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# The Crystal Structures of the $\alpha$ - and $\beta$ -Diastereomers of 4,5-Epoxy-cholestan-3-one

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**Abstract** The  $\alpha$  and  $\beta$ -diastereomers of 4,5-epoxy-cholestan-3-one were obtained by epoxidation of cholest-4en-3-one with H<sub>2</sub>O<sub>2</sub> in basic media. The  $\alpha$ -diastereomer **2a** shows a monoclinic crystal system with dimension of cell unit: a = 11.6088(15), b = 6.3272(8), c = 16.164(2) Å;  $\beta$  = 94.040(11)° and *trans* A/B, B/C and C/D ring junctions and the  $\beta$ -diastereomer **2b** has a orthorhombic crystal system with dimension of cell unit: a = 9.0542(4), b = 10.6737(5), c = 24.9723(9) Å and *cis* A/B, *trans* B/C and *trans* C/D rings junctions.

**Graphical Abstract** The crystal structures of 4,5-epoxy- $5\alpha$ -cholestan-3-one (**2a**) and 4,5-epoxy- $5\beta$ -cholestan-3-one (**2b**) are described.

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## Introduction

Steroids bearing the 4,5-epoxy-3-oxo moiety are of special utility as synthetic precursors of a wide variety of poly-functional derivatives [1–6]. As a part of our program on the synthesis of potentially bioactive steroids, we have become interested on the unambiguous structural characterization of different 4,5-epoxy-3-oxo steroids that are being employed as starting materials in different synthetic protocols. Herein we report on the crystal structures of the  $\alpha$  and  $\beta$  diastereomers of 4,5-epoxy-cholestan-3-one.

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### Experimental

Reactions were monitored by TLC on ALUGRAM<sup>®</sup> SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1 % solution of vanillin in 50 % HClO<sub>4</sub> and heated until color developed. Melting points were measured on a Melt-Temp II apparatus. NMR spectra were recorded in CDCl<sub>3</sub> solutions in a Varian INOVA 400 spectrometer using the solvent signal as references. NMR signals assignments were carried out with the aid of a combination of 1D and 2D NMR techniques that included <sup>1</sup>H, <sup>13</sup>C, COSY, Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Correlation (HSOC) and Heteronuclear Multiple Bond Correlation (HMBC). All 2D NMR spectra were recorded using the standard pulse sequences and parameters recommended by the manufacturer and were processed employing the MestreNova NMR processing program (see http://mestrelab.com/).

4,5-epoxy-5 $\alpha$ -cholestan-3-one (2a) and 4,5-epoxy-5 $\beta$ cholestan-3-one (2b) Methanol (100 mL) 10 % p/v NaOH solution (5.6 mL) and 30 % H<sub>2</sub>O<sub>2</sub> (11.2 mL) were added in this order to a solution of the  $\alpha,\beta$ -unsaturated ketone 1 (7.28 g, 20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and the resulting mixture was stirred for 72 h at room temperature. The mixture was neutralized with 10 % aqueous acetic acid solution, 10 % aqueous Na<sub>2</sub>SO<sub>3</sub> solution (40 mL) was added and the resulting mixture was stirred for 20 min. Evaporation of the organic solvent under vacuum (caution!! abundant spume is produced) produced a solid that was filtered off and washed with water to afford the mixture of the epoxides 2a and 2b (4.89 g). The mother liquor where extracted with ethyl acetate  $(3 \times 150 \text{ mL})$  and the organic layer was washed with water (3  $\times$  150 mL), brine (100 mL) dried (anh., Na<sub>2</sub>SO<sub>4</sub> and evaporated to afford and additional amount (0.96 g) of the mixture of the epoxides 2a and 2b. Total yield 5.85 g (73 %). Recrystallization from hexane/ethyl acetate 9/1 afforded an analytical sample of the epoxide 2b while chromatographic separation employing hexane/ethyl acetate 9/1 as eluent followed by crystallization from hexane, afforded the analytical sample of 2a.

