SYNTHESIS OF DESOXYANTERIDIOL, A LANOSTANE ANALOG OF A FUNGAL SEX HORMONE

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UDC 542.91:547.92

The stereoselective synthesis of a δ-lactone, (22R)-3β-acetoxy-22-hydroxylanosta-8,24(31)-dien-32-oic acid (X), which is the first lanostane analog of the sex hormone of *Achlya* aqueous fungi, was carried out by means of 1,3-dipolar addition of nitrile oxides to lanostane olefin (I) through (22R)-isoxazoline (III) as a key intermediate.

The group of natural products bearing specific substituents and encompassing both steroids and triterpenoids are very rarely encountered. Such derivatives include vitanolides [1,2] and anteridiols [3], which contain a δ-lactone ring at C(22) in the side chain. These compounds hold interest for their anticarcnogenic and other useful biological properties. The major representatives of this group are steroids but two compounds with a lanostane skeleton have been isolated from natural sources [4,5]. Comparison of the biological properties of the two lactone types is interesting in regard to the relationship between structure and function. However, the very low concentration of these compounds in natural sources does not permit research on such a correlation. We have synthesized desoxyanteridiol with a lanostane skeleton from the 24-acid [6] by means of 1,3-dipolar cycloaddition of nitrile oxides, permitting the stereospecific introduction of oxygen functions into the steroid side chain [7]. 3β-Acetoxy-24,25,26,27-tetranorlanosta-8,22-diene (I), which is a terminal olefin readily formed upon the decarboxylation of 3β-acetoxy-25,26,27-trinorlanost-8-en-24-oic acid [8], was selected as the dipolarophile. Isopropylnitrile and benzonitrile oxides, obtained from the oximes of isobutanal and benzaldehyde in situ, were taken as the dipoles. The use of isopropylnitrile oxide gave (22S)- (II) and (22R)-3β-acetoxy-20-(3^1-isopropylisoxazoline-5^1-yl)-4,4,14-trimethylpregn-8-(9)-enes (III) in 20 and 62.6% yield, respectively. The use of benzonitrile oxide gave (22S)- (IV) and (22R)-3β-acetoxy-20-(3^1-phenylisoxazoline-5^1-yl)-4,4,14-trimethylpregn-8(9)-enes (V) in 13 and 61.5% yield, respectively (Scheme 1).

X-ray diffraction structural analysis indicated that (II) is the (22S) isomer [9]. The configuration of the C^{22} sites in the other isoxazolines was assigned on the basis of the form and position of the PMR signals for the 22-H and 18-CH_3 groups (Table 1). Thus, the signals for the 22-protons of isomers (III) and (V) are at δ4.85 and 4.64 ppm as one-proton triplets of doublets with coupling constants of 10 and 3.5 Hz. The chemical shifts of 18-CH_3 are at δ0.76 and 0.73 ppm. On the other hand, the chemical shifts for the 18-CH_3 groups in isomers (II) and (IV) are at δ0.68-0.67 ppm, while the multiplet form of the signals of the 22-protons is complicated in comparison with the form of the 22-protons of (III) and (V) since, as seen in an examination of molecular models, the 23-CH_2 protons, with which they are coupled, are not equivalent in isomers (II) and (IV).

Thus, steroids (II) and (IV) are the (22S) isomers, while (III) and (V) are the (22R) isomers. The PMR spectral data for pure (22S) and (22R) isomers permit us to determine their ratios. The (II)/(III) ratio is 1:3, while the (IV)/(V) ratio is 1:4.7 as determined by integration of the 18-CH_3 proton signals. Examination of the molecular model for the Δ^{22} system in (I) indicates equal probability for the approach of the electrophile from the side of the 21-CH_3 group and the side opposite to this group. Only the 16β-H atom may sterically hinder the approach from this β-region [8]. However, in the case of phenylnitrile oxide, when steric interactions play only a slight role, (22R) isomer (V) becomes predominant. The mixture of (II) and (III) upon reduction according to Akhrem et al. [10] in the presence of boric acid led to a 90% yield of the corresponding ketols (VI) and (VII)

