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Chemical Transformations of 9,11-Ethano-13,15-isoxazolinoprostanoids

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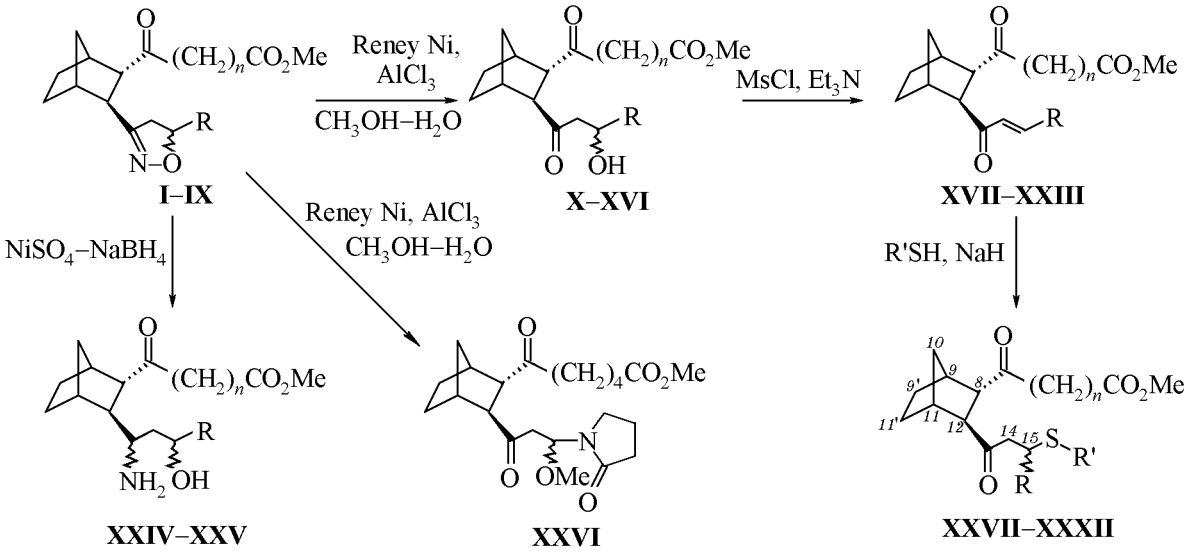
Abstract—Chemical transformations of 9,11-ethano-13,15-isoxazolinoprostanoids furnished new prostanoids with a bufunctional fragment of β-hydroxyketone and γ-aminoalcohol in the ω-chain. The reaction of β-hydroxyketones with methanesulfonyl chloride gave rise to prostanoids with an enone component in the ω-chain. 9,11-Ethano-16-thiaprostanoids were prepared for the first time by nucleophilic addition of thiols to the polarized double bond in the ω-chain. The 1,3-dipolar addition to terminal alkenes of nitrile oxides generated from nitromethylene derivatives of bicycloheptane provided 9,11-ethano-13,15-isoxazolinoprostanoids with an alkyl, phenyl, or additional heterocyclic fragment in the ω-chain.

We formerly established that the structure of the ω-chain significantly affects the range of the biological activity of prostanoids, carbacyclic analogs of PGH [1]. The known distinctive feature of isoxazolines behavior in various reactions is their relative stability against quite a number of reagents. At the same time their N–O bond is labile in the presence of reductants and bases.

We performed transformations of the heterocycle in the molecules of isoxazolinoprostanoids **I–IX** in order to realize some opportunities provided by the bifunctionality of the isoxazoline ring, to perform the necessary modification of the molecule and to obtain as a result new biologically active compounds.

The heterocycle cleavage in isoxazolinoprostanoids **I–VII**, **IX** was performed by a standard procedure of



n = 4 (**II, III, V, VII-IX, XI, XIII, XV, XVI, XVIII, XIX, XXI, XXIII, XXV, XXXI, XXXII**); *n* = 5 (**I, IV, VI, X, XII, XIV, XVII, XX, XXII, XXIV, XXVII–XXX**); R = C_5H_{11} (**I, X, XVII, XXIV, XXVII–XXX**), 1-pyrrolidon-2-yl (**II, XVIII**), C_5H_6 (**V, VI, XIII, XIV, XXI, XXII, XXV**), *p*-chlorophenoxymethyl (**III, IV, XI, XII, XIX, XX**), 2-Py (**VII, XV, XXIII, XXXI–XXXII**), 4-Py (**VIII**), 1-imidazolyl (IX, XVI); R' = C_4H_9 (XXVII, XXXI), C_8H_{17} (**XXVIII**), Ph (**XXIX, XXXII**), $CH_2CO_2CH_3$ (**XXX**).

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catalytic hydrogenolysis in the presence of Raney Ni in a system $AlCl_3$–MeOH–H_2O where the active reductunt is hydrogen formed *in situ* [2]. Under these conditions the cleavage of isoxazolinoprostanoids **I, III–VII, IX** afforded β-hydroxyketones **X–XVI** in 60–65% yield in conformity to the typical cleavage reaction of 2-isoxazolines treated with reductants of this kind [3]. The opening of the isoxazoline ring occurred more readily than with fuzed bicycloheptano-isoxazolines [4]. It is evidenced by the result of reducing 13,15-substituted isoxazoline **II** containing a 1-pyrrolidon-2-yl substituent in position *15*. In this case in the course of the reductive cleavage of compound **II** the arising ketoalcohole suffered spontaneous dehydration to furnish α,β-unsaturated ketone **XVIII** in up to 90% yield. On changing the preparation conditions for the Raney Ni catalyst (the use of larger amount of alkali and increased activation period) the heterocycle opening in the isoxazolino-prostanoid **II** lead to formation alongside enone **XVIII** also of methyl 7,13-dioxo-9,11-ethano-15-methoxy-15-(1-pyrrolidon-2-yl)-1,16,17,18,19,20-hexanorprostanate **XXVI** in up to 10% yield. In the IR spectrum of methoxyketone **XXVI** apart the characteristic bands of the 7-oxo group in the region 1719 cm^{-1} and of the carbonyl group of the terminal ester group in the α-chain at 1740 cm^{-1} appears an absorption band of the methoxy group OCH_3 in the region of 2840 cm^{-1}. In the ^1H NMR spectrum of the prostanoid are observed two singlets at 3.22 and 3.24 ppm corresponding to the methoxy groups of two diastereomers of compound **XXVI**. In the region 5.59 ppm is located the signal from proton H^{15} having a pattern of two doublets of doublets.

