 30.6 (two carbons), 30.2, 22.5, 21.2, 21.2, 14.1; HRMS calcd for $C_{25}H_{36}O_7$+Na^+: 471.2359, found 471.2343.

The mixture of epoxide **6** and 0.5 g of TsOH in 20 mL of acetone was stirred at room temperature until the reaction was complete (30−60 min). Et_3N (1 mL) was added to the solution, which was concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with water and brine, dried with Na_2SO_4, concentrated *in vacuo*. The resulting solid was recrystallized with ethyl acetate and hexane to furnish 4.05 g of desire product **7** (75%).

Compound **7**: $C_{21}H_{28}O_5$; M_W 360.44; $[\alpha]_D$ 88.4 (1.00, $CHCl_3$); white solid; m.p.: 175−176 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (s, 3H, 18-Me), 2.03 (s, 3H, 19-AcH), 4.41 (d, J=11.0 Hz, 2H, 6-H, 19-H), 4.75 (d, J=11.0 Hz, 1H, 19-H), 6.00 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$,101 MHz) δ: 219.9, 199.7, 170.8, 161.9, 128.9, 72.4, 68.1, 54.1, 51.1, 47.5, 41.2, 37.4, 35.6, 34.7, 34.3, 31.6, 29.9, 21.6, 21.1, 20.8, 13.8; HRMS calcd for $C_{21}H_{28}O_5$+Na^+: 383.1829, found 383.1825.

Results and Discussion

There are several known methods to achieve the γ-oxidation of α,β-unsaturated ketone. However, our attempts exhibited that these conventional methods were inefficient to introduce the 6-hydroxyl group into 19-hydroxyandrostenedione or its derivatives in the presence of 19-hydroxyl group (Figure 2). For example, oxidation of enol derivatives of raw material **1** only gave desired product as a mixture of two stereoisomers in less than 30% yield due to undesired Baeyer-Villiger oxidation of product.[5]

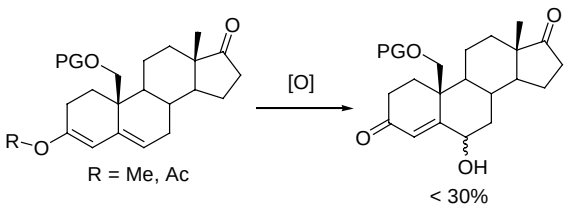


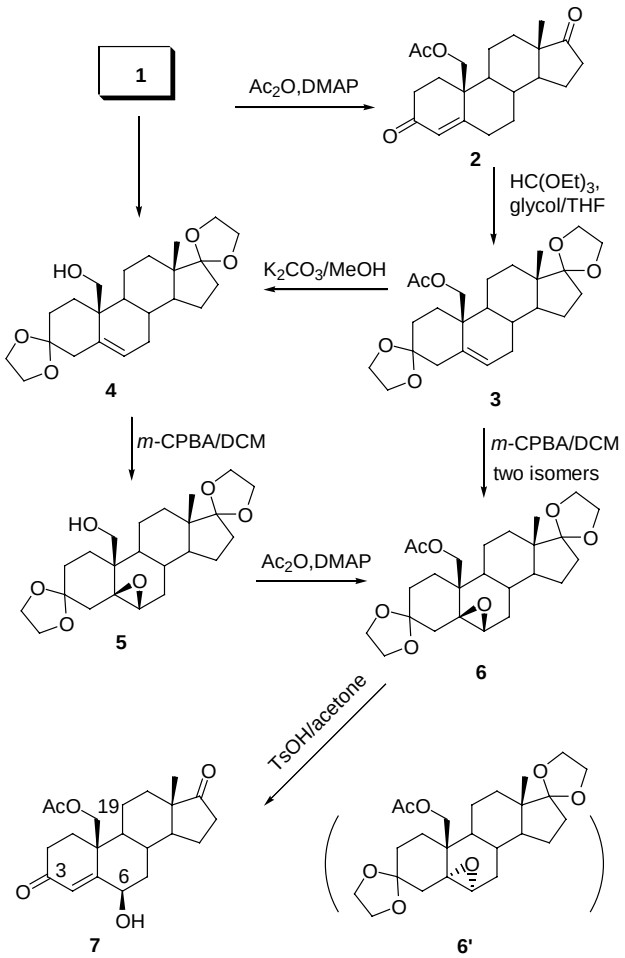
Figure 2 Unsuccessful attempts to introduce 6-hydroxyl group.

 © 2013 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

CHINESE JOURNAL OF CHEMISTRY

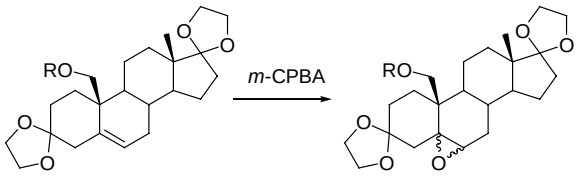
In this paper, enone **2** was converted into a stable 1,3-dioxolane to avoid the side reactions.[6a] The synthetic route is shown in Scheme 1. The direct ketalization of compound **1** with glycol did not give the desired ketal **4** due to the 19-decarbonylation through a retro-aldol reaction under acidic conditions. Therefore, the hydroxyl group must be masked prior to the ketalization. Reaction of raw material **1** with acetic anhydride provided compound **2** quantitatively. However, the ketalization of **2** via the azeotropic distillation under conventional conditions gave a cyclic ketal **3** in less than 50% yield because of the deprotection of 19-acetoxyl group at elevated temperature. Fortunately, this side reaction was suppressed and the cyclic ketal **3** was obtained in 72% yield when triethyl orthoformate was used as the dehydrating agent.[6b] The epoxidation of ketal **3** with *m*-CPBA provided two stereoisomers in high yield (α : β=2 : 3). However, only β-epoxide **6** can be isomerized to the desired product **7** under acidic condition. The attempts for the isomerization of α-isomer **6'** with stronger acidic catalysts or extending reaction time were unsuccessful because the product **7** formed from β-epoxide was isomerized to 3,6-dicarbonyl by-product.[7]

Scheme 1 A six steps synthesis of desired product



Several analogues of cyclic ketal **3** were synthesized to examine the stereoselectivity of epoxidation. Although these stereoisomers could be separated by flash chromatography, the laborious procedures were not acceptable for preparative purposes (Table 1).