#### 4,5-Epoxy-5α-cholestan-3-one (2a)

Mp. 118 °C (from hexane–ethyl acetate) 123–124 °C [5]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 3.03 (s, 1H, H-4 $\beta$ ), 2.39 (ddd, J = 19.6, 7.2, 1.2 Hz, 1H, H-2 $\alpha$ ), 2.24 (dd, J = 7.2, 4.3 Hz, 1H, H-2 $\beta$ ), 1.05 (s, 3H H-19), 0.91 (d, J = 6.5 Hz, 3H, H-21), 0.87 (d, J = 1.9 Hz, 3H, H-26), 0.86 (d, J = 1.9 Hz, 3H, H-27), 0.69 (s, 3H, H-18). <sup>13</sup>C NMR (100.52 MHz)  $\delta$  ppm: 29.1 C-1, 33.1 C-2, 207.2 C-3, 62.9 C-4, 70.3 C-5, 29.8 C-6, 29.0 C-7, 35.4 C-8, 50.7 C-9, 36.7 C-10, 21.4 C-11, 39.7 C-12, 42.5 C-13, 55.6 C-14, 23.8 C-15, 28.2 C-16, 56.2 C-17, 12.0 C-18, 16.5 C-19, 35.8 C-20, 18.7 C-21, 36.1 C-22, 24.2 C-23, 39.5 C-24, 28.0 C-25, 22.8 C-26, 22.6 C-27.

#### 4,5-Epoxy-5β-cholestan-3-one (2b)

Mp. 118–119 °C (from hexane–ethyl acetate) 118–119 °C [5]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.96 (s, 1H, H-4 $\alpha$ ), 2.28 (ddd, J = 19.4, 5.9, 2.2 Hz, 1H, H-2 $\alpha$ ), 2.14 (dd, J = 13.4, 6.5 Hz, 1H, H-2 $\beta$ ), 1.14 (s, 3H, H-19), 0.89 (d, J = 6.5 Hz, 3H, H-21), 0.86 (d, J = 1.8 Hz, 3H, H-26), 0.85 (d, J = 1.8 Hz, 3H, H-27), 0.68 (s, 3H, H-18). <sup>13</sup>C NMR (100.52 MHz)  $\delta$  ppm: 26.1C-1, 32.6 C-2, 206.9 C-3, 62.7 C-4, 70.5 C-5, 29.9 C-6, 30.4 C-7, 35.0 C-8, 46.4 C-9, 37.2 C-10, 21.5 C-11, 39.4 C-12, 42.6 C-13, 55.8 C-14, 23.8 C-15, 28.1 C-16, 56.1 C-17, 12.0 C-18, 19.0 C-19, 35.7 C-20, 18.6 C-21, 36.1 C-22, 24.2 C-23, 39.5 C-24, 28.0 C-25, 22.8 C-26, 22.5 C-27.

## X-ray Crystallography

Suitable single crystals of compounds **2a** and **2b** respectively obtained by slow evaporation of hexane and hexane/ethyl acetate solutions, were mounted on a glass fiber in the goniometer head with a crystal-to-detector distance of 55.00 mm and crystallographic data were collected at 130 K with an Oxford Diffraction Gemini "A" diffractometer ( $\lambda_{MoK\alpha} = 0.71073$  Å, monochromator: graphite) with a CCD area detector. The collected data set consisted of 5 runs of 417 frames of intensity (1° in  $\omega$ ) for **2a** and 3 runs of 165 frames of intensity (1° in  $\omega$ ) for **2b**. The double pass method of scanning was used to exclude any noise. The collected frames were integrated by using an orientation matrix determined from the narrow frame scans.

CrysAlisPro and CrysAlis RED software packages [7] were used for data collection and integration. Analysis of the integrated data did not reveal any decay. Final cell parameters were determined by a global refinement of 2229 ( $3.458^{\circ} < \theta < 30.142^{\circ}$ ) and 3906 ( $3.781^{\circ} < \theta < 29.299^{\circ}$ ) reflections for **2a** and **2b** respectively. Collected data were corrected for absorption effects by analytical numeric absorption [8] using a multifaceted crystal model based on expressions upon the Laue symmetry with equivalent reflections. Structure solution and refinement were carried with the programs SHELXS-2014 and SHELXL-2014 respectively [9]. WinGX v2014.1 software [10] was used to prepare material for publication.

