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Synthesis of 20α-Methylsteroids with an Izoxaline Ring in the Side Chain

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Abstract—1,3-Dipolar addition of acetonitrile oxide to 20α-methyl-22-hydroxy-23-ene-steroids and acetoxy derivatives thereof was investigated. The reaction is stereoselective and affords as the main product 5'S-epimer resulting from syn-addition both in the case of allyl alcohol and its ether.

We studied formerly cycloaddition of nitrile oxides to some derivatives of Δ^{23}-steroids. We established that the substituents located in the α- and β-position to the double bond affected the yield and composition of the cycloadducts [1–3]. For instance, the presence of hydroxy group at C^{22} atom favors stereoselective course of the process, and replacement thereof with an ester moiety results in decreased stereoselectivity and yield of the cycloaddition product. The hydroxy group in β-position weaker affects the stereochemistry of addition, and as a result arise two epimers of 22-isoxazolinylsteroids with respect to $C^{5'}$ atom in approximately equal amounts.

The synthesis of 20α-methyl derivatives is a complicated problem, but it becomes more and more urgent first of all because recently were isolated from natural objects, mainly of sea origin, steroids with the mentioned configuration of the C^{20} atom [4]. We developed earlier a procedure for constructing 20-isosteroid side chain with complicated functions via 20-hydroxy-20-(2-isoxazolinyl)steroids based on revealed 1,2-hydride shift occurring in the course of the ionic hydrogenation of these compounds [5]. The alternative preparation method for the compounds is cycloaddition of nitrile oxides to steroid olefins of the 20-isoseries. The reaction products, isoxalinylsteroids, are of interest as intermediates for constructing side chains of 20-isoanalogs of the natural polyoxysteroids with the use of technique we have developed for brassionsteroids [6–9], ecdysteroids [10], sapogenins of sea organisms [11–13], etc.

The target of this study was to elucidate the effect of C^{20} atom configuration in the Δ^{23}-22-hydroxysteroids on the course of 1,3-dipolar cycloaddition of acetonitrile oxide, and to achieve on this base the synthesis of 20α-methyl-22-isoxazolinylsteroids.

The initial 22-hydroxysteroid olefin (**II**) was obtained from 20-isosteroid aldehyde (**I**) [14] by Normant reaction with vinylmagnesium bromide. In the reaction was observed prevailing (10 : 1) formation of 22*S*-epimer **II** that was separated by crystallization. The acetylation of the secondary hydroxy group in compound **II** with acetic anhydride in pyridine provided Δ^{23}-22-acetoxy derivative (**III**), and by treating 6,6-dioxyethylene derivatives in acid media were obtained the corresponding 6-oxosteroids **IV** and **V**.

The ^{1}H NMR spectra of the steroid olefins obtained contain characteristic signals from vinyl protons at C^{24} atom coupled with the vicinal proton attached to C^{23} atom (J_{trans} 17 and J_{cis} 10–11 Hz). Both resonances are further split due to coupling with each other, but J_{gem} is very small, and actually are observed two slightly distorted doublets in the region 5.12–5.15 and 5.20–5.25 ppm. An octet centered at 5.88 ppm in the spectrum of 22-hydroxy and at 5.78 ppm for 22-acetoxy derivatives belongs to the proton attached to C^{23}. Two coupling constants correspond to the coupling with another vinyl proton, and the third constant (J 7 Hz) appears due to the coupling with allyl proton at the C^{22} atom; the signal from the latter proton appears as a broad singlet at 4.44 in the spectra of alcohols **II, IV**, and at 5.38 in the spectra of acetylated derivatives **III, V**. The comparison of ^{13}C NMR spectra of 20*R*-isomers **II**–**V** and those of 22*S*-isomers [3] demonstrated that the signals of C^{17}, C^{20}, C^{22}, C^{24} atoms are characteristic: The signals in the 20*R*-epimer appear upfield with respect to those of 22*S*-isomers, whereas the signal of C^{23} occurred in weaker field. Thus these signals may be applied to assignment of compounds to a certain series. With the signals of the C^{23} atom the difference amounts to 3.6–3.8 ppm.

