Russian Journal of Organic Chemistry, Vol. 40, No. 10, 2004, pp. 1456–1461. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 10, 2004, pp. 1506–1510.

Synthesis of 5α-Hydroxyecdysteroid Analogs Containing an Isoxazole Ring in the Side Chain

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Received January 23, 2004

Abstract—An analog of 5α-hydroxyecdysteroids having an isoxazole ring in the side chain was synthesized starting from pregnenolone through intermediate 20-hydroxy-20-(3-isopropyl-4,5-dihydroisoxazol-5-yl) derivative. α-Bromination of 6-oxo steroids was accompanied by elimination of the hydroxy group from C^{20} and migration of the double bond thus formed to the heteroring to afford the corresponding 20-isoxazolyl steroid.

Recent studies on the application of the nitrile oxide technique to the synthesis of steroids possessing a modified side chain gave important results. On the one hand, a large number of analogs of natural compounds (brassinosteroids, sapogenins, vitamin D precursors, etc.) having isoxazole or dihydroisoxazole ring in the side chain were obtained [1], and some of the prepared compounds were found to exhibit phytomodulating activity at very small concentrations (1–100 ppm) [2]. On the other hand, these analogs can be converted into steroids with polyfunctional side chains. For example, the side chains typical of such ecdysteroids as ponasterone and pterosterone C were built up for the first time with the use of 20-hydroxy-20-(4,5-dihydroisoxazolyl) derivatives [3]. It should be noted that total synthesis of these natural ecdysteroids has not been reported so far. Therefore, we focused on the preparation of ecdysteroids and their analogs on the basis of dihydroisoxazolyl derivatives. For this purpose, it was necessary to examine the behavior of the dihydroisoxazole ring therein in reactions leading to formation of the Δ^7-2β,3β,5α-trihydroxy-6-oxo moiety which is intrinsic to rings A and B in ecdysteroids. We previously showed that dihydroisoxazole ring remains unchanged during analogous processes resulting in introduction of the brassinosteroid functionality [4].

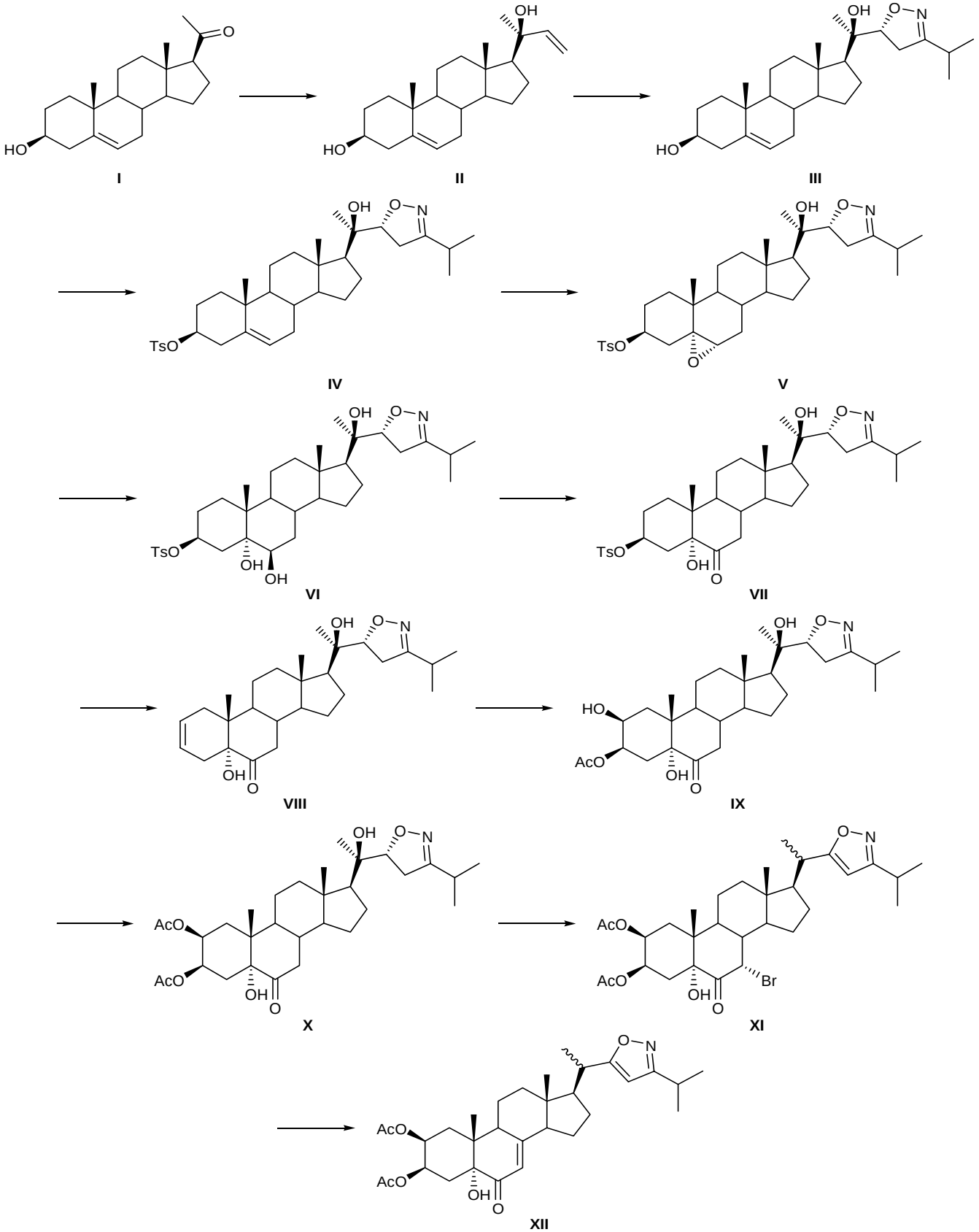
As initial compound we used pregnenolone (**I**). By the Normant reaction of pregnenolone (**I**) with vinylmagnesium bromide we obtained 20-hydroxy-20-vinyl steroid **II** which was brought into 1,3-dipolar cycloaddition to nitrile oxide generated from isobutyraldehyde oxime by the action of *N*-chlorosuccinimide [5, 6]. The adduct was formed as a mixture of two diastereoisomers with respect to the new chiral center at $C^{5'}$. The major isomer (5'*R*-**III**) was isolated by chromatography. Its structure was confirmed by the presence in its ^{1}H NMR spectrum of a triplet signal at δ 4.50 ppm, which is typical of 5'-H, and a two-proton doublet at δ 2.84 ppm, the latter indicating affiliation to the 5'*R*-series [7].