Full-matrix least-squares refinement was carried out by minimizing  $(Fo^2 - Fc^2)^2$ . All nonhydrogen atoms were anisotropically refined. Hydrogen atoms attached to

## Table 1 Crystal data and structure refinement for 2a and 2b compounds

| Identification code                      | 2a   | 2b  |
|--|--|---|
| Empirical formula                        | $C_{27} H_{44} O_2$                                  | C <sub>27</sub> H <sub>44</sub> O <sub>2</sub>          |
| CCDC deposition Number                   | 1417471  | 1417470   |
| Formula weight                           | 400.62   | 400.62  |
| Temperature                              | 130(2) K   | 130(2) K  |
| Wavelength                               | 0.71073 Å  | 0.71073 Å   |
| Crystal system                           | Monoclinic   | Orthorhombic  |
| Space group                              | P 2 <sub>1</sub>                                     | P 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>          |
| Unit cell dimensions                     | a = 11.6058(14)  Å                                   | a = 9.0542(4)  Å  |
|  | b = 6.3296(8)  Å                                     | b = 10.6737(5)  Å                                       |
|  | c = 16.1643(17)  Å                                   | c = 24.9723(9)  Å                                       |
|  | $\beta = 94.008(10)^{\circ}$                         |   |
| Volume                                   | 1184.5(2) Å <sup>3</sup>                             | 2413.37(18) Å <sup>3</sup>                              |
| Z  | 2  | 4   |
| Density (calculated)                     | 1.123 mg/m <sup>3</sup>                              | 1.103 mg/m <sup>3</sup>                                 |
| Absorption coefficient                   | $0.068 \text{ mm}^{-1}$                              | $0.067 \text{ mm}^{-1}$                                 |
| F(000)                                   | 444  | 888   |
| Crystal size                             | $0.30 \times 0.14 \times 0.09 \text{ mm}^3$          | $0.27 \times 0.34 \times 0.53 \text{ mm}^3$             |
| Theta range for data collection          | 3.458–30.142°  | 3.781–29.299°   |
| Index ranges                             | $-14 \le h \le 14, -8 \le k \le 8, -20 \le l \le 22$ | $-12 \le h \le 11,  -8 \le k \le 13,  -33 \le l \le 34$ |
| Reflections collected                    | 12,993   | 10,466  |
| Independent reflections                  | 5364 [R(int) = $0.0647$ ]                            | 5347 [R(int) = $0.0330$ ]                               |
| Completeness to theta = $25.242^{\circ}$ | 99.7 %   | 99.6 %  |
| Refinement method                        | Full-matrix least-squares on F <sup>2</sup>          | Full-matrix least-squares on F <sup>2</sup>             |
| Data/restraints/parameters               | 5364/586/396   | 5347/42/264   |
| Goodness-of-fit on F <sup>2</sup>        | 1.023  | 1.018   |
| Final R indices [I > 2sigma(I)]          | R1 = 0.0582, wR2 = 0.1108                            | R1 = 0.0472, wR2 = 0.0994                               |
| R indices (all data)                     | R1 = 0.1092, wR2 = 0.1488                            | R1 = 0.0581, wR2 = 0.1080                               |
| Absolute structure parameter             | 0.4(10)  | 1.2(7)  |
| Extinction coefficient                   | n/a  | n/a   |
| Largest diff. peak and hole              | 0.169 and $-0.213$ e Å <sup>-3</sup>                 | 0.216 and $-0.265$ e Å $^{-3}$                          |



i) H<sub>2</sub>O<sub>2</sub>, NaOH, CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>