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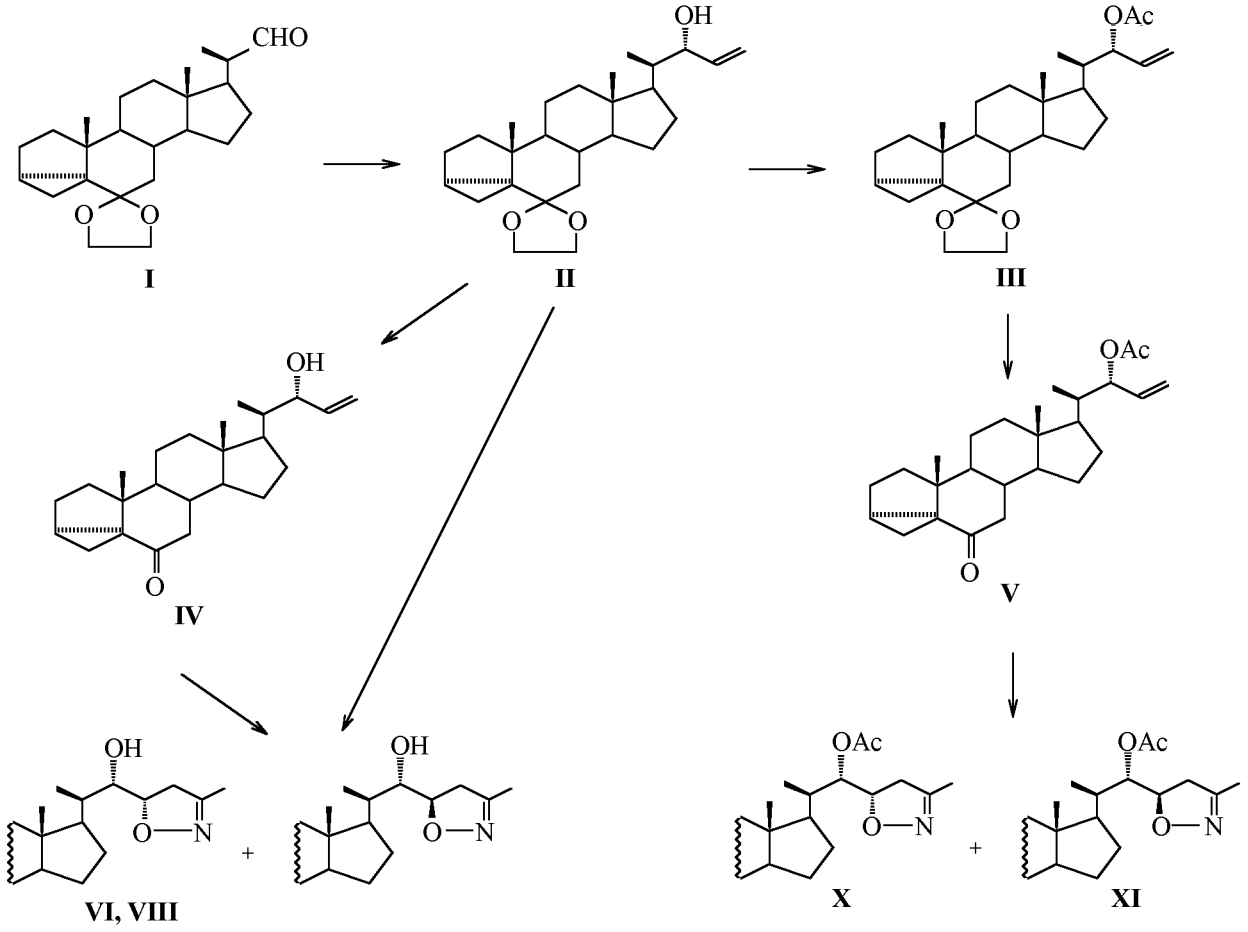

VI, VII—6-ethylenedioxy; **VIII, IX**—6-oxo.