The 3β-hydroxy group in compound **III** was protected by treatment with *p*-toluenesulfonyl chloride, and the subsequent epoxidation of 3β-(*p*-tolylsulfonyloxy)-Δ^5 derivative **IV** with *m*-chloroperoxybenzoic acid in chloroform at –78°C (reaction time 1 h) gave 82% of compound **V** as the only product. Its structure followed from the spectral data: the ^{1}H NMR spectrum lacked signal from vinyl proton on C^6, while a one-proton multiplet appeared at δ 2.82 ppm due to 6-H in the 5α,6α-epoxy derivative.

The reaction of epoxide **V** with perchloric acid in dioxane at room temperature (2 h) resulted in *trans*-opening of the oxirane ring with formation of vicinal diol **VI** in 96% yield. The product was characterized by increased intensity of the OH stretching vibration band (3470 cm^{-1}) in the IR spectrum, and the 6-H signal in the ^{1}H NMR spectrum was observed in a weaker field (δ 4.84 ppm).

The secondary 6β-hydroxy group in diol **VI** was oxidized with pyridinium chlorochromate in chloroform to obtain 82% of 5α-hydroxy-6-oxo derivative

Scheme 1.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XII

VII. In the IR spectrum of **VII**, we observed weakening of the OH stretching vibration band, and carbonyl absorption band appeared at 1730 cm^{-1}; the 6-H signal disappeared from the ^1H NMR spectrum.

In order to introduce double $C^2=C^3$ bond, 3β-(*p*-tolylsulfonyloxy) derivative **VII** was brought into reaction with lithium bromide in dimethylformamide. As a result, Δ^2-6-oxo steroid **VIII** was isolated in 61% yield. The ^1H NMR spectrum of **VIII** contained a two-proton multiplet centered at δ 5.64 ppm from the olefinic protons on C^2 and C^3, while signals from aromatic protons in the *p*-tolylsulfonyl group disappeared from the spectrum.