The assignment of proton signals in the ^1H NMR spectra of the newly prepared compounds was performed by analyzing geminal, vicinal, and remote coupling constants in the spectra of double ^1H-^1H resonance. In the IR spectra of compounds **X, XIII–XVI** in contrast to the spectra of the initial isoxazolinoprostanoids appeared a characteristic absorption band of the stretching vibrations of the hydroxy group at 3380–3450 cm^{-1} whereas the band of the C=N group in the region 1610 cm^{-1} was lacking. In the ^1H NMR spectra of hydroxyketones **X, XIII–XVI** the characteristic signals of the protons H^{14} and H^{15} are shifted upfield compared to the corresponding resonances of these protons in the spectra of the initial 13,15-substituted isoxazolines and appear in the regions 2.4–3.5 and 4.0–5.9 ppm respectively apparently due to disappearance of the anisotropic C=N bond of the isoxazoline. In the spectra of compounds **X, XIII–XVI** in the region 3.09, 3.44, 3.43, 4.28, and 4.35 ppm respectively a broad singlet of the hydroxy proton is observed. We failed to effect the opening of the isoxazoline ring in prostanoid **VIII** possessing a 4-pyridyl substituent in position *15* applying the reductant systems under study.

β-Hydroxyketones **X–XVI** were brought into reaction with methanesulfonyl chloride in pyridine solution. The reaction furnished prostanoids **XVII–XXIII** with enone fragment in the ω-chain. Enones **XVII–XXIII** also easily formed at dehydration of hydroxyketones **X–XVI** by mesyl chloride in the presence of triethylamine. Both procedures afford the target products in high yields. The structure of the products is confirmed by their spectra. In the IR spectra of enones lacks the absorption band of the hydroxy group stretching vibrations. In addition to the absorption band of an isolated carbonyl group in the α-chain at 1710 cm^{-1} in the spectra is observed a band of a keto group conjugated to a double bond in the region 1695 cm^{-1} and a band of a double bond conjugated to a carbonyl in the region 1620 cm^{-1} characteristic of enone structure. In the ^1H NMR spectra of prostanoids **XVII–XXVII** as characteristic signals serve those of protons H^{14} and H^{15} at the double bond conjugated to a carbonyl in the ω-chain. The nuclei of these hydrogens suffer deshielding by the labile π-electrons of the anisotropic 13-oxo group, an thus their signals are shifted downfield with respect to the proton signals at an isolated double bond [5]. Proton signals from H^{14} and H^{15} in the spectra of prostanoids **XVII–XXIII** appear as doublets in the regions 5.58–7.27 and 6.89–8.08 ppm respectively with vicinal coupling constants $^3J_{14,15}$ 15.3–16.0 Hz. The largest shift of the proton signal is observed for the H^{15} proton in enone **XVIII** with a 1-pyrrolidon-2-yl substituent due to the presence in the substituent of a nitrogen atom with an unshared electron pair and of a carbonyl group. The resonance signal of the proton is located at 8.08 ppm.

In addition to reduction of the isoxazoline ring on the Raney nickel we performed hydrogenolysis of compounds **I, V** to obtain γ-aminoalcohols by treating the prostanoids with sodium borohydride in the presence of nickel sulfate. The reaction afforded a mixture of diastereomeric aminoalcohols **XXIV–XXV** in up to 65% yield. The parameters of IR and ^1H NMR spectra are in agreement with the assumed structure of the aminoalcohols. Multiplets at 2.63, 3.73 ppm (**XXIV**) and 2.48, 4.48 ppm (XXV) were assigned to the methine protons attached to carbon atoms bearing amino and hydroxy groups.

We formerly synthesized 9,11-ethano-13-thiaprostanoids [4, 6, 7]. In this study we obtained for the first time carbacyclic analogs of PGH with a sulfur atom in *16* position and with natural configuration of the α- and ω-chains **XXVII–XXXII**. The 16-thiaprostanoids were synthesized by nucleophilic addition. No nucleophilic addition of thiols to the polarized double bond of the enone fragment of prostanoids occurred even at the use of triethylamine and 1,1,4,4-tetramethylguanidine. The reaction was successfully carried out in benzene in the presence of catalytic amounts of NaH. The sodium hydride was brought into the reaction mixture as a suspension in an anhydrous benzene. All the thiols we used turned out to be reactive under these conditions. The reaction completed within 1 h affording products of 1,4-addition, 16-thiaprostanoids **XXVII–XXXII** in 95–97% yield.

The thiyl moiety added to the electron-deficient carbon of the double bond regioselectively in keeping with the general rules of the electron effects action in the nucleophilic attack on an activated double bond. As a result formed isomeric adducts with an asymmetric carbon in *15* position. Since the enones brought into the reaction were enantiomeric mixtures, the isolated products consisted of a mixture of four isomers (of two diastereomeric pair of enantiomers). In the ^{1}H NMR spectra registered on spectrometer Bruker AVANCE 400 at 400 MHz the signals of diastereomeric 16-thiaprostanoids are distinguished. The chemical shifts of protons H^{8}, H^{9}, H^{11}, H^{12} of epimers differ by 0.02–0.07 ppm, by 0.07–0.27 ppm for H^{14}. In the spectra of compounds **XXIX** and **XXXII** two signals are observed from H^{8} proton belonging to isomeric adducts; these signals appear as triplets of doublets with characteristic vicinal coupling constant $^3J_{8,12}$ 4.80, 4.80 Hz for the adduct with a 16-phenyl substituent and 4.80, 4.55 Hz for the adduct with substituents 15-(2-pyridyl) and 16-phenyl. The respective remote coupling constants $^3J_{8,9'}$ are 1.73, 1.51 and 1.56, 1.8 Hz. The signals of H^{12} protons appear separately almost in all spectra. They are seen as broadened doublets in the region 2.85–3.02 and 2.86–3.04 ppm (in the spectra of diastereomers tentatively designated as A and B) with a coupling constant $^3J_{12,8}$ 5.21–5.37 Hz. The *exo,endo*-configuration of protons H^{8} and H^{12} was established from the characteristic pattern of their signals, and also from the values of $^3J_{8,12}$ and by comparison of these values with published data [6]. The signals of H^{14} protons strongly differ in the chemical shift values, and therefore the unambiguous attribution of proton signals is facilitated. The spectra of compounds **XXVII–XXXII** contain four doublets of doublets in the region 2.36–3.68 ppm corresponding to protons H^{14}. Here the geminal coupling constants $^2J_{14,14}$ amount to 14.60–18.00 Hz, and the vicinal constants $^3J_{14,15}$ equal to 5.05–9.35 Hz.

The H^{15} proton in the spectra of compounds **XXVII, XXVIII** with butyl and octyl substituents resonates in the region of 3.07 ppm. A phenyl attached to position *16* effects a deshielding influence on the proton H^{15} shifting its signal downfield. In prostanoid **XXIX** the signal is shifted downfield by 0.51 ppm with respect to the spectra of the prostanoids cited above due to significant magnetic anisotropy of the aromatic ring. Still greater deshielding suffers the H^{15} proton in compound **XXXI** where the C^{15} carbon is directly linked to the 2-pyridyl substituent: The signal of the proton appears at 4.39 ppm. The maximal downfield shift of the H^{15} proton to 4.80 ppm is observed in the spectrum of compound **XXXII** having a 2-pyridyl substituent in position *15* and a phenyl in position *16*. In this spectrum the shift of the H^{15} proton compared to the prostanoids with alkyl substituents amounts to 1.73 ppm.

