

**(R)-5-[(1R,2R)-1-Ethyl-2-(4-oxocyclohexyl)butyl]oxepan-2-one,
an Enantiopure ‘Pseudosteroid’**

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The title compound $C_{18}H_{30}O_3$ represents an optically pure member of a class of ‘pseudosteroids’, *i. e.* perhydrostilbene derivatives which mimic steroidal androgens (in the way like hexestrols or stilbestrols serve to substitute natural estrogens). The molecule **2** is characterized by three consecutive chiral centers leading to eight possible stereoisomers including four diastereomers. All enantiomers have been separated and their biological profile has been determined. As the result of the crystal structure presented here the two symmetry independent molecules display the configuration *R,R,R* at the centers of chirality.

Key words: Pseudosteroid, Perhydrostilbenes,
Androgenic Activity, Crystal Structure

Results and Discussion

Since 1943 several investigations have been undertaken to synthesize nonsteroidal compounds with androgenic activity [1] – in analogy to the estrogens. First of all the perhydro derivatives *meso-1* and *rac-1* were examined. They lack any biological activity. Later on a successful resolution of *rac-1* by means of the crystalline amine bisulfite adduct with L-(-)- α -phenylethylamine led to the pure *3R,4R* antipode [2]. A third chiral center was introduced by statistical Baeyer-Villiger oxidation on *3R,4R-1*. The mixture of diastereomers **2** formed in 46% yield had to be submitted to several thin layer purifications until the more polar needles (m. p. 129–130 °C) could be separated from rocky crystals (m. p. 99–100 °C).

The enantiopure diastereomeric lactones **2a, b** displayed inverse signs of optical rotations. The higher

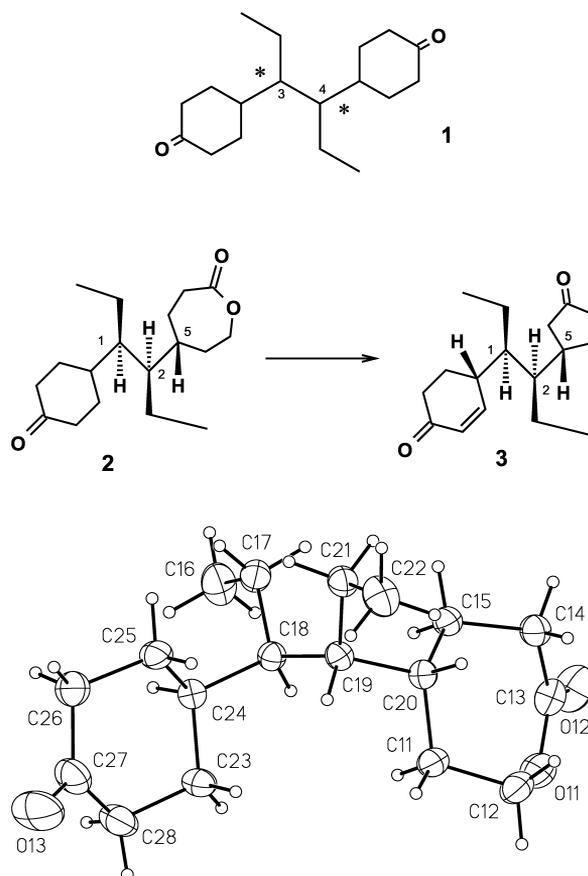


Fig. 1. The crystal structure of $C_{18}H_{30}O_3$ (**2**) showing 25% probability displacement ellipsoids. Only one of two symmetry independent molecules in the unit cell is shown. For the atom numbering of the second molecule the first digit has to be increased by 2. H atoms were calculated and are displayed as circles with a radius of 0.1 Å.