Fig. 1 ORTEP drawing of the asymmetric unit of 2a with the thermal ellipsoids drawn at the 50 % of probability

| 2a                          |                 |            | 2b               |              |  |
|-----------------------------|-----------------|------------|------------------|--------------|--|
| Bond                        | Dis             | stance (Å) | Bond             | Distance (Å) |  |
| C-1a–C-10a                  | 1.4             | 8(3)       | C-1-C-2          | 1.524(4)     |  |
| C-1a–C-2a                   | 1.5             | 1(3)       | C-1-C-10         | 1.533(3)     |  |
| C-2a-C-3                    | 1.57(2)         |            | C-2-C-3          | 1.502(3)     |  |
| C-3-O-1                     | 1.225(4)        |            | C-3-O-1          | 1.215(3)     |  |
| C-3C-4                      | 1.468(6)        |            | C-3-C-4          | 1.491(3)     |  |
| C-40-2                      | 1.458(4)        |            | C-4–O-2          | 1.461(2)     |  |
| C-4C-5                      | 1.477(5)        |            | C-4-C-5          | 1.481(3)     |  |
| C-5-O-2                     | 1.458(4)        |            | C-5–O-2          | 1.449(2)     |  |
| C-5–C-10a                   | 1.584(9)        |            | C-5-C-10         | 1.527(3)     |  |
| C10a-C-19                   | 1.4             | 73(12)     | C-10-C-19        | 1.540(3)     |  |
| C-13-C-18                   | 1.5             | 25(5)      | C-13-C-18        | 1.534(3)     |  |
| C-16a–C-17                  | 1.4             | 77(13)     | C-16-C-17        | 1.559(3)     |  |
| C-17–C-20a                  | 1.5             | 00(17)     | C-17-C-20        | 1.545(3)     |  |
| C-20a-C-21a                 | 1.50(3)         |            | C-20-C-21        | 1.533(3)     |  |
| C-24a–C-25a                 | 1.5             | 32(12)     | C-24-C-25        | 1.532(3)     |  |
| C-25a–C-26a                 | C-26a 1.502(15) |            | C-25–C-26a       | 1.553(9)     |  |
| Bond                        |                 | Angle (°)  | Bond             | Angle (°)    |  |
| C10a–C1a–C2a                |                 | 115.2(17)  | C-2-C-1-C-10     | 114.8(2)     |  |
| C-1a-C-2a-C-3               |                 | 110.4(15)  | C-3-C-2-C-1      | 114.0(2)     |  |
| O-1-C-3-C-4                 |                 | 120.3(4)   | O-1-C-3-C-4      | 119.9(2)     |  |
| O-1–C-3–C-2a                |                 | 122.0(8)   | O-1-C-3-C-2      | 122.5(2)     |  |
| O-2-C-4-C-3                 |                 | 115.0(3)   | O-2-C-4-C-5      | 59.02(12)    |  |
| O-2-C-4-C-5                 |                 | 59.6(2)    | O-2-C-4-C-3      | 115.58(18)   |  |
| C-3C-4C-5                   |                 | 120.7(3)   | C-5-C-4-C-3      | 121.83(19)   |  |
| C-16a–C-17–C-20a 1          |                 | 112.0(9)   | C-20-C-17-C-16   | 112.58(16)   |  |
| C-22a–C-24a–C-25a 114.1     |                 | 114.1(9)   | C-23-C-24-C-25   | 114.35(19)   |  |
| C-26a-C-25a-C-27a 105.9(10) |                 | 105.9(10)  | C-27a-C-25-C-26a | 113.3(3)     |  |

Table 2 Selected bond lengths [Å] and angles [°] for 2a and 2b

carbons were placed in geometrically idealized positions and refined as riding on their parent atoms, with C–H = 0.97-1.00 Å with Uiso (H) = 1.2Ueq(C) for methylene and methyne groups, and Uiso (H) = 1.5 Ueq(C) for methyl groups.

In the crystal structure almost all atoms of 2a show disorder over two sites with occupancies 0.65:0.35, while in **2b** C-26 and C-27 shows disorder over two sites with occupancies 0.54:0.46. Crystal data and experimental details of the structure determination are listed in Table 1.

The absolute configuration of the title compounds can be assumed without risk, as that known for the starting material considering that the synthetic transformations carried out do not affect the absolute configuration of the chiral centres in the naturally occurring steroid framework.

