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An efficient one-pot synthesis of 5, 9-cyclo-1, 11-oxido-pregn-16-ene-3, 20-dione from 9-bromide-11-hydroxypregna-1, 4, 16-trien-3, 20-dione by two annulation reactions

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ABSTRACT

An efficient method to prepare 5, 9-cyclo-1, 11-oxido-pregn-16-ene-3, 20-dione in one pot was reported. Treatment of 9-bromide-11-hydroxypregna-1, 4, 16-trien-3, 20-dione with Raney Ni in absolute ethanol afforded 5, 9-cyclo-1, 11-oxido-pregn-16-ene-3, 20-dione by two annulation reactions in reasonable yield. The absolute configuration was also confirmed by X-ray crystal analysis.

1. Introduction

Steroids have attracted much attention because of their special biological activities [1]. Some steroids have been developed as drugs for the treatment of disease including autoimmune diseases, brain tumors, breast cancer, cardiovascular, prostate cancer, osteoarthritis [2,3]. Except for the naturally occuring substances, most of steroidal pharmaceuticals were semi-synthetic compounds. The development of new compounds to improve the selectivity and to minimize side effects of steroidal drugs has been a challenge for a long time [4]. For many years, the main direction of steroid research focused on the search for novel compounds with a normal tetracyclic skeleton, which differed mainly by their functional groups. At the same time, a number of pharmacologically active substances belonging to non-tetracyclic skeleton steroids were found [5–7].

5, 9-Cyclo-1, 11-oxidosteroids stood out as very potent anti-inflammatory agents. For instance, the compound 5, 9-cyclo-1, 11-oxidopregnance-17α, 21-diol-3, 20-dione has activity equal to or better than hydrocortisone when administered topically [8]. Furthermore, 5, 9-cyclo-1, 11-oxidosteroids are also very useful intermediate for preparing novel steroids [9], due to the presence of a tetrahydrofuran ring and a cyclopropane ring with high reactivity. However, the reported methods to prepare this type of compounds are not satisfied, because of their multiple steps, low yields or poor stereoselectivities [9].

We now report a simple synthetic method to prepare this type of compound 5, 9-cyclo-1, 11-oxidopregn-16-ene-3, 20-dione **1** through only one step with high stereoselectivities, using debromination followed by simultaneous annulation reactions (Scheme 1). The stereochemistry of the product was also determined by X-ray.

2. Experimental

Melting points were obtained on a B-540 Büchi melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AM-400 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm), relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (*J* values) are in Hertz. Multiplicities are designated as singlet (s), doublet (d), triplet (t), multiplet (m), or broad (br). Mass spectra (MS), ESI (positive) were recorded on a Esquire-LC-00075 spectrometer.

2.1. Synthesis of 9-bromide-11-hydroxypregna-1, 4, 16-trien-3, 20-dione *3*

Pregna-1, 4, 9(11), 16-tetraene-3, 20-dione **2** (618 mg, 2 mmol) in tetrahydrofuran (20 ml) containing 0.48 N aqueous perchloric acid (6 ml) was cooled to 2 °C. Then the mixture was treated with *N*-bromosuccinimide (495 mg, 2.78 mmol) below 5 °C with stirring for 3 h. Saturated aqueous sodium sulfite (3 ml) was added and

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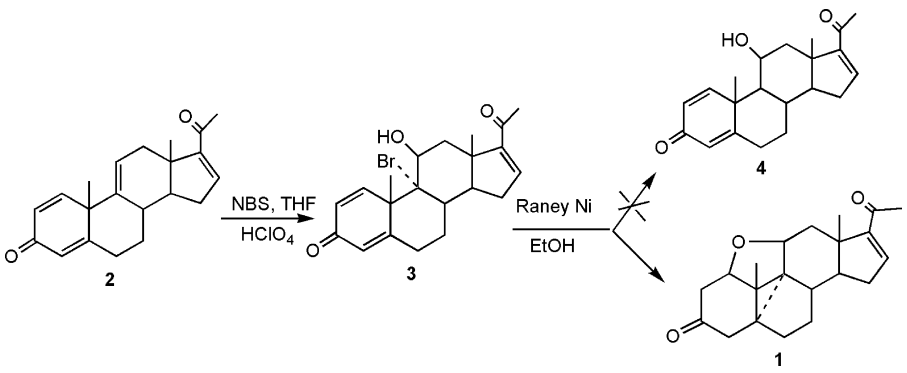

Scheme 1. Synthesis of **1**.

the most of tetrahydrofuran was removed under reduced pressure. Water (50 ml) was added and stirred to precipitate solid. The solid was filtered and washed with water (100 ml) and dried to afford white solid. The solid was purified by further recrystallization from methanol and chloroform to give 770 mg of **3**. yield 95%; mp 170 °C (dec); ^{1}H NMR (400 MHz, DMSO-d6) δ: 1.15 (s, 3H), 1.56 (m, 1H), 1.69(s, 3H), 1.99(m, 1H), 2.05(m, 2H), 2.20(s, 3H), 2.22–2.40(m, 5H), 2.66–2.68 (m, 1H), 4.55(s, 1H), 5.63(brs, 1H), 5.98(t, J = 1.2 Hz,1H), 6.22 (dd, J = 1.6 Hz, J = 10.0 Hz, 1H), 6.87(dd, J = 1.2 Hz, J = 2.8 Hz, 1H), 7.34(d, J = 10.0 Hz,1H); MS: m/z = 404(M^+), 406 (M^++2).