From the values of integral intensity of protons signals of diastereomers appearing in sufficiently diverse spectral regions we succeeded in evaluating the ration of the diastereomers obtained.

The biological tests of the synthesized prostanoids revealed among them compounds with membrane-active and antiaggregation properties, and also immunodepressants.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from thin films. ^{1}H NMR spectra were registered on spectrometer Bruker AC-200 (operating frequency 200 MHz) from solutions in $CDCl_3$ or $CDCl_3$–CCl_4 (1 : 1)and on spectrometer Bruker AC-400 (operating frequency 400 MHz) from solutions in $CDCl_3$, internal reference TMS. Mass spectra were measured on Varian-MAT-311A instrument.

The reaction progress was monitored and the purity and homogeneity of compounds synthesized was checked by TLC on plates Silufol UV-254, (Serva), DC-Plastikfolien Kieselgel 60 F_{254} (Merck) and DC-Alufolien Kieselgel 60 F_{254} (Merck) using solvent systems ethyl ether–hexane, 70 : 30; ether; ether–ethyl acetate. 95 : 5. The development was carried out under UV irradiation, with iodine vapor,

and by a solution containing 5% of anisaldehyde, 5% of sulfuric acid, and 90% of ethanol. The products were separated by column chromatography on silica gel 40/100 μ (Czechia) at gradient elution with a mixture ethyl ether–hexane, chloroform–methanol, and also by preparative TLC on glass plates with adsorbent Silicagel LL_{254} 5/40 μ using as eluents mixtures ether–hexane, 10 : 90; chloroform–methanol, 90 : 10; and ether.

Methyl 15-hydroxy-7,13-dioxo-9,11-ethano-15-R-prostanates (X, XIII–XVI). To a solution of 1 mmol of isoxazolinoprostanoid I–IX in 6 ml of a mixture methanol–water, 5 : 1, was added by small portions 600 mg of $AlCl_3$ and 500 mg of Raney Ni. The suspension was stirred for 24 h. The reaction mixture was dissolved in a two-fold volume of chloroform, filtered through a glass frit, then 1/3 of water volume was added thereto. The methanol and chloroform were distilled off in a vacuum. The hydroxyketone was thrice extracted with chloroform from the water residue, the extract was dried on $MgSO_4$, the solvent was distilled off in a vacuum. The residue was subjected to column chromatography on silica gel at gradient elution with ether–hexane mixture.

Methyl 15-hydroxy-7,13-dioxo-9,11-ethano-prostanate (X). We obtained 0.34 g of hydroxyketone **X** as viscous oily substance (yield 73%). IR spectrum, cm^{-1}: 1445 [δ(CH_2 sciss.)], 1719 [ν(C=O)], 1750 [ν(CO_2CH_3)], 2878 [ν_s(CH_2)], 2960 [ν_{as}(CH_2)], 3530 [ν(OH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.89 t (3H, CH_3, $^3J_{20,19}$ 6.5), 1.05–1.20 m (1H, $H^{11'}_{endo}$), 1.24–1.53 m (11H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 8H, 4CH_2, α-chain, ω-chain), 1.53–1.70 m (8H: 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 6H, 3CH_2, α-chain, ω-chain), 2.32 t (2H, $\underline{CH}_2CO_2CH_3$, $^3J_{2,3}$ 7.2), 2.41–2.51 m [4H: 2.45 t, 2H, CH_2C(O), $^3J_{6,5}$ 7.3; 1H, H^9; 1H, H^{14}), 2.60–2.73 m (2H: 2.67 br.d, 1H, H^{11}, $^2J_{11,11'}$ 2.5; 1H, H^{14}), 3.05 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 4.9), 3.09 br.s (1H, OH), 3.27 t.d (1H, H^8_{exo}, $^3J_{8,12}$ 4.9, $^4J_{8,9'}$ 1.4), 3.67 s (3H, CH_3O), 4.0 m (1H, H^{15}). Mass spectrum, *m/z*: 394 $[M]^+$.

Methyl 15-hydroxy-7,13-dioxo-15-phenyl-9,11-ethano-1,16,17,18,19,20-hexanorprostanate (XIII). We obtained 0.25 g of hydroxyketone **XIII** as viscous oily substance (yield 68%). IR spectrum, cm^{-1}: 1455 [δ(CH_2 sciss.)], 1705 [ν(C=O)], 1737 [ν(CO_2CH_3)], 2880 [$\nu_s CH_2$), 2960 [ν_{as}(CH_2)], 3500 [ν(OH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.99–1.13 m (1H, $H^{11'}_{endo}$), 1.20–1.68 m (9H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, H^{11}_{exo}; 4H, 2CH_2, α-chain), 2.31 t (2H, $\underline{CH}_2CO_2CH_3$, $^3J_{3,4}$ 7.0), 2.44 br.t [2H, CH_2C(O)], 2.68 br.s (1H, H^9), 2.80– 3.08 m (4H: 2H, H^{14}, $^3J_{14,15}$ 9.25; 1H, H^{11}; 3.04 d.d, 1H, H^{12}_{endo}, $^3J_{12,8}$ 5.25), 3.25 t.d (0.5 H, H^8_{exo}, $^3J_{8,12}$ 5.25, $^3J_{8,9'}$ 3.0), 3.32 t.d (0.5H, H^8_{exo}, $^3J_{8,12}$ 5.25, $^3J_{8,9'}$ 3.0), 3.44 br.s (1H, OH), 3.66 s (3H, CH_3O), 5.13 d.t (1H, H^{15}), 7.21–7.39 m (5H, C_6H_5). Mass spectrum, *m/z*: 386 $[M]^+$.

Methyl 15-hydroxy-7,13-dioxo-15-phenyl-9,11-ethano-16,17,18,19,20-pentanorprostanate (XIV). We obtained 0.29 g of hydroxyketone **XIV** as viscous oily substance (yield 68%). IR spectrum, cm^{-1}: 1456 [δ(CH_2 sciss.)], 1710 [ν(C=O)], 1739 [ν(CO_2CH_3), 2880 [ν_s(CH_2)], 2960 [ν_{as}(CH_2)], 3500 [ν(OH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.00–1.16 m (1H, $H^{11'}_{endo}$), 1.22–1.69 m (11H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 6H, 3CH_2, α-chain), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 7.2), 2.45 br.t [2H, CH_2C(O)], 2.65 br.s (1H, H^9), 2.82–3.08 m (4H: 2H, H^{14}, $^3J_{14,15}$ 9.5; 1H, H^{11}; 3.03 d.d, 1H, H^{12}_{endo}, $^3J_{12,8}$ 5.0), 3.27 t.d (0.5 H, H^8_{exo}, $^3J_{8,12}$ 5.0, $^3J_{8,9'}$ 3.4), 3.35 t.d (0.5 H, H^8_{exo}, $^3J_{8,12}$ 5.0, $^3J_{8,9'}$ 3.4), 3.43 br.s (1H, OH), 3.66 s (3H, CH_3O), 5.15 d.t (1H, H^{15}), 7.24–7.40 m (5H, C_6H_5). Mass spectrum, *m/z*: 400 $[M]^+$.

Methyl 15-hydroxy-7,13-dioxo-15-(2-pyridyl)-9,11-ethano-1,16,17,18,19,20-hexanorprostanate (XV). We obtained 0.42 g of hydroxyketone **XV** as viscous oily substance (yield 70%). IR spectrum, cm^{-1}: 1440 [δ(CH_2 sciss.)], 1709 [ν(C=O)], 1740 [ν(CO_2CH_3)], 2880 [ν_s(CH_2)], 2960 [ν_{as}(CH_2)], 3490 [ν(OH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.81–0.95 m (1H, $H^{11'}_{endo}$), 0.95–1.54 m (5H: H^{10}_{anti}; $H^{10,9'}_{syn,endo}$; $H^{9'}_{exo}$; H^{11}_{exo}), 1.60 m (4H, 2CH_2, α-chain), 2.32 t (2H, $\underline{CH}_2CO_2CH_3$, $^3J_{3,4}$ 7.2), 2.45 t [2H, CH_2C(O), $^3J_{5,6}$ 7.0], 2.55 br.d (1H, H^{11}, $^3J_{11,11'}$ 5.0), 2.67 br.s (1H, H^9), 2.85 d.d (1H, H^{14}, $^2J_{14,14}$ 11.9, $^3J_{14,15}$ 5.44), 2.96–3.26 m (2H: H^{14}, H^{12}_{endo}), 3.23 m (2H, H^8_{exo}), 3.67 s (3H, CH_3O), 4.28 br.s (1H, OH), 5.20 two d.d (1H, H^{15}), 7.19 d.d (1H, Py, $H^{5'}$), 7.41 m (1H, Py, $H^{3'}$), 7.69 t.t (1H, Py, $H^{4'}$, $^4J_{4',6'}$ 2.0), 8.52 br.d (2H, Py, $H^{6'}$, $^3J_{5',6'}$ 4.5). Mass spectrum, *m/z*: 387 $[M]^+$.

Methyl 15-hydroxy-7,13-dioxo-15-(1-imidazolyl)-9,11-ethano-1,16,17,18,19,20-hexanorprostanate (XVI). We obtained 0.14 g of hydroxyketone **XVI** as viscous oily substance (yield 65%). IR spectrum, cm^{-1}: 1450 [δ(CH_2 sciss.)], 1720 [ν(C=O)], 1752 [ν(CO_2CH_3)], 2880 [ν_s(CH_2)], 2962 [ν_{as}(CH_2)], 3410 [ν(OH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.79–0.95 m (1H, $H^{11'}_{endo}$), 1.12–1.40 m (3H: $H^{9'}_{endo}$; $H^{9'}_{exo}$; H^{10}_{anti}), 1.48– 1.87 m (6H: 1H, H^{10}_{syn}; 1H, H^{11}_{exo}; 4H, CH_2, α-chain), 2.26–2.40 m (3H: 2.32 br.t, $CH_2CO_2CH_3$; 1H, H^{11}), 2.47 br.t [2H, CH_2C(O)],

2.62–2.80 m (2H: H^{9}; H^{14}), 2.91 d.d (1H, H^{12}_{endo}), 3.31 t.d (0.5H, H^{8}_{exo}), 3.40 t.d (0.5H, H^{8}_{exo}), 3.43–3.53 two d.d (1H, H^{14}), 3.67 s (3H, CH_3O), 4.35 br.s (1H, OH), 5.90 d.t (1H, H^{15}, $^3J_{15,14}$ 6.0, $^3J_{15,OH}$ 6.0), 7.78 br.s (1H, pyrazole, $H^{4'}$), 8.09 br.s (1H, pyrazole, $H^{5'}$), 8.60 br.s (1H, pyrazole, $H^{2'}$). Mass spectrum, *m/z*: 376 $[M]^+$.

Methyl 7,13-dioxo-9,11-ethano-15-R-prost-14Z-enate (XVII–XXIII). (a) To a solution of 0.25 mmol of hydroxyketone **X–XV** in 5 ml of anhydrous benzene at 0°C was added 0.5 mmol of methanesulfonyl chloride and 0.6 ml (3-fold excess) of pyridine. The mixture was stirred for 2 h at room temperature. On completion of reaction 1–2 ml of ether was added to remove excess pyridine, and the mixture was stirred for another 15 min. Then the precipitate was separated and washed with ether on the filter. The filtrate was washed with a saturated solution of $NaHCO_3$, dried on $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel with gradient elution by a mixture hexane–ether, or the isolation was performed by TLC (eluent hexane–ether, 9 : 1).

(b) To a solution of 0.25 mmol of hydroxyketone **X–XV** in 5 ml of anhydrous benzene at low temperature was added 0.28 mmol of methanesulfonyl chloride and 0.28 mmol of triethylamine. The mixture was stirred at room temperature for 2 h till complete disappearance of the initial hydroxyketone (TLC monitoring). Om completion of the reaction the reaction mixture was washed with a saturated solution of $NaHCO_3$, then with 1% solution of HCl, dried on $MgSO_4$, and evaporated in a vacuum. The residue was subjected to column chromatography on silica gel with gradient elution by a mixture hexane–ether, or the isolation was performed by TLC (eluent hexane–ether, 9 : 1).

Methyl 7,13-dioxo-9,11-ethanoprost-14Z-enate (XVII). We obtained 0.28 g of enone **XVII** as viscous oily substance (yield 85%). IR spectrum, cm^{-1}: 1456 [$\delta(CH_2$ sciss.)], 1630 [ν(C=C, conjug. to C=O)], 1695 [ν(C=O, α,β-unsatur.)], 1710 [ν(C=O)], 1740 [$\nu(CO_2CH_3)$], 2878 [$\nu_s(CH_2)$], 2960 [$\nu_{as}(CH_2)$]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.90 t (3H, CH_3, $^3J_{20,19}$ 6.1), 1.00–1.18 m (1H, $H^{11'}_{endo}$), 1.18–1.74 m (17H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 12H, $6CH_2$, α-chain, ω-chain), 2.20 d.t (2H, H^{16}, $^3J_{16,15}$ 7.1, $^3J_{16,17}$ 7.0), 2.31 t (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ 7.2), 2.38–2.54 m [3H: 2.43 t, 2H, CH_2C(O), $^3J_{6,5}$ 7.2; 1H, H^{11}), 2.68 br.s (1H, H^9), 3.24 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.0), 3.42 t.d (1H, H^{8}_{exo}, $^3J_{8,12}$ 5.0, $^4J_{8,9'}$ 1.3), 3.67 s (3H, CH_3O), 6.12 d (1H, H^{14}, $^3J_{14,15}$ 16), 6.89 d.t (1H, H^{15}, $^3J_{15,14}$ 16, $^3J_{15,16}$ 7.1). Mass spectrum, *m/z*: 376 $[M]^+$.

Methyl 7,13-dioxo-15-(1-pyrrolidon-2-yl)-9,11-ethano-1,16,17,18,19,20-hexanorprost-14Z-enate (XVIII). We obtained 0.31 g of enone **XVIII** as viscous oily substance (yield 90%). IR spectrum, cm^{-1}: cm^{-1}: 1445 [$\delta(CH_2$ sciss.)], 1630 [ν(C=C, conjug. to C=O), 1689 [ν(C=O, α,β-unsatur.)], 1715 [ν(C=O)], 1740 $\nu(CO_2CH_3)$], 2880 [$\nu_s(CH_2)$], 2963 [$\nu_{as}(CH_2)$]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.04–1.19 m (1H, $H^{11'}_{endo}$), 1.25 d.m (1H, H^{10}_{anti}, $^2J_{10,10}$ 9.5), 1.32–1.50 m (2H, $H^{9'}_{endo}$; $H^{9'}_{exo}$), 1.60 m (6H: 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 4H, $2CH_2$, α-chain), 2.19 d.t (2H, pyrrolidone, $H^{4'}$), 2.32 t (2H, $CH_2CO_2CH_3$), 2.39–2.42 m [3H: 1H, H^{11}; 2H, CH_2C(O)], 2.57 t (2H: pyrrolidone, $H^{3'}$, $^3J_{3',4'}$ 8.0), 2.58 t (2H, pyrrolidone, $H^{5'}$, $^3J_{5',4'}$ 7.3), 2.70 br.s (1H, H^9), 3.20 br.d (1H, H^{12}_{endo}, $^3J_{8,12}$ 4.7), 3.42 t.d (1H, H^{8}_{exo}, $^3J_{8,12}$ 4.7), 3.66 s (3H, CH_3O), 5.58 d (1H, H^{14}, $^3J_{14,15}$ 14.8), 8.08 d (1H, H^{15}, $^3J_{14,15}$ 14.8). Mass spectrum, *m/z*: 375 $[M]^+$.

Methyl 17-oxa-7,13-dioxo-17-(4-chlorophenyl)-9,11-ethano-1,18,19,20-tetranorprost-14Z-enate (XIX). We obtained 0.27 g of enone **XIX** as viscous oily substance (yield 81%). IR spectrum, cm^{-1}: 1450 [$\delta(CH_2$ sciss.)], 1640 [ν(C=C, conjug. to C=O)], 1663 [ν(C=O, α,β-unsatur.)], 1709 [ν(C=O)], 1738 [$\nu(CO_2CH_3)$], 2880 [$\nu_s(CH_2)$], 2970 [$\nu_{as}(CH_2)$]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.00–1.12 m (1H, $H^{11'}_{endo}$), 1.21–1.47 m (3H: 1H, $H^{9'}_{exo}$; 1H, $H^{9'}_{endo}$; 1H, H^{10}_{anti}), 1.51 d.m (1H, H^{10}_{syn}, $^2J_{10,10}$ 10.0), 1.53–1.70 m (5H: 1H, $H^{11'}_{exo}$; 4H, CH_2, α-chain), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 7.0), 2.44 t [2H, CH_2C(O), $^3J_{6,5}$ 7.2], 2.47 br.d (1H, $H^{11'}$, $^3J_{11,11'}$ 3.4), 2.71 br.s (1H, H^9), 3.22 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.0), 3.35 t.d (1H, H^{8}_{exo}, $^3J_{8,12}$ 5.0, $^4J_{8,9'}$ 1.1), 3.66 s (3H, CH_3O), 4.67 d.d (2H, H^{16}, $^3J_{16,15}$ 4.3, $^4J_{16,14}$ 1.6), 6.42 d.t (1H, H^{14}, $^3J_{14,15}$ 15.3, $^4J_{14,16}$ 1.6), 6.80 d (2H, C_6H_5, $H^{2'}$, $H^{6'}$, $^3J_{2',3'} = {}^3J_{6',5'}$ 8.9), 6.90 d.t (1H, H^{15}, $^3J_{15,16}$ 4.3, $^3J_{15,14}$ 15.3), 7.24 d (2H, C_6H_5, $H^{3'}$, $H^{5'}$, $^3J_{3',2'} = {}^3J_{5',6'}$ 8.9). Mass spectrum, *m/z*: 432 $[M]^+$.

Methyl 17-oxa-7,13-dioxo-17-(4-chlorophenyl)-9,11-ethano-18,19,20-trinorprost-14Z-enate (XX). We obtained 0.19 g of enone XX as viscous oily substance (yield 81%). IR spectrum, cm^{-1}: 1450 [$\delta(CH_2$ sciss.)], 1640 [ν(C=C, conjug. to C=O), 1669 [ν(C=O, α,β-unsatur.)], 1705 [ν(C=O)], 1739 [$\nu(CO_2CH_3)$], 2880 [$\nu_s(CH_2)$], 2969 [$\nu_{as}(CH_2)$].

^{1}H NMR spectrum (200 MHz), δ, ppm: 1.04–1.15 m (1H, $H^{11'}_{endo}$), 1.25–1.50 m (5H: 1H, $H^{9'}_{exo}$; 1H, $H^{9'}_{endo}$; 1H, H^{10}_{anti}; 2H, CH_2, α-chain), 1.52 d.m (1H, H^{10}_{syn}, $^2J_{10,10}$ 9.8), 1.56–1.73 m (5H: 1H, $H^{11'}_{exo}$; 4H, CH_2, α-chain), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 7.3), 2.43 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 7.2], 2.47 br.d (1H, H^{11}, $^3J_{11,11'}$ 3.6), 2.71 br.s (1H, H^9), 3.26 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 4.8), 3.39 t.d (1H, H^8_{exo}, $^3J_{8,12}$ 4.8, $^4J_{8,9'}$ 1.2), 3.67 s (3H, CH_3O), 4.69 d.d (2H, H^{16}, $^3J_{16,15}$ 4.1, $^4J_{16,14}$ 1.8), 6.46 d.t (1H, H^{14}, $^3J_{14,15}$ 15.8, $^4J_{14,16}$ 1.8), 6.84 d (2H, C_6H_5, $H^{2'}$, $H^{6'}$, $^3J_{2',3'} = {}^3J_{6',5'}$ 9.1), 6.95 d.t (1H, H^{15}, $^3J_{15,16}$ 4.1, $^3J_{15,14}$ 15.8), 7.25 d (2H, C_6H_5, $H^{3'}$, $H^{5'}$, $^3J_{3',2'} = {}^3J_{5',6'}$ 9.1). Mass spectrum, *m/z*: 446 $[M]^+$.