A *cis*-2β,3β-diol moiety intrinsic to ecdysteroids was built up by hydroxylation of the double bond with silver acetate and iodine in aqueous acetic acid according to Woodward. As the major product (yield 37%) we isolated 2β,5α-dihydroxy-3β-acetoxy-6-oxo steroid **IX** which was subjected to acetylation with acetic anhydride in pyridine to obtain 2β,3β-diacetoxy-5α-hydroxy-6-oxo derivative **X**. In the IR spectrum of **X**, absorption bands due to stretching vibrations of the acetoxy groups (1750 and 1250 cm^{-1}), 6-oxo group (1730 cm^{-1}), and 5α-hydroxy group (3450 cm^{-1}) were present. The acetyl protons in **X** gave rise to two singlets at δ 2.06 and 2.16 ppm in the ^1H NMR spectrum, and protons on C^2 and C^3 appeared as a two-proton multiplet with its center at δ 5.64 ppm.

The $C^7=C^8$ bond was created by a conventional procedure including allylic bromination and subsequent dehydrobromination. The bromination of **X** in acetic acid in the presence of hydrobromic acid on heating afforded the desired 2β,3β-diacetoxy-7α-bromo-5α-hydroxy-6-oxo steroid which showed a positive test for halogen (Beilstein's test); in the ^1H NMR spectrum of the product, a signal from methine proton appeared at δ 4.18 ppm. However, considerable weakening of the OH stretching vibration band in the IR spectrum and the presence in the ^1H NMR spectrum of a signal at δ 5.82 ppm, which is typical of isoxazole ring, led us to presume that the product is 20-isoxazolyl steroid **XI** as a mixture of two epimers with respect to C^{20}. The assumed structure was also supported by comparing the spectral parameters of **XI** with those of structurally related compounds of the pregnane series, which were reported by us previously [8]. The configuration of the C^{20} remains unclear; the final conclusion could be drawn on the basis of X-ray diffraction data.

7α-Bromo derivative **XI** was subjected to dehydrobromination by heating in dimethylformamide for 3.5 h at 120°C in the presence of lithium carbonate and lithium bromide. We thus obtained 41% of 2β,3β-diacetoxy-5α-hydroxy-Δ^7-6-oxo steroid **XII** whose structure was confirmed by spectral data [9]. In the UV spectrum of **XII** we observed a strong absorption band at λ 245 nm, which is typical of Δ^7-6-oxo steroids. Compound **XII** showed in the IR spectrum absorption bands at 1690 and 1630 cm^{-1} due to carbonyl group conjugated with double bond. The ^1H NMR spectrum of **XII** contained a triplet at δ 5.66 ppm, belonging to the olefinic proton on C^7.

Thus we have synthesized an analog of 5α-hydroxyecdysteroids, which possesses an isoxazole ring in the side chain. Our results showed that the bromination of 6-oxo steroids is accompanied by elimination of the hydroxy group from C^{20} with subsequent migration of the newly formed double bond to the heteroring.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker A-200 spectrometer at 200 MHz using chloroform-*d* as solvent and TMS as internal reference. The IR spectra were obtained on a UR-20 instrument from samples prepared as thin films or KBr pellets. The UV spectra were measured on a Specord M-400 spectrophotometer from solutions in methanol. The melting points were determined on a Kofler device. The progress of reactions was monitored by TLC on Kieselgel 60 F_{254} plates (Merck). Preparative chromatography was performed using Kieselgel 60 silica gel (40–60 μm, Merck).

(20*S*)-20-Vinylpregn-5-ene-3,20-diol (II). A calcined three-necked flask was charged in a stream of argon with 4.4 g (183 mmol) of magnesium, a few crystals of iodine were added, the flask was heated, 260 ml of THF was added, the mixture was cooled to 0°C, and a solution of 13 ml of vinylmagnesium bromide in 130 ml of THF was added dropwise under stirring. A solution of 8.6 g (27.2 mmol) of ketone **I** in 100 ml of THF was then added, and the mixture was stirred for 2 h at room temperature, heated for 2 h under reflux, cooled, treated with a saturated solution of ammonium chloride, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated, and the residue was subjected to chromatography on silica gel using cyclohexane–ethyl acetate (5:1) as eluent. Yield 7.8 g (80%), oily

substance. IR spectrum (film), ν, cm^{-1}: 3440, 905. ^1H NMR spectrum, δ, ppm: 0.84 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.34 s (3H, 21-Me), 3.52 m (1H, 3-H), 4.96 d.d (1H, 23-H, J_1 = 10.5, J_2 = 1.5 Hz), 5.15 d.d (1H, 23-H, J_1 = 17, J_2 = 1.5 Hz), 5.36 d (1H, 6-H, J = 4.5 Hz), 6.0 d.d (1H, 22-H, J_1 = 10.5, J_2 = 17 Hz).

(5'*R*,20*R*)-20-(3-Isopropyl-4,5-dihydroisoxazol-5-yl)pregn-5-ene-3,20-diol (III). *N*-Chlorosuccinimide, 10.5 g, was dispersed in 50 ml of dry chloroform containing 0.1 ml of pyridine, 11 g of isobutyraldehyde oxime was added, and the mixture was stirred for 15 min until it became homogeneous. A solution of 9 g (25 mmol) of steroid **II** in 100 ml of chloroform was added, and a solution of 9 ml of triethylamine in 40 ml of chloroform was then added dropwise over a period of 4 h. The mixture was stirred for 12 h, washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was subjected to chromatography on silica gel using cyclohexane–ethyl acetate (5:1). The major product was dihydroisoxazole derivative **III**; yield 10.93 g (75%), mp 200–201°C (from methanol). IR spectrum, ν, cm^{-1}: 3420, 1485, 1390. ^1H NMR spectrum, δ, ppm: 0.84 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.16 d (9H, 21-Me, CH**Me**$_2$, J = 7 Hz), 2.70 m (1H, C**H**Me$_2$), 2.84 d (2H, 4'-H, J = 10 Hz), 3.54 m (1H, 3-H), 4.50 m (1H, 5'-H), 5.36 d (1H, 6-H, J = 4.5 Hz).

(5'*R*,20*R*)-20-(3-Isopropyl-4,5-dihydroisoxazol-5-yl)-3-(*p*-tolylsulfonyloxy)pregn-5-ene (IV). Compound **III**, 2.7 g (8.54 mmol), was dissolved in 30 ml of pyridine, 4.84 g (24.6 mmol) of *p*-toluenesulfonyl chloride was added, and the mixture was kept for 24 h at room temperature and poured into water. The precipitate was filtered off and dissolved in ethyl acetate, and the solution was dried over sodium sulfate. Removal of the solvent afforded 3.4 g (93%) of 3-(*p*-tolylsulfonyloxy) derivative **IV**, mp 158–159°C (from hexane–ethyl acetate). IR spectrum, ν, cm^{-1}: 3550, 3450, 1610, 1350. ^1H NMR spectrum, δ, ppm: 0.79 s (3H, 18-Me), 0.98 s (3H, 19-Me), 1.12 d (9H, 21-Me, CH**Me**$_2$, J = 7 Hz), 2.44 s (3H, **Me**C_6H_4), 2.70 m (1H, C**H**Me$_2$), 2.84 d (2H, 4'-H, J = 10 Hz), 4.32 m (1H, 3-H), 4.46 m (1H, 5'-H), 5.28 d (1H, 6-H, J = 4.5 Hz), 7.34 d and 7.80 d (4H, C_6H_4, J = 7.5 Hz).

(5'*R*,20*R*)-5α,6α-Epoxy-20-(3-isopropyl-4,5-dihydroisoxazol-5-yl)-3-(*p*-tolylsulfonyloxy)pregnan-20-ol (V). Compound **IV**, 2.6 g (5.07 mmol), was dissolved in 30 ml of chloroform, the solution was cooled to –78°C, and 1.55 g of *m*-chloroperoxybenzoic acid was added under stirring. The mixture was stirred for 30 min at –78°C, allowed to warm up to room temperature, washed with water, dried over anhydrous sodium sulfate, and evaporated, and the residue was purified by recrystallization. Yield 2.46 g (82%), mp 172–173°C (hexane–ethyl acetate). IR spectrum (film), ν, cm^{-1}: 3530, 1360. ^1H NMR spectrum, δ, ppm: 0.74 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.16 d (9H, 21-Me, CH**Me**$_2$, J = 7 Hz), 2.36 m (1H, 6-H), 2.42 s (3H, **Me**C_6H_4), 2.68 m (1H, C**H**Me$_2$), 2.82 d (2H, 4'-H, J = 10 Hz), 4.48 m (1H, 5'-H), 4.59 m (1H, 3-H), 7.34 d and 7.80 d (4H, C_6H_4, J = 7.5 Hz).

(5'*R*,20*R*)-20-(3-Isopropyl-4,5-dihydroisoxazol-5-yl)-3-(*p*-tolylsulfonyloxy)pregnane-5α,6β,20-triol (VI). Epoxy derivative **V**, 0.9 g (1.5 mmol), was dissolved in a mixture of 80 ml of dioxane and 20 ml of water, and 18 ml of 70% perchloric acid was added. The mixture was stirred for 2 h at room temperature, treated with a saturated solution of sodium carbonate to neutralize excess perchloric acid, and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was distilled off to obtain 0.88 g (96%) of triol **VI**, mp 213–214°C (from hexane–ethyl acetate). IR spectrum (film), ν, cm^{-1}: 3520, 3470, 1610, 1360. ^1H NMR spectrum, δ, ppm: 0.82 s (3H, 18-Me), 1.12 s (6H, 19-Me, 21-Me), 1.16 d (6H, CH**Me**$_2$, J = 7 Hz), 2.44 s (3H, **Me**C_6H_4), 2.70 m (1H, C**H**Me$_2$), 2.82 d (2H, 4'-H, J = 10 Hz), 3.48 m (1H, 6-H), 4.48 m (1H, 5'-H), 4.92 m (1H, 3-H), 7.34 d and 7.80 d (4H, C_6H_4, J = 7.5 Hz).

(5'*R*,20*R*)-5α,20-Dihydroxy-20-(3-isopropyl-4,5-dihydroisoxazol-5-yl)-3-(*p*-tolylsulfonyloxy)-pregnan-6-one (VII). Triol **VI**, 0.9 g (1.46 mmol), was dissolved in 30 ml of dry chloroform, and 0.49 g (2.32 mmol) of pyridinium chlorochromate was added. The mixture was stirred for 6 h at room temperature and filtered through a layer of silica gel, the solvent was distilled off from the filtrate, and the residue was subjected to column chromatography on silica gel using cyclohexane–ethyl acetate (1:1) as eluent. Yield 0.74 g (82%), mp 127–128°C (from hexane–ethyl acetate). IR spectrum (film), ν, cm^{-1}: 3510, 1390. ^1H NMR spectrum, δ, ppm: 0.76 s (6H, 18-Me, 19-Me), 1.12 s (3H, 21-Me), 1.16 d (6H, CH**Me**$_2$, J = 7 Hz), 2.46 s (3H, **Me**C_6H_4), 2.50 m (1H, C**H**Me$_2$), 2.84 d (2H, 4'-H, J = 10 Hz), 4.48 m (1H, 5'-H), 4.82 m (1H, 3-H), 7.34 d and 7.80 d (4H, C_6H_4).

(5'*R*,20*R*)-5α,20-Dihydroxy-20-(3-isopropyl-4,5-dihydroisoxazol-5-yl)pregn-2-en-6-one (VIII). Anhydrous lithium bromide, 0.944 g (10.85 mmol),

was added under argon to a solution of 2.4 g (3.9 mmol) of compound **VII** in 50 ml of dimethylformamide, and the mixture was heated for 2 h at 120–125°C. The mixture was then poured into 2 l of water and extracted with ethyl acetate. The extract was washed with 2 N hydrochloric acid and a 5% solution of sodium carbonate and dried over sodium sulfate. The solvent was distilled off, and the residue was subjected to column chromatography on silica gel using cyclohexane–ethyl acetate (1:1) as eluent to isolate 1.1 g (61%) of Δ^2-steroid **VIII**, mp 202–203°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3450, 1710, 1400. ^{1}H NMR spectrum, δ, ppm: 0.70 s (3H, 18-Me), 0.80 s (3H, 19-Me), 1.17 d (9H, 21-Me, CH**Me**$_2$, *J* = 7 Hz), 2.78 m (1H, C**H**Me$_2$), 2.84 d (2H, 4'-H, *J* = 10 Hz), 4.48 m (1H, 5'-H), 5.64 m (2H, 2-H, 3-H).

(5'*R*,20*R*)-2-Acetoxy-3β,5*α*,20-trihydroxy-20-(3-isopropyl-4,5-dihydroisoxazol-5-yl)pregnan-6-one (IX). Compound **VIII**, 1.1 g (2.39 mmol), was dissolved in 84 ml of a 20:1 acetic acid–water mixture, 1.4 g of silver acetate was added, and 0.9 g of finely powdered iodine was then added under stirring. After 1.5 h, the precipitate was filtered off and washed with ethanol, the filtrate was evaporated, the residue was dissolved in chloroform, and the solution was washed with water and a saturated solution of sodium hydrogen carbonate and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was subjected to chromatography on silica gel using cyclohexane–ethyl acetate (2:1) as eluent to isolate 0.474 g (37%) of monoacetate **IX**, mp 148–150°C (from ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 3420, 1730 br, 1390, 1250. ^{1}H NMR spectrum, δ, ppm: 0.84 s (3H, 18-Me), 0.98 s (3H, 19-Me), 1.12 d (6H, CH**Me**$_2$, *J* = 7 Hz), 1.16 s (3H, 21-Me), 2.02 s (3H, MeCO), 2.68 m (1H, C**H**Me$_2$), 2.86 d (2H, 4'-H, *J* = 10 Hz), 4.40 m (1H, 2-H), 4.50 m (1H, 5'-H), 5.31 m (1H, 3-H).