#### **Results and Discussion**

Treatment of a methanol/CH<sub>2</sub>Cl<sub>2</sub> solution of the  $\alpha$ , $\beta$ -unsaturated ketone **1** with H<sub>2</sub>O<sub>2</sub> and NaOH afforded 73 % yield of a mixture of the diasteromeric epoxides **2a** and **2b** that were separated by fractional crystallization from hexane/ethyl acetate and column chromatography (Scheme 1).

In compound **2a** (see Fig. 1) the A/B, B/C and C/D rings junctions are *trans* and the steroid skeleton bears  $\beta$ -oriented the C-18 and C-19 methyl groups attached to C-10 and C-13 respectively. Almost all carbon atoms are disordered over two sites with occupancies 0.65:0.35. Selected bond lengths and angles for the higher occupancy are presented in Table 2.

A comparison of the positions of the atoms with higher occupancy in the ring A of **2a** with the equivalent fragment







Fig. 3 Crystal structure of 2b with the thermal ellipsoids drawn at 50 % of probability

| Rings | 2b versus 2b |
|-------|--------------|
| А     | 0.0389       |
| В     | 0.0189       |
| С     | 0.0138       |
| D     | 0.0156       |
|       |              |

(C-1–C-2, C-2–C-3, C-3–C-4 and C-4–C-5) of the starting material cholest-4-en-3-one (1) [11] shows differences in the bond lengths and torsion angles that may be attributed to the disorder over two sites on the crystal structure of **2a** that lacks the double bond present in the staring material (1), and the distortion exerted by epoxy moiety (rms deviation of fitted atoms = 0.0604 Å in **2a** vs rms deviation of fitted atoms = 0.0316 Å in **1**). The A ring of **2a** assumes a distorted half-chair conformation [puckering parameters: [12] Q = 0.51(2) Å,  $\theta = 56.7(19)$ ,  $\varphi = 349.8(18)^\circ$ , if the calculation starts from C-1 to C-10 and proceeds in counterclockwise direction]. Asymmetry parameters [13] are:  $\Delta C_2(C-2-C-3) = 64.1(19)$ ,  $\Delta C2(C-3-C-4) = 24(2)$ ,  $\Delta C2(C-4-C-5) = 40.6(16)$ ,  $\Delta Cs(C-3) = 41.3(16)$  and  $\Delta Cs(C-5) = 49.3(14)^\circ$ .

B ring assumes a slightly distorted chair conformation [puckering parameters Q = 0.617(12) Å,  $\theta = 12.5(10)$ ,  $\varphi = 208(5)^{\circ}$ , if the calculation starts from C-5 to C-10 and proceeds in counterclockwise direction]. Rotational symmetry is dominant; a pseudo-C2 axis bisects the C-6–C-7 bond. Asymmetry parameters are:  $\Delta C_2(C-6-C-7) = 15.3$   $(11)^{\circ}$  and  $\Delta C_s(C-7) = 12.7(8)^{\circ}$  and the average magnitude of the torsion angles is 57.0(4)°.

Ring C also assumes a slightly distorted chair conformation [puckering parameters Q = 0.602(18) Å,  $\theta =$ 11.9(17) and  $\phi = 288(8)^{\circ}$  if the calculation starts from C-8 to C-14 and proceeds in clockwise direction]. The fivemembered D ring shows a twisted conformation on C-13– C-14 [puckering parameters  $q^2 = 0.43(1)$  Å and  $\phi_2 =$ 195.5(19)°]. Asymmetry parameters [14] are:  $\Delta = 713.8$ ,  $\tau_m = 45.5(8)$ ,  $\Delta Cs(C-13) = 14.9(12)$  and  $\Delta C2(C-13,$ C-14) = 4.0(12)°.

In the crystal structure there is one interaction C–H…O of hydrogen bond type. Each molecule features one interaction C-19–H-19b…O-2 (2.42 Å) to its neighbor related by the symmetry operation -x, -1/2 + y, -z: forming the  $C_1^1(7)$  motif [15]. This intermolecular interaction is observed along the b-c plane and leads to infinite laminar array in the supramolecular network (see Fig. 2).