Methyl 7,13-dioxo-15-phenyl-9,11-ethano-1,16,17,18,19,20-hexanorprost-14Z-enate (XXI). We obtained 0.36 g of enone **XXI** as viscous oily substance (yield 83%). IR spectrum, cm^{-1}: 1448 [δ(CH_2 sciss.)], 1655 [ν(C=C, conjug. to C=O), 1680 [ν(C=O, α,β-unsatur.)], 1709 [ν(C=O)], 1738 [ν(CO_2CH_3)], 2880 [$\nu_s(CH_2)$], 2960 [$\nu_{as}(CH_2)$]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.02–1.10 m (1H, $H^{11'}_{endo}$), 1.12–1.72 m (9H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, H^{11}_{exo}; 4H, $2CH_2$, α-chain), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ 7.0), 2.45 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 7.1], 2.52 br.d (1H, H^{11}, $^3J_{11,11'}$ 4.2), 2.70 br.s (1H, H^9), 3.30 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 4.8), 3.45 t.d (1H, H^8_{exo}, $^3J_{8,12}$ 4.8), 3.68 s (3H, CH_3O), 6.76 d (1H, H^{14}, $^3J_{15,14}$ 15.7), 7.44 m (3H, C_6H_5, $H^{3'}$, $H^{4'}$, $H^{5'}$), 7.56 m (2H, C_6H_5, $H^{2'}$, $H^{6'}$), 7.57 d (1H, H^{15}, $^3J_{14,15}$ 15.7). Mass spectrum, *m/z*: 368 $[M]^+$.

Methyl 7,13-dioxo-15-phenyl-9,11-ethano-16,17,18,19,20-pentanorprost-14Z-enate (XXII). We obtained 0.40 g of enone **XXII** as viscous oily substance (yield 83%). IR spectrum, cm^{-1}: 1450 [δ(CH_2 sciss.)], 1655 [ν(C=C, conjug. to C=O), 1686 [ν(C=O, α,β-unsatur.)], 1706 [ν(C=O)], 1739 [ν(CO_2CH_3)], 2880 [$\nu_s(CH_2)$], 2960 [$\nu_{as}(CH_2)$]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.06–1.11 m (1H, $H^{11'}_{endo}$), 1.15–1.75 m (11H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, H^{11}_{exo}; 6H, $3CH_2$, α-chain), 2.31 t (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ 7.2), 2.47 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 7.2), 2.54 br.d (1H, H^{11}, $^3J_{11,11'}$ 4.1), 2.74 br.s (1H, H^9), 3.36 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.1), 3.46 t.d (1H, H^8_{exo}, $^3J_{8,12}$ 5.1), 3.66 s (3H, CH_3O), 6.78 d (1H, H^{14}, $^3J_{15,14}$ 16.0), 7.40 m (3H, C_6H_5, $H^{3'}$, $H^{4'}$, $H^{5'}$), 7.56 m (2H, C_6H_5, $H^{2'}$, $H^{6'}$), 7.61 d (1H, H^{15}, $^3J_{14,15}$) 16.0). Mass spectrum, *m/z*: 382 $[M]^+$.

Methyl 7,13-dioxo-15-(2-pyridyl)-9,11-ethano-1,16,17,18,19,20-hexanorprost-14Z-enate (XXIII). We obtained 0.45 g of enone **XXIII** as viscous oily substance (yield 88%). IR spectrum, cm^{-1}: cm^{-1}: 1458 [δ(CH_2 sciss.)], 1665 [ν(C=C, conjug. to C=O), 1695 [ν(C=O, α,β-unsatur.)], 1710 [ν(C=O)], 1740 [ν(CO_2CH_3)], 2878 [$\nu_s(CH_2)$], 2959 [$\nu_{as}(CH_2)$]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.06–1.22 m (1H, $H^{11'}_{endo}$), 1.28 d.m (1H, H^{10}_{anti}; $^2J_{10,10}$ 9.0), 1.42–1.54 m (2H: $H^{9'}_{endo}$; $H^{9'}_{exo}$), 1.54–1.68 m (6H: H^{10}_{syn}; H^{11}_{exo}, 4H, $2CH_2$, α-chain), 2.33 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 6.9), 2.49 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 7.0], 2.58 br.d (H^{11}, $^3J_{11,11'}$ 4.0), 2.73 br.s (1H, H^9), 3.38 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.0), 3.52 t.d (1H, H^8_{exo}, $^3J_{8,9}$ 4.7, $^3J_{8,9'}$ 1.7, $^3J_{8,12}$ 4.6), 3.67 s (3H, CH_3O), 7.27 d (1H, H^{14}, $^3J_{15,14}$ 15.8), 7.30 d.d.d (1H, Py, $H^{5'}$, $^3J_{5',4'}$ 8.0, $^3J_{5',6'}$ 4.7, $^4J_{5',3'}$ 1.0), 7.46 d.d (1H, Py, $H^{3'}$, $^3J_{3',4'}$ 8.0), 7.60 d (1H, H^{15}, $^3J_{14,15}$ 15.8), 7.74 t.d (1H, Py, $H^{4'}$, $^3J_{4',3'}$ 8.0, $^3J_{4',5'}$ 8.0), 8.67 d.d (1H, Py, $H^{6'}$, $^3J_{6',5'}$ 4.7). Mass spectrum, *m/z*: 369 $[M]^+$.

Methyl 13-amino-15-hydroxy-7-oxo-9,11-ethano-15-R-prostanates (XXIV, XXV). To a solution of 0.5 mmol of isoxazoline and 0.5 mmol of $NiSO_4$ in 10 ml of methanol cooled to −25°C was added 2.5 mmol of sodium borohydride. In 15 min the cooling was removed, and the mixture was stirred for 1 h. Then 10 ml of 25% aqueous ammonia was added, the product was extracted into ether, the extract was dried on Na_2SO_4, the solvent was evaporated, the residue was subjected to chromatography on plates or column charged with silica gel, elution with a mixture chloroform–methanol, 20 : 1.

Methyl 13-amino-15-hydroxy-7-oxo-9,11-ethano-prostanate (XXIV). We obtained 0.09 g of aminoalcohol **XXIV** as viscous oily substance (yield 70%). IR spectrum, cm^{-1}: 1457 [δ(CH_2 sciss.)], 1705 [ν(C=O)], 1739 [ν(CO_2CH_3)], 2879 [$\nu_s(CH_2)$], 2960 [$\nu_{as}(CH_2)$], 3300, 3378, 3060–3600 [ν(NH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.82 t (3H, CH_3, $^3J_{20,19}$ 7.0), 1.00–1.10 m (1H, $H^{11'}_{endo}$), 1.10–1.47 m (13H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 8H, $4CH_2$; 2H, H^{14}), 1.47–1.70 m (8H: 1H, H^{10}_{syn}; 1H, H^{11}_{exo}; 6H, $3CH_2$), 2.12 br.d (1H, H^{11}), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ 7.2), 2.34–2.43 m (2H: H^8_{exo}; H^{12}_{endo}), 2.47 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 7.3), 2.57–2.63 m (1H, H^{13}), 2.68 br.s (1H, H^9), 3.67 s (3H, CH_3O), 3.73 m (1H, H^{15}), 3.78–3.88 br.s (NH_2, OH). Mass spectrum, *m/z*: 395 $[M]^+$.