Table 1 The effect of protective groups on stereoselectivity



R	Me	MOM	TES	Ac
dr (α : β)[a]	10 : 90	17 : 83	23 : 77	40 : 60
	TBS	Bz	Piv	TBDPS
	47 : 53	50 : 50	60 : 40	75 : 25

[a] ^{1}H NMR ratio of stereoisomers.

Finally, a stereospecific three-step synthesis was designed to address this problem. Thus the cyclic ketal **3** was hydrolyzed to the corresponding alcohol **4** in 89% yield, which reacted with *m*-CPBA to provide β-epoxide **5** as a single isomer in 93% yield. Unexpectedly, the direct hydrolysis of epoxide **5** under acidic condition gave a large amount of 3,6-dicarbonyl by-product. Acetylation of **5** offered epoxide **6** in 96% yield, which was hydrolyzed to desired product **7** in 92% yield.

This six-step route from raw material **1** to provide product **7** sufficed for our purposes, however, it is hardly ideal. We attempted to simplify the operation to prepare the product **7** on a large-scale without laborious chromatography. Considering the high yield in the six-step procedure, intermediates might be used without purification. However, a six-step procedure, in which the intermediates only were purified by extraction and washing gave a mixture of product **7** and by-products, which could only be purified by chromatography.

The preparation of 1,3-dioxolane (**2**→**3**) was found to offer a little by-products, which retarded the subsequent reactions and yielded a significant amount of by-products. Although the crystallization of crude **3** was unsuccessful, the cyclic ketal **4** was suitable for purification by crystallization. Thus, on a 30-gram scale, the pure **4** was obtained from raw material **1** (77%, 3 steps). On a 5-gram scale, pure ketal **4** was converted into product **7** in three steps, which was purified by recrystallization to offer pure product **7** in 75% overall yield.

Conclusions

In summary, 6,19-dihydroxyandrostenedione was successfully prepared in six steps from commercially available raw material **1**. The migration of double bond during the ketalization of enone avoided side reactions. The process can be carried out on a large scale without laborious chromatography. Its applications in the synthesis of natural products and steroidal drugs are cur-

 © 2013 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

rently pursued and will be reported in due course.

Acknowledgement

We are grateful for financial support of this work by the National Natural Science Foundation of China (No. 20902098).

References

[1] (a) Acebedo, S. L.; Alonso, F.; Ramirez, J. A.; Galagovsky, L. R. *Tetrahedron* **2012**, *68*, 3685; (b) Akhtar, M.; Calder, M. R.; Corina, D. L.; Wright, J. N. *J. Chem.*, *Soc.*, *Chem. Comm.* **1981**, 129; (c) Jing, Y.; Xu, C. G.; Ding, K.; Lin, J. R.; Jin, R. H.; Tian, W. S. *Tetrahedron Lett.* **2010**, *51*, 3242.

[2] (a) Kozlovsky, A. G.; Zhelifonova, V. P.; Ozerskaya, S. M.; Vinokurova, N. G.; Adanin, V. M.; Grafe, U. *Pharmazie* **2000**, *55*, 470; (b) Amagata, T.; Amagata, A.; Tenney, K.; Valeriote, F. A.; Lobkovsky, E.; Clardy, J.; Crews, P. *Org. Lett.* **2003**, *5*, 4393; (c) Marinho, A. M. D.; Rodrigues, E.; Ferreira, A. G.; Santos, L. S. *J. Braz. Chem. Soc.* **2005**, *16*, 1342; (d) Du, L.; Zhu, T. J.; Fang, Y. C.; Gu, Q. Q.; Zhu, W. M. *J. Nat. Prod.* **2008**, *71*, 1343.

[3] (a) Aladro, F. J.; Guerra, F. M.; Moreno-Dorado, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron* **2001**, *57*, 2171; (b) Nozawa, M.; Suka, Y.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 1365.

[4] (a) Templeton, J. F.; Lin, W. Y.; Ling, Y. Z.; MajgierBaranowska, H.; Marat, K. *J. Chem. Soc.*, *Perkin. Trans. 1* **1997**, 2037; (b) Lovett, J. A.; Darby, M. V.; Counsell, R. E. *J. Med. Chem.* **1984**, *27*, 734; (c) Dyer, R. L.; Harrow, T. A. *Steroids* **1979**, *33*, 617.

[5] An analogue was obtained smoothly via the oxidation of dienol ether in our previous work. See: Ding, K.; Sun, Y. S.; Tian, W. S. *J. Org. Chem.* **2011**, *76*, 1495.

[6] (a) de Leeuw, J. W.; de Waard, E. R.; Beetz, T.; Huisman, H. O. *Recueil des Travaux Chimiques des Pays-Bas* **1973**, *92*, 1047; (b) Wuts, P. G. M.; Ritter, A. R. *J. Org. Chem.* **1989**, *54*, 5180.

[7] Wijnberg, J. B. P. A.; de Groot, A. *Steroids* **1989**, *54*, 333.

(Lu, Y.)

 © 2013 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim