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Reaction of (13*S*)-13-iodo-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstane-14,17-dione with hydroxylamine and its application to the synthesis of new 13,14-seco steroids

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Abstract

The synthesis of 13,14-seco steroids starting from easily available (13*S*)-13-iodo-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androsta-14, 17-dione is described. The C-17 ketone was converted regioselectively into its oxime with simultaneous stereoselective deiodination at C-13. The remaining C-14 carbonyl group was then reduced stereoselectively with Ca(BH$_4$)$_2$. The configurations at the relevant stereocenters of the thus obtained hydroxy oxime were determined by X-ray analysis. Successful regeneration of the C-17 carbonyl group was achieved by treatment of the corresponding oxime acetate with TiCl$_3$.
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1. Introduction

Studies on 5,10-seco steroids have shown that modification of the rigid tetracyclic steroidal carbon skeleton by cleavage of an internal C–C bond provides more flexible compounds with new biological properties [1–6]. Radical oxidation of C-5 alcohols has been the most studied process for the preparation of 5,10-seco steroids [7–11], but only a few articles have been published on the radical oxidation of C-14 alcohols for synthesis of 13,14-seco steroids [12–14]. Comparison of the biological properties of such compounds with those of the tetracyclic natural steroids is of great interest and is stimulated further by the occurrence of 13,14-seco steroids in nature [15–17].

Earlier, we reported on the radical oxidation of 17-functionalized 14α-hydroxy steroids [14], and the stereochemistry at C-13 was established (Scheme 1). The yield of this reaction was improved up to 85%, which made it an attractive route for preparation of a variety of 13,14-seco steroids. As compound **2** contains keto groups at C-14 and C-17, one of them has to be differentiated from the other to allow further synthetic manipulations and to prevent easy recyclization. An additional problem is the deiodination step, which may be accompanied by a change of stereochemistry at C-13.

We now report a synthetic route to 13,14-seco steroids with different functional groups at C-14 and C-17 using oximation with simultaneous dehalogenation of **2**. The stereochemistry of one of the reaction products was determined by X-ray.

2. Experimental

Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets. ^{1}H and ^{13}C NMR spectra were taken on a Bruker AC-200 (200 MHz for ^{1}H, 50 MHz for ^{13}C) spectrometer using

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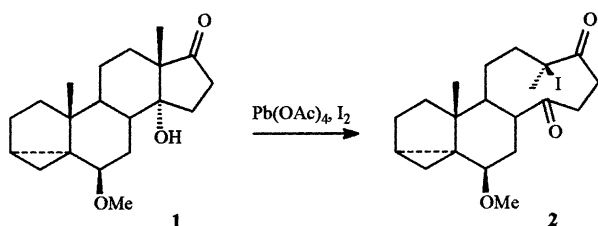
Scheme 1.

TMS as an internal standard in CDCl$_3$, and chemical shifts are given in δ (ppm). Exact mass was determined by ESI-TOF analysis performed on a Perkin Elmer Q-STAR XL TOF spectrometer. X-ray data collection (Nicolet R3m diffractometer) was performed via the $\omega/2\theta$ scan mode. The structure was solved by direct methods (SIR97) [18] and refined by full-matrix least squares (SHELXL 97) [19]. Positions of hydrogen atoms were calculated and refined by using the riding model [19]. All chemicals were of analytical grade. Reactions were monitored by TLC using aluminium or plastic sheets, silica gel 60 F$_{254}$ precoated (Merck Art. 5715). Column chromatography was carried out on Kieselgel 60 (Merck Art. 7734).