Methyl 13-amino-15-hydroxy-7-oxo-15-phenyl-9,11-ethano-1,16,17,18,19,20-hexanorprostanate (XXV). We obtained 0.11 g of aminoalcohol **XXIV** as viscous oily substance (yield 65%). IR spectrum, cm^{-1}: 1455 [δ(CH_2 sciss.)], 1708 [ν(C=O)], 1740 [ν(CO_2CH_3)], 2879 [$\nu_s(CH_2)$], 2959 [$\nu_{as}(CH_2)$],

3305, 3460, 3000–3600 [ν(NH)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 0.94–1.80 m (11H: 1H, $H^{11'}_{endo}$; 1H, H^{10}_{anti}; 1H, $H^{9'}_{endo}$; 2H, H^{14}; 1H, $H^{9'}_{exo}$; 1H, H^{11}_{exo}; 4H, $2CH_2$), 1.93 d.t (1H, H^{10}_{syn}, $^2J_{10,10}$ 13.0, $^4J_{10,11'}$ 2.3), 2.13 br.d (1H, H^{11}), 2.21–2.66 m [6H: 1H, H^{12}_{endo}; 1H, H^{13}; 2H, $CH_2CO_2CH_3$; 2H, $CH_2C(O)$]; 2.61 br.s (1H, H^9), 2.84 t.d (1H, H^8_{exo}, $^3J_{8,12}$ 4.2), 3.66 s (3H, CH_3O), 4.48 m (1H, H^{15}), 7.18–7.36 m (5H, C_6H_5). Mass spectrum, *m/z*: 387 $[M]^+$.

Methyl 15-methoxy-7,13-dioxo-15-(1-pyrrolidon-2-yl)-9,11-ethano-1,16,17,18,19,20-hexanorprostanate (XXVI). To a solution of 0.25 mmol (100 mg) of isoxazolinoprostanoid **II** in 3 ml of water–-methanol (1 : 5) mixture was added by small portions 159 mg of $AlCl_3$ and 130 mg of Raney Ni.The suspension was stirred for 24 h. The reaction mixture was dissolved in a two-fold volume of chloroform, filtered through a glass frit, then to the filtrate was added 1/3 by volume of water. Methanol and chloroform were removed in a vacuum. The reaction product was thrice extracted from the water residue by chloroform. The extract was dried by $MgSO_4$ and evaporated in a vacuum.The residue was subjected to column chromatography on silica gel at gradient elution with a mixture ether–hexane. Yield 10.4 mg (10%). IR spectrum, cm^{-1}: 1470 [δ(CH_2 sciss.)], 1710 [ν(C=O)], 1740 [ν(CO_2CH_3)], 2840 [ν(OCH_3)], 2883 [ν_s(CH_2)], 2960 [ν_{as}(CH_2)]. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.00–1.14 m (1H, $H^{11'}_{endo}$), 1.20–1.32 m (1H, H^{10}_{anti}), 1.32–1.51 m (2H, $H^{9'}_{endo}$, $H^{9'}_{exo}$), 1.51–1.69 m (6H: 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 4H, $2CH_2$), 2.04 d.t (2H, pyrrolidone, $H^{4'}$), 2.32 br.t (2H, $CH_2CO_2CH_3$), 2.38–2.56 m [5H: 2.46 t, 2H, $CH_2C(O)$; 1H, H^{11}; 2H, pyrrolidone, $H^{3'}$], 2.56–2.74 m (2H: 2.69 br.s, 1H, H^9; 1H, H^{14}, $^3J_{14,15}$ 5.2), 2.84–3.10 m (2H: 1H, H^{14}, $^3J_{14,15}$ 8.0, $^2J_{14,14}$ 18.7; 1H, H^{12}_{endo}), 3.22 c (1.5H, OCH_3), 3.24 c (1.5H, OCH_3), 3.26–3.48 m (3H: 1H, H^8_{exo}; 2H, pyrrolidone, $H^{5'}$), 3.66 c (3H, CH_3O), 5.59 d.d (1H, H^{15}). Mass spectrum, *m/z*: 407 $[M]^+$.

Methyl 7,13-dioxo-15-R-16-thia-16-R'-9,11-ethanoprostanates (XXVII–XXXII). To a solution of 0.11 mmol of enone in 3 ml of anhydrous benzene was added 0.11 mmol of thiol and several drops of 1–5% suspension of NaH in anhydrous benzene. The mixture was stirred for 1 h. Then the reaction mixture was washed with 3 ml of 1% water solution of HCl, the reaction products were extracted into chloroform, the extract was dried on Na_2SO_4, the solvent was evaporated in a vacuum. The reaction products were subjected to chromatography on plates with silica gel (eluent hexane–ether, 7 : 1) or on a column packed with silica gel (gradient elution with a mixture Hexane–ether).

Methyl 7,13-dioxo-15-pentyl-16-thia-9,11-ethanoprostanate (XXVII). We obtained 0.33 g of thiaprostanoid **XXVII** as viscous oily substance (yield 97%). IR spectrum, cm^{-1}: 1448 [δ(CH_2 sciss.)], 1719 [ν(C=O)], 1750 [ν(CO_2CH_3)], 2880 [ν_s(CH_2)], 2965 [ν_{as}(CH_2)]. ^{1}H NMR spectrum, 400 MHz, δ, ppm: 0.90 t.d (6H, $2CH_3$), 1.01–1.13 m (1H, $H^{11'}_{endo}$), 1.20–1.71 m (23H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 6H, $3CH_2$, α-chain 4H, $2CH_2$, butyl; 8H, $4CH_2$, pentyl), 2.30 t.d (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ 7.48, $^4J_{2,4}$ 1.01), 2.45 m [5H: 2H, $CH_2C(O)$; 2H, SCH_2; 1H, H^{11}], 2.58 d.d (0.4H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 16.99, $^3J_{14,15}$ 5.89), 2.65 d (1.2H: 0.6H, $H^{14\text{-}1}_B$; 0.6H, $H^{14\text{-}2}_B$, $^3J_{14,15}$ 7.07), 2.67 br.s (1H, H^9), 2.81 d.d (0.4H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.19, $^3J_{14,15}$ 7.78), 2.98 br.d (0.4H, H^{12}_{endo}, $^3J_{12,8}$ 5.21), 3.01 br.d (0.6H, H^{12}_{endo}, $^3J_{12,8}$ 4.50), 3.07 m (1H, H^{15}), 3.32 m (1H, H^8_{exo}), 3.66 s (3H, CH_3O). Mass spectrum, *m/z*: 466 $[M]^+$.