melting one showed $[\alpha]_{578} = +26^\circ$, the lower melting one $[\alpha]_{578} = -37^\circ$ ($T = 25^\circ\text{C}$). The question arose which one corresponded to the *R* and *S* configuration, respectively, at the newly introduced center C-5. The answer is given by the crystal structure presented here. The low melting isomer **2** crystallizes in the monoclinic space group $P2_1$ with $a = 8.310(3)$, $b = 11.956(2)$, $c = 9.214(2)$ Å, and $\beta = 111.57(2)^\circ$, $D_m = 1.14\text{ Mg m}^{-3}$, $Z = 2$, but its structure could not be solved. Therefore, the structure of the higher melting crystals had to be determined [3, 4] which contains two symmetry independent molecules per asymmetric unit (space group $P2_12_12_1$, $Z = 8$). One of these is displayed in Fig. 1. The (1*R*,2*R*,5*R*)-configuration

Table 1. Crystal data and structure refinement of (1*R*, 2*R*, 5*R*)-**2**.

Empirical formula	C ₁₈ H ₃₀ O ₃
Formular weight	294.42
Crystal system; space group	orthorhombic; <i>P</i> 2 ₁ 2 ₁ 2 ₁
	<i>a</i> = 9.048(2) Å
	<i>b</i> = 15.799(3) Å
	<i>c</i> = 24.331(5) Å
	<i>V</i> = 3478.1(12) Å ³
Formular units per cell, <i>Z</i>	8
Calculated density, <i>D_x</i>	1.125 Mg m ⁻³
Crystal size	0.15 × 0.25 × 0.50 mm ³
Absorption coefficient, μ(Cu-Kα)	0.586 mm ⁻¹
<i>F</i> (000)	1296
Θ Range for data collection	3.34° to 57.53°
Range for <i>hkl</i>	0–9, 0–17, 0–26
Independent reflections	2694
Reflections with <i>I</i> > 2σ(<i>I</i>)	2357
Data:parameter ratio	7.1
Goodness-of-fit on <i>F</i> ²	1.023
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0442; <i>wR</i> 2 = 0.1171
<i>R</i> Indices (all data)	<i>R</i> 1 = 0.0502; <i>wR</i> 2 = 0.1224
Largest diff. peak and hole	0.210 and –0.136 e/Å ³

can be attributed to this structure, since the (3*R*, 4*R*) antipode of **1** served as starting material [5, 6]. The geometry of the two symmetry independent molecules of the asymmetric unit does not deviate significantly from averaged values. The rings are connected equatorially and reveal a chair conformation. Three weak hydrogen bonds of the type C–H...O with distances C...O between 3.322(5) and 3.484(5) Å and angles at the H atom in the range of 147 to 164° connect the molecules. Later on **2** was transformed for physiological assays into the target molecule **3** containing four contiguous chiral centers, but the separation of the diastereomers failed. This diastereomeric mixture **3**

– although well defined – disclosed a biological activity of about 25% of androsterone.

Experimental Section

According to a published procedure [7] the (-)-(3*R*, 4*R*)-diketone **1** was treated with 13% acetic peracid over night at 40 °C, leading to 40% starting material, 12% dilactone, and 46% crude product **2**. To our knowledge this means the first application of a statistical Baeyer-Villiger reaction. Full experimental details are given in [5]. Boiling of the high melting diastereomer in ethanol with sulfuric acid transformed it into the corresponding hydroxy ester. Very short treatment of this material with CrO₃ in acetone [8] resulted in the appropriate ester acid with 92% yield. The carboxylic acid function by introduction of excess diazomethane was transformed into a diester, followed by protection of the remaining ketone function by means of ethyleneglycol. Now the stage was set for Dieckmann cyclisation. Subsequent ester decarboxylation (heating in pyridine for 5 h), and deprotection led to the dihydro derivative of **3**.

Crystallographic data of **2** are presented in Table 1. The intensities of the reflections have been measured at room temperature with a diffractometer Syntex P2₁ using monochromatized Cu-Kα radiation and an ω-scan. The structure has been solved by direct methods [3] and refined in the usual way [4]. All H atoms have been added in calculated positions and were included in the refinement in a riding mode. Positional and atomic displacement parameters have been deposited with the Cambridge Crystallographic Data Centre, CCDC-281176. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336-033; e-mail for inquiry: data_request@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk/data_request/cif).

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