The acetonitrile oxide generated from the corresponding aldehyde oxime under N-chlorosuccinimide action followed by treatment with triethylamide reacts with olefins **II** and **IV** regioselectively giving rise to mixtures of 5'-epimers **VI**, **VII** and **VIII**, **IX** respectively. In both cases the epimers ratio is 2:1. Thus the selectivity of reaction with 20*R*-olefins is lower than that with 20*S*-derivatives where this ratio is 4:1 [1, 3].

The absolute configuration of 22-isoxazolinylsteroid **IV** was established by X-ray diffraction analysis [15]. The conclusions on the structures of the other compounds obtained follows from the analysis of their spectral characteristics as compared with the parameters of compound **IV**. The most informative turned out to be the ^{1}H NMR spectra. The one-proton doublet of doublets signal is characteristic of the proton at C^{22} atom that for 5'*S*-epimers **VI** and **VIII** it appears in stronger field (δ 3.72 ppm for 5'*S* and 3.94 ppm for the 5*R*-epimer). The one-proton multiplet corresponding to the proton at the chiral center $C^{5'}$ arising after the cycloaddition is situated downfield in the spectrum of the main 5'*S*-epimer (δ 4.49 ppm for 5'*S* and 4.51 ppm for the 5'*R*-epimer). As the most characteristic should be indicated the signals from methylene protons of the isoxazoline ring. In the spectra of 5'*S*-epimers the resonances form two doublets of doublets with different coupling constants that degenerate into two doublets for 5'*R*-epimers. In the IR spectra of 22-hydroxy-22-isoxazolinylsteroids appears the absorption band of hydroxy group stretching vibrations (3480 cm^{-1}), and in the spectra of 6-oxoderivatives is observed an additional band of the keto group (1690 cm^{-1}). The mass spectra contain peak of the molecular ion and fragment peaks corresponding to elimination of methyl group, water, and elements of isoxazoline ring.

The stereoselectivity of 1,3-dipolar cycloaddition of acetonitrile oxide increases when as dipolarophile in the reaction is used 22-acetoxy-Δ^{23}-steroid (**V**): in overall yield 44% 5'*S* (**X**) and 5'*R*-epimers (**XI**) formed in the ratio 4.5:1. Such behavior is in contrast to the pattern observed with 20β-analogs [3].

However the common feature is a relatively low yield of the cycloaddition products.

The spectral characteristics of acetoxy derivatives **X** and **XI** agree with the assumed structure. In the ^{1}H NMR spectrum the signal of proton at C^{22} shifts downfield, the multiplet of the proton at $C^{5'}$ behaves similarly. The form of signals at $C^{4'}$ atom is virtually the same as in the spectra of 22-hydroxysteroids. In the IR spectra of acetoxy derivatives lacks the band of stretching vibrations corresponding to hydroxy group, but appear two new absorption bands belonging to the acetoxy group (1740 and 1250 cm^{-1}). The fragmentation in the mass spectra results in peaks due to elimination of methyl group, acetic acid, and the elements of the isoxazoline ring.

The transformations described above ensure the synthesis of new isoxazolinylsteroids of 20-isoseries. The synthesis can also be applied to preparation of the corresponding derivatives with a polyfunctional open side chain. It should be specially noted that in the examples of 1,3-dipolar cycloaddition of acetonitrile oxide forms predominantly treo-isomer, a product of *syn*-addition, as we have previously observed with 20β-steroids. This result is radically different from the published data [16, 17].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on spectrometers Bruker WM-360 (360 MHz) and Bruker A-200 (200 MHz) from solutions in $CDCl_3$, internal reference TMS. IR spectra were recorded on UR-20 spectrophotometer from thin film or KBr pellets. Mass spectra were measured on Varian MAT-311 or Shimadzu QP-5000 instruments with direct input, ramp from 30 to 350°C at the rate 20 deg min^{-1}, ionizing irradiation 70 eV. Melting points were determined on Koeffler heating block.