2.1. Radical dehalogenation of (2)

AIBN (1 mg, 0.006 mmol) and Bu$_3$SnH (0.4 ml, 1.50 mmol) were added to a solution of (13S)-13-iodo-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstane-14,17-dione **2** (100 mg, 0.23 mmol, prepared according to [14]) in dry benzene (5 ml), and the reaction mixture was refluxed for 30 min. Then, the solvent was evaporated, and the residue was dissolved in MeCN (5 ml) and washed three times with pentane. The solvents were evaporated, and the remaining oil was purified on SiO$_2$ (EtOAc:petroleum ether, 1:1) to give: (i) inseparable mixture of C-13 epimers of 6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstane-14, 17-dione **3** (50 mg, 70%) as an oil. IR (cm^{-1}): 1715, 1470, 1450, 1380, 1330, 1090. ^{1}H NMR δ: 0.45–0.55 (m, 1H, 4-H), 0.63–0.71 (m, 1H, 4H), 1.03 (s, 3H, 18–H), 0.98–1.02 (m, 6H, 18- and 19-H), 2.93 (m, 1H, 6-H), 3.31 (s, 2/3H, OMe), 3.32 (s, 1/3H, OMe); (ii) 6β-methoxy-14β-hydroxy-3α,5-cyclo-5α-androstan-17-one **4** (10 mg, 14%) as an oil. IR (cm^{-1}): 1745, 1460, 1380, 1290, 1100, 965. ^{1}H NMR δ: 0.45–0.60 (m, 1H, 4-H), 0.65–0.80 (m, 1H, 4H), 1.03 (s, 3H, 18-H), 1.09 (s, 3H, 19-H), 2.91 (m, 1H, 6-H), 3.36 (s, 3H, OMe). ^{13}C NMR δ: 13.0, 13.4, 19.1, 21.4, 21.5, 24.9, 26.7, 29.4, 32.2, 33.1, 33.6, 34.7, 36.6, 43.7, 44.0, 53.8, 56.6, 82.0, 82.2, 221.6.

2.2. (13S)-6β-Methoxy-3α,5-cyclo-13,14-seco-5α-androstane-14,17-dione 17-oxime (5)

NH$_2$OH•HCl (470 mg, 6.8 mmol) was added to a solution of diketone **2** (1.0 g, 2.25 mmol) in pyridine (20 ml). The obtained solution was kept at room temperature for 24 h, then

diluted with water, and extracted with CHCl$_3$. The solvents were evaporated, and the residue was chromatographed on SiO$_2$ (EtOAc:petroleum ether, 1:2) to give oxime **5** (490 mg, 65%). Mp 190–192 °C (hexane–EtOAc). IR (cm^{-1}): 1710, 1450, 1385, 1110, 1090. ^{1}H NMR δ: 0.42–0.56 (m, 1H, 4-H), 0.64–0.72 (m, 1H, 4-H), 0.98 (d, 1H, $J = 7$ Hz, 18-H), 1.02 (s, 3H, 19-H), 2.81 (m, 1H, 6-H), 3.31 (s, 3H, OMe). ^{13}C NMR δ: 13.0, 18.5, 18.7, 20.3, 21.3, 21.4, 24.6, 24.8, 26.4, 32.8, 33.0, 34.3, 39.3, 41.7, 45.3, 48.6, 48.9, 56.7, 81.5, 165.8, 220.4.

2.3. (13S,14S)-14-Hydroxy-6β-methoxy-3α,5-cyclo-13, 14-seco-5α-androstan-17-one 17-oxime (6)

NaBH$_4$ (23.9 mg, 0.63 mmol) in water (0.1 ml) was added to a solution of ketoxime **5** (70 mg, 0.21 mmol) and CaCl$_2$ (69.9 mg, 0.63 mmol) in 95% ethanol (3 ml). After 5 min, the reaction mixture was diluted with water and extracted with EtOAc and CHCl$_3$. The organic layers were dried and evaporated. The residue was chromatographed on SiO$_2$ (hexane:EtOAc, 1:1) to give alcohol **6** (40 mg, 57%) as white crystals. Mp 189–192 °C (hexane-EtOAc). ^{1}H NMR δ: 0.40–0.52 (m, 1H, 4-H), 0.62–0.68 (m, 1H, 4-H), 0.98 (s, 3H, 19-H), 1.10 (d, 3H, $J = 7$ Hz, 18-H), 2.85 (m, 1H, 6-H), 3.32 (s, 3H, OMe), 4.21 (m, 1H, 14-H). ^{13}C NMR δ: 12.9, 17.9, 18.5, 21.7, 24.8, 25.4, 28.3, 29.1, 33.8, 34.5, 35.5, 35.9, 39.9, 39.9, 43.5, 46.6, 56.5, 71.7, 82.4, 165.5.

2.4. (13S,14S)-14,17-Diacetoxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstan-17-one 17-oxime (7)

A solution of hydroxy oxime **6** (500 mg, 1.49 mmol) and Ac$_2$O (1.0 ml, 6.75 mmol) in pyridine (5 ml) was left at room temperature for 16 h. Then, it was diluted with water, and extracted with CHCl$_3$, and the solvents were evaporated. The residue was chromatographed on SiO$_2$ (hexane:EtOAc, 1:2) to give diacetate **7** (500 mg, 85%). Mp 123–125 °C (hexane:EtOAc). IR(cm^{-1}): 1780, 1740, 1640, 1480, 1470, 1380, 1270, 1080. ^{1}H NMR δ: 0.36–0.46 (m, 1H, 4-H), 0.60–0.66 (m, 1H, 4-H), 0.94 (s, 3H, 19-H), 1.22 (d, $J = 7$ Hz, 3H, 18-H), 2.04 (s, 3H, OAc), 2.20 (s, 3H, OAc), 2.80 (m, 1H, 6-H), 3.26 (s, 3H, OMe), 5.32 (m, 1H, 14-H). ^{13}C NMR δ: 12.9, 16.7, 18.4, 19.8, 21.5, 21.8, 24.6, 26.4, 27.7, 28.2, 32.7, 33.5, 35.5, 37.2, 40.2, 46.4, 56.2, 75.1, 81.8, 169.3, 170.4, 173.5.

2.5. (13S,14S)-14-Acetoxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstan-17-one (8)

A solution of KOAc (2.76 g, 28 mmol) in water (0.5 ml) was added to a stirred solution of diacetate **7** (110 mg, 0.28 mmol) in acetone (5 ml). This was followed by treatment with a 15% solution of TiCl$_3$ in water (2.80 ml, 2.80 mmol). The mixture was stirred for 2 h, then filtered,

diluted with water, and extracted with EtOAc and Et$_2$O. The combined extracts were dried (Na$_2$SO$_4$) and evaporated, and the residue was chromatographed on silica gel (hexane:EtOAc, 3:1) to give the acetoxy ketone **8** (50 mg, 52%) as an oil. IR (cm^{-1}): 1740, 1715, 1460, 1380, 1255, 1100, 1030. ^{1}H NMR δ: 0.38–0.46 (m, 1H, 4-H), 0.60–0.68 (m, 1H, 4-H), 0.94 (s, 3H, 19-H), 1.06 (d, $J = 7$ Hz, 3H, 18-H), 2.04 (s, 3H, OAc), 2.81 (m, 1H, 6-H), 3.28 (s, 3H, OMe), 5.38 (d, $J = 7$ Hz, 1H, 14-H). ^{13}C NMR δ: 12.9, 14.8, 18.5, 21.5, 21.8, 24.7, 27.1, 28.9, 32.1, 33.5, 35.4, 37.2, 39.2, 39.7, 46.4, 47.5, 56.2, 75.4, 81.7, 170.7, 218.7. HRMS calculated for C$_{22}$H$_{35}$O$_4$ [M+H]$^+$: 363.2535; found: 363.2516.

3. Results and discussion

Our first experiments with iodo diketone **2** showed that this compound was prone to an easy loss of iodine, followed by an aldol reaction of the intermediate **3** to give the 14β-alcohol **4** (Scheme 2). Earlier, this sequence was suggested for 14α-hydroxy-17-ketones as a convenient method to invert the stereochemistry at C-14 [12]. The reduction of **2** with various reagents, its treatment with base, and its attempts to protect the carbonyl group(s), all led to formation of hydroxy ketone **4**. Only radical dehalogenation with Bu$_3$SnH resulted in diketone **3** in a good yield (70%) together with the cyclization product **4** (14%). However, isomerization at C-13 accompanied the dehalogenation, which made the synthetic value of this reaction doubtful.

A good result was achieved by treatment of iodo ketone **2** with hydroxylamine. The reaction led to oximation of the 17-keto group with simultaneous deiodination at C-13 to give **5** in 65% yield. Hydride reduction of **5** gave alcohol **6**. It is worth mentioning that both transformations were stereoselective. The unambiguous assignment of the stereochemistry at C-13 and C-14 in **6** was provided by a single-crystal X-ray diffraction study, which showed that the reductive
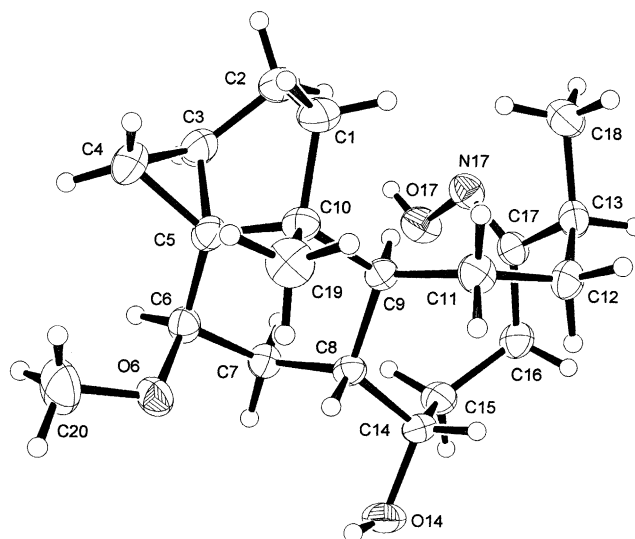