2.2. Synthesis of 5, 9-cyclo-1, 11-oxidopregn-ene-3, 20-dione *1*

To a solution of 9-bromide-11-hydroxyl pregna-1, 4, 16-trien-3, 20-dione **3** (200 mg, 0.49 mmol) in absolute ethanol (20 ml) was added 1.2 g Raney nickel. The mixture was stirred for four hours at room temperature. The solution was filtered and the nickel was washed with ethanol. After evaporation of the ethanol the residue was taken up in chloroform, washed with water and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography with methanol and dichloromethane (v:v = 1:30) to give 120 mg. of **1**. Yield: 75%; mp 217–219 °C; ^{13}C NMR (400 MHz, DMSO-d6) δ: 209.44, 196.05, 153.44, 143.97, 83.94, 76.56, 52.66, 51.20, 47.94, 44.01, 41.16, 41.10, 40.92, 40.52, 38.51, 38.16, 33.27, 32.62, 27.04, 18.19, 10.82; ^{1}H NMR (400 MHz, DMSO-d6) δ: 6.68 (dd, J = 2.0 Hz, J = 3.6 Hz, 1H), 4.57 (t, J = 2.8 Hz, 1H), 4.16 (dd, J = 2.0 Hz, 9.2 Hz, 1H), 2.77 (d, J = 18.8, 1H), 2.64 (d, J = 18.4, 1H), 2.47–2.35 (m, 3H), 2.21–1.58 (m, 9H), 2.25 (s, 3H), 1.31 (s, 3H), 0.94 (s, 3H); MS: m/z = 327 (M^++1) (Table 1).

3. Results and discussion

Debromination of 9α-bromo-steriod with Raney Ni in glacial acetic acid and acetone has been known as a reliable synthetic method [10]. We planned to apply this methodology to obtain

Table 1
Crystal data, data collection, and structure refinement.

	Compound	
	3	**1**
Empirical formula	$C_{21}H_{25}BrO_3$	$C_{21}H_{26}O_3$
Formula weight	405.33	326.43
Crystal size (mm)	0.38, 0.33, 0.24	0.45, 0.41, 0.38
Temperature (K)	298(1)	
Crystal system	Orthorhombic	Orthorhombic
Space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1
a (Å)	8.255(2)	7.001(3)
b (Å)	10.438(2)	11.876(3)
c (Å)	21.110(6)	20.981(6)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
Volume (Å^3)	1819.0(8)	1744.3(10)
Z	4	4
Density (calculated) (mg m^{-3})	1.480	1.243
Absorption coefficient (mm^{-1})	2.283	0.081
Diffractometer	Rigaku RAXIS-RAPID	
Radiation	Mo Ka	
λ	0.71075	
F(0 0 0)	840	704.00
Range for data collection	$0.998 < \theta < 27.48$	$0.999 < \theta < 27.48$
Index range	$-10 < h < 10$, $-13 < k < 13$, $-27 < l < 27$	$-9 < h < 9$, $-15 < k < 15$, $-24 < l < 27$
Reflections collected	17,983	17,231
Independent reflections	4156[R(int) = 0.031]	3992[R(int) = 0.029]
Completeness to θ = 27.48	100.0%	
Absorption correction	Multi-scan (Higashi, 1995)	
Refinement method	Full-matrix least-squares on F2	
Data/restraints/parameters	4156/0/228	3992/0/228
Computing	Larson	
Goodness-of-fit	1.004	1.002
R_1	0.0236	0.0394
ωR_2	0.0513	0.0825
($\Delta\rho$) max, min (e Å^{-3})	0.55, −0.40	0.48, −0.41

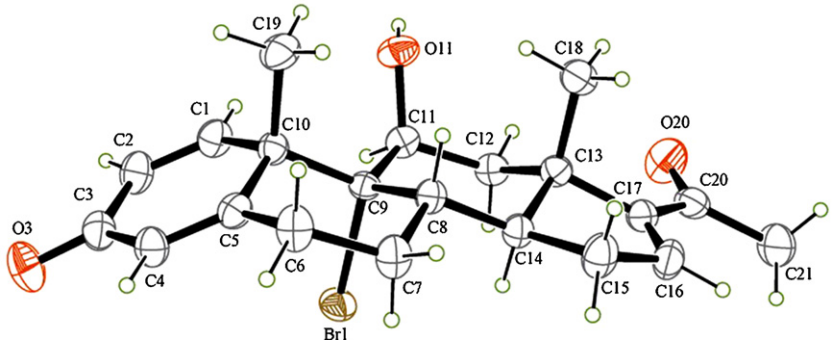

Fig. 1. X-ray structure of **3**. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 627288.