(5'*R*,20*R*)-2β,3β-Diacetoxy-5*α*,20-dihydroxy-20-(3-isopropyl-4,5-dihydroisoxazol-5-yl)pregnan-6-one (X). Compound **IX**, 0.474 g (0.89 mmol), was dissolved in 8 ml of pyridine, 0.4 ml (3 mmol) of acetic anhydride was added, and the mixture was left to stand for 24 h at room temperature. It was then poured into water, and extracted with ethyl acetate. The extract was washed with 1% hydrochloric acid and dried over anhydrous sodium sulfate, and the solvent was distilled off to obtain 0.437 g (85%) of diacetate **X**, mp 144–145°C (from hexane–ethyl acetate). IR spectrum, ν, cm^{-1}: 3450 br, 1750, 1730, 1380, 1260. ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H, 18-Me), 0.97 s (3H, 19-Me), 1.14 s (3H, 21-Me), 1.17 d (6H, CH**Me**$_2$, *J* = 7 Hz), 2.05 s (3H, MeCO), 2.08 s (3H, MeCO), 2.68 m (1H, C**H**Me$_2$), 2.84 d (2H, 4'-H, *J* = 10 Hz), 4.48 m (1H, 5'-H), 5.24 m (1H, 2-H), 5.30 m (1H, 3-H).

(5'*R*,20*R*)-2β,3β-Diacetoxy-7*α*-bromo-5*α*-hydroxy-20-(3-isopropyl-5-isoxazolyl)pregnan-6-one (XI). Diacetate **X**, 0.2 g (0.35 mmol), was dissolved in 3 ml of acetic acid, one drop of hydrobromic acid was added, and 0.45 ml of a 2 M solution of bromine in glacial acetic acid was then added. The mixture was heated to 50–60°C, poured into water, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, the solvent was removed, and the residue was subjected to column chromatography on silica gel using toluene as eluent to isolate 0.078 g (40%) of bromo derivative **XI** as an oily substance. IR spectrum (film), ν, cm^{-1}: 3440, 1750, 1720, 1240, 1260. ^{1}H NMR spectrum, δ, ppm: 0.72 s (3H, 18-Me), 0.98 s (3H, 19-Me), 1.22 d (9H, 21-Me, CH**Me**$_2$, *J* = 7 Hz), 1.98 s and 2.03 s (6H, MaCO), 2.82 m (1H, 20-H), 3.02 m (1H, C**H**Me$_2$), 4.18 d (1H, 7-H, *J* = 4.5 Hz), 5.28 m (2H, 2-H, 3-H), 5.82 s (1H, 4'-H).

(5'*R*,20*R*)-2β,3β-Diacetoxy-5*α*-hydroxy-20-(3-isopropyl-5-isoxazolyl)pregn-7-en-6-one (XII). Compound **XI**, 0.07 g, was dissolved in 1 ml of DMF, 0.077 g of lithium bromide and 0.132 g of lithium carbonate were added, and the mixture was heated for 3.5 h at 120–125°C, cooled, diluted with water, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was subjected to column chromatography on silica gel using cyclohexane–ethyl acetate (4:1) as eluent to isolate 0.024 g (41%) of compound **XII** as an oily substance. IR spectrum (film), ν, cm^{-1}: 3440, 1750, 1690, 1630, 1240, 1260. UV spectrum: λ_{max} 245 nm (ε = 13920). ^{1}H NMR spectrum, δ, ppm: 0.60 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.20 s (3H, 21-Me), 1.25 d (6H, CH**Me**$_2$, *J* = 7 Hz), 2.01 s (3H, MeCO), 2.05 s (3H, MeCO), 2.84 m (1H, C**H**Me$_2$), 3.12 m (1H, 20-H), 5.28 m (2H, 2-H, 3-H), 5.66 t (1H, 7-H, *J* = 2 Hz), 5.82 s (1H, 4'-H).

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