The reactions progress was monitored by TLC on Silufol UV-254 and Merck (Kieselgel 60 F_{254}). The chromatographic separation was carried out on silica gel 40/60 μ (Kieselgel 60, Merck).

Steroid olefins II, IV. Normant reaction. Into a preheated tree-neck flask in an argon flow was placed 70 mmol of magnesium turnings, then several iodine crystals, and the flask was heated. Then was added 200 ml of THF, the flask was cooled to 0°C, and 5 ml of vinyl bromide in 75 ml of THF was added dropwise. Then was added a solution of 10 ml of steroid aldehyde **I** in 50 ml of THF. The mixture was stirred at room temperature for 2 h and then treated with a saturated solution of ammonium chloride. The reaction products were extracted into ether, the extract was dried with sodium sulfate. The separation was carried out by chromatography on silica gel (eluent hexane–ether).

(20*R*,22*R*)-22-Hydroxy-3α,5-cyclo-6,6-ethylenedioxy-5α-chol-23-ene (II) was prepared from 0.372 g of aldehyde **I** [14]. Yield 0.280 g (70%). mp 90–92°C (EtOAc–hexane). IR spectrum (film, ν, cm^{-1}): 3440, 905. ^{1}H NMR spectrum (δ, ppm): 0.33 m (1H, cyclopropane), 0.62 m (1H, cyclopropane), 0.76 s (3H, 18–Me), 0.82 d (3H, 21-Me, *J* 7 Hz), 1.03 s (3H, 19-Me), 3.70–4.10 m (4H, OCH_2CH_2O), 4.42 m (1H, H^{22}), 5.14 d (1H, H^{24}, *J* 11 Hz), 5.24 d (1H, H^{24}, *J* 17 Hz), 5.87 octet (1H, H^{23}, J_1 4, J_2 11, J_3 17 Hz). Mass spectrum (*m/z*): 400 $[M]^+$, 385 $[M–Me]^+$, 382 $[M–H_2O]^+$.

(20*R*,22*R*)-22-Hydroxy-3α,5-cyclo-5α-chol-23-en-6-one (IV) was prepared from 0.350 g of aldehyde **I** along the above procedure followed by treatment of dioxolane derivative with 10% hydrochloric acid in THF. Yield 0.260 g (70%), mp 115–117°C (MeOH–CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 3445, 1680. ^{1}H NMR spectrum (δ, ppm): 0.76 s (3H, 18-Me), 0.82 d (3H, 21-Me, *J* 7 Hz), 1.03 s (3H, 19-Me), 4.44 br.s (1H, H^{22}), 5.15 d (1H, H^{24}, *J* 11 Hz), 5.24 d (1H, H^{24}, *J* 17 Hz), 5.88 octet (1H, H^{23}, J_1 4, J_2 11, J_3 17 Hz). ^{13}C NMR spectrum (δ_C, ppm): 11.7 (C^4), 12.0 (C^{18}), 12.5 (C^{19}), 19.7 (C^{21}), 22.8 (C^{11}), 24.0 (C^2), 25.9 (C^{15}), 27.4 (C^{16}), 33.5 (C^1), 34.7 (C^8), 35.3 (C^3), 39.1 (C^{12}), 39.8 (C^{20}), 42.6 (C^5), 44.8 (C^7), 46.2 (C^9), 46.3 (C^{10}), 46.8 (C^{13}), 51.5 (C^{17}), 56.6 (C^{14}), 73.7 (C^{22}), 114.0 (C^{24}), 140.8 (C^{23}), 209.6 (C^6). Mass spectrum (*m/z*): 356 $[M]^+$, 338 $[M–H_2O]^+$, 299 [*M*–rupture at C^{20}–$C^{22}]^+$.

Acetylation of the secondary steroid alcohols. In 5 ml of pyridine was dissolved 1 mmol of the steroid alcohol and was added dropwise 0.5 ml (5 mmol) of acetic anhydride. The reaction mixture was left standing for 18–20 h, then treated with water (10 ml), the reaction products were extracted into ether. The extracts were washed with 0.5% solution of hydrochloric acid till neutral, then with water, and dried on anhydrous sodium sulfate. On evaporation the residue was dissolved in a little chloroform, and the solution was purified by passing through a layer of silica gel. Yield of acetoxy derivatives 92–95%.

(20*R*,22*R*)-22-Acetoxy-3α,5-cyclo-6,6-ethylenedioxy-5α-chol-23-ene (III) was prepared by acetylation of alcohol **II**. Oily substance. IR spectrum (film, ν, cm^{-1}): 1735, 1685, 1250. ^{1}H NMR spec-

trum (δ, ppm): 0.33 m (1H, chlopropane), 0.62 m (1H, cyclopropane), 0.74 s (3H, 18-Me), 0.90 d (3H, 21-Me, *J* 7 Hz), 1.00 s (3H, 19-Me), 2.11 s (3H, $COCH_3$), 3.70–4.10 m (4H, OCH_2CH_2O), 5.10 d (1H, H^{24}, *J* 17 Hz), 5.18 d (1H, H^{24}, *J* 10 Hz), 5.38 br.s (1H, H^{22}), 5.76 septet (1H, H^{23}, J_1 5, J_2 10, J_3 17 Hz). Mass spectrum (*m/z*): 398 $[M]^+$, 380 $[M–H_2O]^+$, 338 $[M–AcOH]^+$, 299 [*M*–rupture at $C^{20}–C^{22}]^+$, 281, 270.

(20*R*,22*R*)-22-Acetoxy-3α,5-cyclo-5α-chol-23-en-6-one (V) was prepared by acetylation of alcohol **IV**. mp 130–132°C (MeOH–CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1740, 1700, 1250. ^1H NMR spectrum (δ, ppm): 0.74 s (3H, 18–Me), 0.94 d (3H, 21-Me, *J* 7 Hz), 1.03 s (3H, 19-Me), 2.12 s (3H, $COCH_3$), 5.12 d (1H, H^{24}, *J* 17 Hz), 5.20 d (1H, H^{24}, *J* 10.5 Hz), 5.38 br.s (1H, H^{22}), 5.78 septet (1H, H^{23}, J_1 5, J_2 10.5, J_3 17 Hz). ^{13}C NMR spectrum (δ, ppm): 11.7 (C^4), 12.0 (C^{18}), 12.5 (C^{19}), 19.7 (C^{21}), 21.2 ($COCH_3$), 22.8 (C^{11}), 24.0 (C^2), 25.9 (C^{15}), 27.4 (C^{16}), 33.5 (C^1), 34.7 (C^8), 35.3 (C^3), 39.1 (C^{12}), 39.8 (C^{20}), 43.0 (C^5), 44.8 (C^7), 46.1 (C^9), 46.4 (C^{10}), 46.8 (C^{13}), 51.2 (C^{17}), 56.7 (C^{14}), 76.7 (C^{22}), 115.6 ($C^{4'}$), 135.7 ($C^{5'}$), 170.4 ($COCH_3$), 209.3 (C^6). Mass spectrum (*m/z*): 398 $[M]^+$, 380 $[M–H_2O]^+$, 338 $[M–AcOH]^+$, 299 [*M*–rupture at $C^{20}–C^{22}]^+$, 281, 270.

Cycloaddition of nitrile oxides to steroid olefins. To a suspension of 0.005 mol of *N*-chlorosuccinimide in 10 ml of chloroform with 1–2 drops of pyridine was added dropwise at stirring within 15 min 0.006 mol of the appropriate aldehyde oxime. The stirring was continued till a transparent solution formed, then was added 0.005 mol of the steroid olefin, and the stirring was carried on for another 30 min. Then very slowly (within 2 h) was added 0.005 mol of triethylamine in 5 ml of chloroform, and the stirring was continued for 10–12 h more. The reaction mixtures was then poured into water, the reaction products were extracted with chloroform, the extracts were dried with anhydrous sodium sulfate and then subjected to column chromatography on silica gel (eluent hexane–ethyl acetate, from 5:1 to 10:1).