For **2b**, the asymmetric unit consist of one unit of 4,5epoxy-5 $\beta$ -cholestan-3-one with C-26 and C-27 disordered over two sites with occupancies 0.54:0.46. Selected bond lengths and angles for the higher occupancy are presented in Table 2. Compound **2b** has *cis* A/B and *trans* B/C and C/D rings junctions. The steroid skeleton bears the  $\beta$ -oriented C-18 and C-19 methyl groups attached to C-10 and C-13 respectively (Fig. 3). The bond lengths C-1–C-2, C-2–C-3 and the nearly planar grouping C-2, C-3, C-4, C-5, O-1 are similar to those of the starting material **1** (rms deviation of fitted atoms = 0.0371 Å for **2b** versus rms



Fig. 4 Crystal array of 2b; view along the axis b; with perspective to the plane formed by a and c axes emphasizing the  $R_2^2(9)$  and  $R_2^2(12)$  motifs

deviation of fitted atoms = 0.0316 Å in **1**). However, there are differences in the torsion angles C-1–C-2–C-3–C-4 and C-2–C-3–C-4–C-5 attributed to the distorting effect of epoxide moiety in compound **2b**, that lacks the C-4–C-5 double bond present in the cholest-4-en-3-one (**1**).

In order to establish differences between 2b and the previously reported data for this compound (2b'), that was collected at room temperature [16], a least-squares overlay analysis of the structures by pairs was performed with the Mercury program [17] (Table 3). The obtained data evidence small differences in the A ring with a rms 0.0389 and in the C-23–C-24–C-25–C-26 torsion angle with 171.30 for 2b and 163.85° for 2b'.

In compound **2b**, the A ring assumes a twisted conformation on C-1–C-2 [puckering parameters: Q = 0.458(2) Å,  $\theta = 122.9(3)$ ,  $\varphi = 169.0(3)^{\circ}$ , if the calculation starts from C-1 to C-10 and proceeds in counterclockwise direction. Asymmetry parameters are:  $\Delta C_2$ (C-2– C-3) = 55.1(3),  $\Delta C2$ (C-3–C-4) = 19.8(3),  $\Delta C2$ (C-4–C-5) = 35.4(3),  $\Delta Cs$ (C-3) = 35.2(2) and  $\Delta Cs$ (C-5) = 42.6(2)°.

The B ring assumes a perfect chair conformation [puckering parameters Q = 0.577(2) Å,  $\theta$  = 2.3(2),  $\varphi$  = 327(6)°, if the calculation starts from C-5 to C-10 and proceeds in counterclockwise direction. Rotational symmetry is dominant; a pseudo-C2 axis bisects the C-6–C-7 bond. Asymmetry parameters are:  $\Delta C_2$ (C-6–C-7) = 4.4(2)° and  $\Delta C_s$ (C-7) = 3.5(2)° and the average magnitude of the torsion angles is 56.2(8)°.

Ring C also assumes a chair conformation [puckering parameters Q = 0.582(2) Å,  $\theta = 4.8(2)$  and  $\phi = 272(2)^{\circ}$  if the calculation starts from C-8 to C-14 and proceeds in clockwise direction].

The five-membered D ring shows a twisted conformation on C-13–C-14 [puckering parameters  $q^2 = 0.450(2)$  Å and  $\phi_2 = 194.1(3)^\circ$ ]. Asymmetry parameters are:  $\Delta =$ 713.8,  $\tau_m = 45.8(1)$ ,  $\Delta Cs(C-13) = 14.5(2)$  and  $\Delta C2(C-13)$ , C-14) = 4.2(2)°.

The crystal structure of 2b (Fig. 4) shows three intermolecular contacts of hydrogen bond type (C-14–H-14…O- 1 2.70, C-7–H-7b····O2 2.69 Å and C-19–H-19a···O1 2.63 Å). These intermolecular interactions with symmetry operations 1/2 + x, 3/2 - y, -z and -1/2 + x, 3/2 - y, -z show  $R_2^2(9)$  and  $R_2^2(12)$  motifs and lead to infinite laminar array along the *a*–*c* plane.

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