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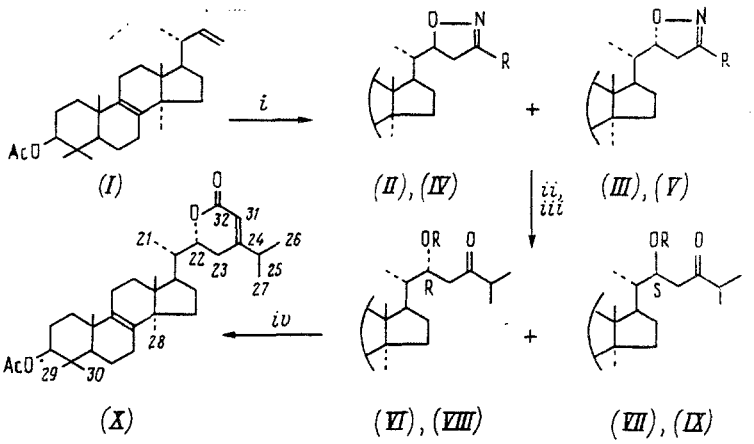
 0568-5230/91/4004-0864$12.50

Scheme 1



Reagents and reaction conditions: i) N-chlorosuccinimide, triethylamine, $CHCl_3$, RCH=N–OH; R = i-C_3H_7, Ph; ii) Raney Ni, H_3BO_3, MeOH–H_2O, THF, H_2; iii) Ac_2O, pyridine; iv) Zn, $BrCH_2CO_2Et$, 1:1 ether benzene, Δ 30 min; Ac_2O, Δ.
R = iC_3H_7 (II), (III), Ph (IV), (V), H (VI), (VII), Ac (VIII), (IX).

in 3:1 ratio. On the basis of the configuration for the C^{22} site in (II) and (III), we may assume that the predominant (less polar) product (VI) is the (22R) hydroxyketone (mp 211-212°C), while the minor (more polar) product (VII) is the (22S) alcohol [8]. The predominant 22-acetoxy-24-ketone (VIII) (mp 201°C) obtained according to ordinary acetylation of (VI) was transformed by the Reformatskii reaction using zinc and $BrCH_2CO_2Et$ with subsequent heating in acetic anhydride at reflux to unsaturated δ-lactone (X). The structure of (X) was supported by its mass spectrum (M^+ 524) and PMR spectrum indicating the (R) configuration at C^{22}. In particular, nuclear Overhauser effect experiments showed strong coupling between the protons of the side chain at C^{22} and C^{23} and the vinyl protons of the α,β-unsaturated δ-lactone ring. The data obtained (δ, ppm: 4.4 d.t, J = 13 and 3.5 Hz (22-H); 5.79 s (vinyl proton); 2.46 m (25-H), and 2.36 m (23-CH_2) are in complete accord with the data of Weihe and McMorris [3] for analogous steroidal α,β-unsaturated δ-lactones.

EXPERIMENTAL

The melting points were determined on a Koeffler block after recrystallization of the samples from ethyl acetate. The IR spectra were taken for KBr pellets or chloroform solution on a UR-20 spectrometer. The UV spectra were taken for chloroform solutions on a Unicam-700 spectrometer. The mass spectra were taken on a Varian MAT-311 mass spectrometer with direct sample inlet into the ion source at 70 eV. The PMR spectra were taken on Bruker WM-250 and WM-400 spectrometers. The chemical shifts were measured from TMS in $CDCl_3$. Thin-layer chromatography was carried out on silica gel 5/40μ (+13% gypsum) or Silufol R UV-254 with detection by 2% $Ce(SO_4)_2$ in 2 N H_2SO_4 upon heating and in UV light. The mixtures were separated on columns packed with silica gel 40/100μ in a nitrogen atmosphere.

Reaction of 3β-Acetoxy-24,25,26,27-tetranorlanosta-8,22-diene (I) with Isopropylnitrile Oxide. A solution of 414 mg (1 mmole) olefin [8] in 7 ml chloroform was added to a solution of 534 mg (4 mmoles) N-chlorosuccinimide in 20 ml chloroform, 0.03 ml pyridine, and 0.5 ml (4.5 mmoles) isobutanal oxime. After 6 h, 0.5 ml (6 mmoles) triethylamine in 5 ml $CHCl_3$ was added and stirred for 15 h. Then, an additional 234 mg N-chlorosuccinimide, 0.2 ml oxime, and 0.2 ml triethylamine were added. The reaction mixture was treated with water. The organic layer was dried over Na_2SO_4. The solvent was evaporated. Chromatogra-

TABLE 1. PMR, Mass, IR, and UV Spectral Data of Compounds (II)-(V) and (X).