Fig. 1. ORTEP [22] view of (13S,14S)-14-hydroxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstan-17-one 17-oxime **6**. Displacement ellipsoids are drawn at 40% probability level.

deiodination of **2** with NH$_2$OH had proceeded with inversion of the configuration at C-13 (Fig. 1, Table 1).

Treatment of oximes with trivalent titanium is often used to transform these compounds into their parent ketones [20]. However, in our case, the reaction of **6** with TiCl$_3$ led to the formation of unidentified products. The use of oxime O-acetates has been described for the transformation of sensitive ketoximes into ketones [21]. Acetylation of hydroxy oxime **6** gave the diacetate **7** (Scheme 2), and treatment of this compound with TiCl$_3$ indeed led to the desired acetoxy ketone **8**.

In summary, a new synthesis of 13,14-seco steroids has been developed via the acetoxy ketone **8**. In this compound, the keto group at C-17 and the acetoxy group at C-14 can be modified independently, thus allowing for various transformations into a variety of substituted 13,14-seco steroids.
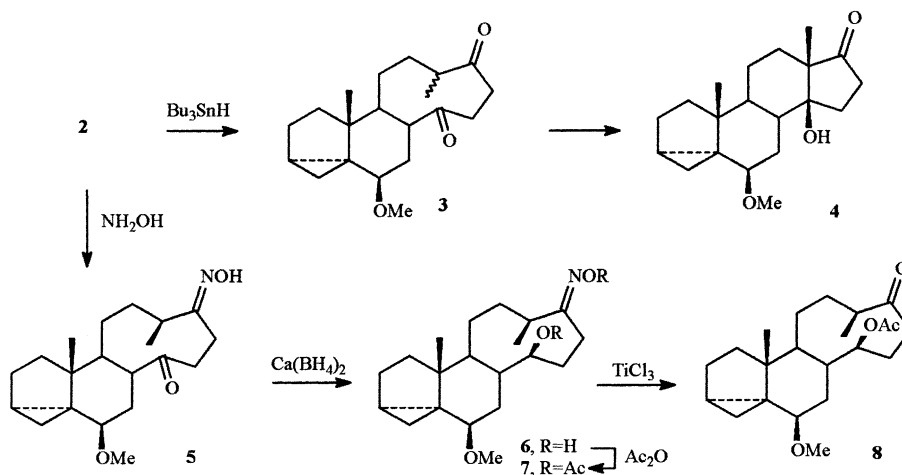
Scheme 2.

Table 1
Crystal data and structure refinement for (13*S*,14*S*)-14-hydroxy-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androstan-17-one 17-oxime **6**

Empirical formula	$C_{20}H_{33}NO_3$
Formula weight	335.47
Temperature	293(2)K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 7.669(1)$ Å; $\alpha = 90°$
	$b = 9.015(1)$ Å; $\beta = 90°$
	$c = 26.536(4)$ Å; $\gamma = 90°$
Volume	1834.6(4) Å^3
Z	4
Density (calculated)	1.215 mg m^{-3}
Absorption coefficient	0.080 mm^{-1}
$F(000)$	736
Crystal size	$0.62 \times 0.52 \times 0.34$ mm^3
Theta range for data collection	1.53–30.06°.
Index ranges	$0 \le h \le 10$, $0 \le k \le 12$, $-1 \le l \le 37$
Reflections collected	3191
Independent reflections	3169 [R(int) = 0.0091]
Completeness to theta = 30.06°	100.0%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3169/0/222
Goodness-of-fit on F^2	1.046
Final R indices ($I > 2$sigma(I)]	$R1 = 0.0367$, w$R2 = 0.0975$
R indices (all data)	$R1 = 0.0437$, w$R2 = 0.1033$
Largest diff. peak and hole	0.160 and -0.145 e.Å^{-3}

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