The addition of acetonitrile oxide to 0.200 g (0.5 mmol) of olefin **II** along the above procedure afforded 0.141 g (62%) of isoxazoline **VI** and 0.082 g (36%) of isoxazoline **VII**.

(20*R*,22*S*,5'*S*)-22-Hydroxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedioxy-23-nor-5α-cholane (VI). Oily substance IR spectrum (film, ν, cm^{-1}): 3480, 1630, 1570. ^1H NMR spectrum (δ, ppm): 0.33 m (1H, cyclopropane), 0.62 m (1H, cyclopropane), 0.73 s (3H, 18-Me), 0.93 d (3H, 21-Me, *J* 7 Hz), 1.02 s (3H, 19-Me), 2.04 s (3H, 3'-Me), 2.63 d.d (1H, $H^{4'}$, J_1 8.5, J_2 17 Hz), 3.00 d.d (1H, $H^{4'}$, J_1 10, J_2 17 Hz), 3.70–4.10 m (4H, OCH_2CH_2O), 3.72 d.d (1H, H^{22}, J_1 2, J_2 7 Hz), 4.58 m (1H, $H^{5'}$). Mass spectrum (*m/z*): 457 $[M]^+$, 442 $[M–Me]^+$, 439 $[M–H_2O]^+$, 373 [*M*–isoxazoline cycle]$^+$, 299.

(20*R*,22*S*,5'*R*)-22-Hydroxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedioxy-23-nor-5α-cholane-6 (VII). Oily substance IR spectrum (film, ν, cm^{-1}): 3480, 1630, 1570. ^1H NMR spectrum (δ, ppm): 0.33 m (1H, cyclopropane), 0.62 m (1H, cyclopropane), 0.75 s (3H, 18-Me), 0.90 d (3H, 21-Me, *J* 7 Hz), 1.02 s (3H, 19-Me), 2.00 s (3H, 3'-Me), 2.97 d (1H, $H^{4'}$, *J* 10 Hz), 3.03 d (1H, $H^{4'}$, *J* 8 Hz), 3.70–4.10 m (4H, OCH_2CH_2O), 3.94 d.d (1H, H^{22}, J_1 2, J_2 7 Hz), 4.51 m (1H, $H^{5'}$). Mass spectrum (*m/z*): 457 $[M]^+$, 442 $[M–Me]^+$, 439 $[M–H_2O]^+$, 373 [*M*–isoxazoline cycle]$^+$, 299.

The addition of acetonitrile oxide to 0.2 g (0.56 mmol) of olefin **IV** along the above procedure afforded 0.11 g (47%) of isoxazoline **VIII** and 0.053 g (23%) of isoxazoline **IX**.

(20*R*,22*S*,5'*S*)-22-Hydroxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-23-nor-5α-cholan-6-one (VIII). mp 183–185°C (MeOH–CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 3480, 1690. ^1H NMR spectrum (δ, ppm): 0.73 s (3H, 18-Me), 0.92 d (3H, 21-Me, *J* 7 Hz), 1.02 s (3H, 19-Me), 2.04 s (3H, 3'-Me), 2.62 d.d (1H, $H^{4'}$, J_1 8, J_2 17 Hz), 3.00 d.d (1H, $H^{4'}$, J_1 10, J_2 17 Hz), 3.78 d.d (1H, H^{22}, J_1 1.5, J_2 8 Hz), 4.60 m (1H, $H^{5'}$). ^{13}C NMR spectrum (δ_C, ppm): 11.7 (C^4), 12.0 (C^{18}), 12.5 (C^{19}), 13.2 (3'-CH_3), 19.7 (C^{21}), 22.8 (C^{11}), 23.8 (C^2), 25.9 (C^{15}), 27.7 (C^{16}), 33.5 (C^1), 34.8 (C^8), 35.3 (C^3), 37.1 (C^{20}), 39.2 ($C^{4'}$), 41.1 (C^{12}), 42.5 (C^5), 44.7 (C^7), 46.0 (C^9), 46.3 (C^{10}), 46.7 (C^{13}), 51.4 (C^{17}), 56.8 (C^{14}), 74.1 (C^{22}), 82.3 ($C^{5'}$), 155.7 ($C^{3'}$), 209.6 (C^6). Mass spectrum (*m/z*): 413 $[M]^+$, 398 $[M–Me]^+$, 395 $[M–H_2O]^+$, 329 [*M*–isoxazoline cycle]$^+$, 299.

(20*R*,22*S*,5'*R*)-22-Hydroxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-23-nor-5α-cholan-6-one (IX). mp 169–172°C (MeOH–$CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3480, 1690. ^1H NMR spectrum (δ, ppm): 0.75 s (3H, 18-Me), 0.90 d (3H, 21–Me, *J* 7 Hz), 1.02 s (3H, 19-Me), 2.00 s (3H, 3'-Me), 3.00 t (2H, $H^{4'}$, *J* 9 Hz), 3.94 d.d (1H, H^{22}, J_1 2.5, J_2 7 Hz), 4.51 m (1H, $H^{5'}$). ^{13}C NMR spectrum (δ_C, ppm): 11.7 (C^4), 11.9 (C^{18}), 12.4 (C^{19}), 13.2 (3'

CH_3), 19.7 (C^{21}), 22.9 (C^{11}), 24.0 (C^2), 25.9 (C^{15}), 27.6 (C^{16}), 33.5 (C^1), 34.7 (C^8), 35.5 (C^3), 36.6 (C^{20}), 39.3 ($C^{4'}$), 40.9 (C^{12}), 42.6 (C^5), 44.7 (C^7), 46.1 (C^9), 46.3 (C^{10}), 46.7 (C^{13}), 51.8 (C^{17}), 56.9 (C^{14}), 73.1 (C^{22}), 81.5 ($C^{5'}$), 156.0 ($C^{3'}$), 209.5 (C^6). Mass spectrum (*m/z*): 413 $[M]^+$, 395 $[M-H_2O]^+$, 329 [*M*–isoxazoline cycle]$^+$, 299.

The acetonitrile addition to 0.140 g (0.35 mmol) of olefin **V** along the above procedure afforded 0.057 g (36%) of isoxazoline **X** and 0.012 g (8%) of isoxazoline **XI**.

(20*R*,22*S*,5'*S*)-22-Acetoxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-23-nor-5α-cholan-6-one (X). mp 155–156°C (MeOH–CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1740, 1685, 1250. ^1H NMR spectrum (δ, ppm): 0.72 s (3H, 18-Me), 0.97 d (3H, 21-Me, *J* 7 Hz), 1.00 s (3H, 19-Me), 1.98 s (3H, 3'-Me), 2.12 s (3H, $COCH_3$), 2.67 d.d (1H, $H^{4'}$, J_1 8, J_2 17 Hz), 3.00 d.d (1H, $H^{4'}$, J_1 10, J_2 17 Hz), 4.67 m (1H, $H^{5'}$), 5.09 d.d (1H, H^{22}, J_1 2.5, J_2 7 Hz). Mass spectrum (*m/z*): 395 [*M*–AcOH]$^+$, 372 [*M*– isoxazoline cycle]$^+$, 329, 299, 269.

(20*R*,22*R*,5'*R*)-22-Acetoxy-22-(3-methylisoxazolin-5-yl)-3α,5-cyclo-23-nor-5α-cholan-6-one (XI). mp 147–149°C (MeOH–CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1740, 1685, 1250. ^1H NMR spectrum (δ, ppm): 0.75 s (3H, 18-Me), 0.96 d (3H, 21-Me, *J* 7 Hz), 1.02 s (3H, 19-Me), 2.01 s (3H, 3'-Me), 2.10 s (3H, $COCH_3$), 2.89 d.d (2H, $H^{4'}$, J_1 1, J_2 2.5 Hz), 4.58 m (1H, $H^{5'}$), 5.13 d.d (1H, H^{22}, J_1 1, J_2 8 Hz). Mass spectrum (*m/z*): 395 [*M*–AcOH]$^+$, 372, 329, 299, 269.

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