Compound	PMR spectra δ, ppm, J, Hz						MS, m/z	IR spectrum, ν, cm^{-1}	Mp, °C
	18-H	22-H	23-H	25-H	19-H	4,4,14,21-CH_3			
(II)	0,68	4,67 m	2,63; 2,95 m	2,70 m	1,00	0,85–0,88	497 (M), 482 422	1260, 1380 1480, 1640 1735	249–250
(III)	0,73	4,64 t.d (10; 3,5)	2,58; 2,70 m.d (10)	2,70m	1,00	0,82–0,89	497 (M), 482 422	1260, 1380 1375, 1640 1730	255–258
(IV)	0,67	4,18 m	2,58; 2,80 m	–	0,98	0,82–0,91	531 (M), 516, 456	1370, 1650 1737	105–106
(V)	0,76	4,85 t.d (10; 3,5)	3,12 m.d (10.5)	–	1,02	0,88–0,90	531 (M), 516 456	1370, 1650 1740	210–215
(X)	0,76	4,40 t.d (13; 3,5)	2,36 m	2,46 m	1,01	0,87–0,90	524 (M), 509 449	1260, 1680 1710, 1730	148–150

phy gave 70 mg (I) and 330 mg of a mixture of isoxazolines (II) and (III). Crystallization from ethyl acetate gave (22S)-3β-acetoxy-20-(3^1-isopropylisoxazoline-5^1-yl)-4,4,14-trimethylpregn-8(9)-ene (II), mp 249-250°C. Crystallization of the mother liquor from DMSO gave (22R) isomer (III), mp 255-258°C. The mp of the mixture of isomers was 180-220°C. The (II)/(III) ratio in the mixture was 1:3.

Reaction of (I) with Benzonitrile Oxide. A sample of 0.146 ml (1 mmole) triethylamine was added dropwise over 4 h to a solution of 133.5 mg N-chlorosuccinimide, 0.03 ml pyridine, 121 mg (1 mmole) benzaldoxime, and 250 mg (0.6 mmole) steroid (I) in chloroform. Ordinary work-up and column chromatography using ether–hexane as the eluent gave 100 mg (I), 118 mg (V), and 25 mg (IV).

3β,22-Diacetoxy-22R-lanost-8(9)-en-24-one (VIII). A mixture of 150 mg (II) and (III) (in 1:3 ratio as indicated by PMR spectroscopy) in 10 ml 5:1 methanol–water and 10 ml THF, 75 mg H_3BO_3, and 15 mg Raney nickel was stirred for 10 h in a hydrogen stream and monitored by thin-layer chromatography. The mixture was filtered through Celite, washed with water, and extracted with CH_2Cl_2. The extract was washed with saturated aq. NaCl, dried over $MgSO_4$, and evaporated. Separation on a column using ether–hexane (8-10% ether) as the eluent gave 100 mg (VI), mp 211-212°C, and 30 mg (VII). Acetylation of (VI) under ordinary conditions gave 110 mg (VIII), mp 213-214°C.

3β-Acetoxy-22R-22-hydroxylanosta-8,24(31)-dien-32-oic Acid, δ-Lactone (X). A sample of 120 mg (VIII) in 6 ml 1:1 ether–benzene and iodine crystals was added to 60 mg activated zinc. Then, a sample of 0.1 ml ethyl bromoacetate was added at reflux under argon. The mixture was heated at reflux for 30 min and cooled. Then, 2% hydrochloric acid was added and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated. The residue was heated at reflux in 5 ml acetic anhydride and monitored by thin-layer chromatography. Chromatographic separation gave 45 mg (VIII) and 40 mg conjugate lactone (X), R_f = 0.63(4:1 ether–hexane), mp 148-150°C.

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