Methyl 7,13-dioxo-15-pentyl-16-thia-9,11-ethano-1-nor-21,22,23,24-tetrahomoprostanate (XXVIII). We obtained 0.23 g of thiaprostanoid **XXVIII** as viscous oily substance (yield 97%). IR spectrum, cm^{-1}: 1449 [δ(CH_2 sciss.)], 1720 [ν(C=O)], 1753 [ν(CO_2CH_3)], 2881 [ν_s(CH_2)], 2965 [ν_{as}(CH_2)]. ^{1}H NMR spectrum (400 MHz), δ, ppm: 0.88 t.d (6H, $2CH_3$), 1.01–1.12 m (1H, $H^{11'}_{endo}$), 1.19–1.68 m (31H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 6H, $3CH_2$, α-chain 12H, $6CH_2$, octyl; 8H, $4CH_2$, pentyl), 2.30 t.d (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ 6.97, $^4J_{2,4}$ 1.57), 2.45 m [5H: 2H, $CH_2C(O)$; 2H, SCH_2; 1H, H^{11}], 2.58 d.d (0.4H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 16.99, $^3J_{14,15}$ 5.89), 2.65 d (1.2H: 0.6H, $H^{14\text{-}1}_B$; 0.6H, $H^{14\text{-}2}_B$, $^3J_{14,15}$ 7.07), 2.67 br.s (1H, H^9), 2.81 d.d (0.4H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.24, $^3J_{14,15}$ 7.79), 2.98 br.d (0.4H, H^{12}_{endo}, $^3J_{12,8}$ 5.21), 3.01 br.d (0.6H, H^{12}_{endo}, $^3J_{12,8}$ 4.50), 3.07 m (1H, H^{15}), 3.32 m (1H, H^8_{exo}), 3.66 s (3H, CH_3O). Mass spectrum, *m/z*: 522 $[M]^+$.

Methyl 7,13-dioxo-15-pentyl-16-thia-16-phenyl-9,11-ethano-1,17,18,19,20-pentanorprostanate (XXIX). We obtained 0.45 g of thiaprostanoid **XXIX** as viscous oily substance (yield 97%). IR spectrum, cm^{-1}: 1448 [δ(CH_2 sciss.)], 1720 [ν(C=O)], 1750 [ν(CO_2CH_3)], 2880 [ν_s(CH_2)], 2968 [ν_{as}(CH_2)]. ^{1}H NMR spectrum (400 MHz), δ, ppm: 0.87 m (3H,

CH_3), 0.99–1.11 m (1H, $H^{11'}_{endo}$), 1.18–1.66 m (19H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 6H, $3CH_2$, α-chain; 8H, $4CH_2$, pentyl), 2.28 t (2H, $CH_2CO_2CH_3$), 2.36–2.43 m [3.5H: 1H, H^{11}; 2H, $CH_2C(O)$; 0.5H, $H^{14\text{-}1}_A$], 2.59 d.d (0.5H, $H^{14\text{-}1}_B$, $^2J_{14,14}$ 17.90, $^3J_{14,15}$ 6.63), 2.63 m (1.5H: 1H, H^9; 0.5H, $H^{14\text{-}2}_B$, $^3J_{14,15}$ 6.62), 2.81 d.d (0.5H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.40, $^3J_{14,15}$ 6.60), 2.95 br.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.00), 3.22 t.d (0.5H, H^8_{exo}, $^3J_{8,12}$ 4.8, $^3J_{8,9'}$ 1.73), 3.29 t.d (0.5H, H^8_{exo}, $^3J_{8,12}$ 4.80, $^3J_{8,9'}$ 1.51), 3.58 m (1H, H^{15}), 3.65 s (3H, CH_3O), 7.19 t.m (1H, C_6H_5, $H^{4'}$, $^3J_{4',3'} = {}^3J_{4',5'}$ 7.1, $^4J_{4',2'} = {}^4J_{4',6'}$ =1.22), 7.26 t.d (2H, C_6H_5, $H^{3'}$, $H^{5'}$, $^3J_{3',2'} = {}^3J_{3',2'}$ 7.58, $^4J_{3',5'} = {}^4J_{3',5'} = 1.48$), 7.36 br.d (2H, C_6H_5, $H^{2'}$, $H^{6'}$, $^3J_{2',3'} = {}^3J_{6',5'}$ 7.58, $^4J_{2',6'}$ 1.52). Mass spectrum, *m/z*: 486 $[M]^+$.

Methyl 17-methoxycarbonyl-7,13-dioxo-15-pentyl-16-thia-16-phenyl-9,11-ethano-18,19,20-trinorprostanate (XXX). We obtained 0.15 g of thiaprostanoid **XXX** as viscous oily substance (yield 95%). IR spectrum, cm^{-1}: 1442 [δ(CH_2 sciss.)], 1710 [ν(C=O)], 1745 [ν(CO_2CH_3)], 2880 [$\nu_s(CH_2)$], 2960 [$\nu_{as}(CH_2)$]. ^1H NMR spectrum (200 MHz), δ, ppm: 0.88 m (3H, CH_3), 1.02–1.14 m (1H, $H^{11'}_{endo}$), 1.18–1.79 m (19H: 1H, $H^{9'}_{endo}$; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{anti}; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$; 6H, $3CH_2$, α-chain; 8H, $4CH_2$, pentyl), 2.31 t (2H, $CH_2CO_2CH_3$; 1H, H^{11}), 2.37–2.48 m [3H: 2H, $CH_2C(O)$; 1H, H^{14}], 2.58–2.76 m (2H: 1H, H^9; 1H, H^{14}), 2.75 br.d (1H, H^{12}_{endo}), 3.00 t.d (0.5H, H^8_{exo}), 3.11 t.d (0.5H, H^8_{exo}), 3.29 two t (1H, H^{15}), 3.48 m (2H, SCH_2), 3.60 s (3H, CH_3O, ω-chain), 3.66 s (3H, CH_3O, α-chain). Mass spectrum, *m/z*: 482 $[M]^+$.

Methyl 7,13-dioxo-15-(2-pyridyl)-16-thia-9,11-ethano-1-mononorprostanate (XXXI). We obtained 0.24 g of thiaprostanoid **XXXI** as viscous oily substance (yield 95%). IR spectrum, cm^{-1}: 1440 [δ(CH_2 sciss.)], 1712 [ν(C=O)], 1748 [ν(CO_2CH_3)], 2880 [$\nu_s(CH_2)$], 2961 [$\nu_{as}(CH_2)$]. ^1H NMR spectrum (200 MHz), δ, ppm: 0.84 t (3H, CH_3, $^3J_{20,19}$ 7.00), 0.98–1.24 m (3H: 1H, $H^{9'}_{endo}$; 1H, H^{10}_{anti}; 1H, $H^{11'}_{endo}$), 1.24–1.52 m (8H: 1H, $H^{9'}_{exo}$; 1H, $H^{11'}_{exo}$; 6H, $3CH_2$, butyl), 1.52– 1.67 m (5H: 1H, H^{10}_{syn}; 4H, $2CH_2$, α-chain), 2.60 m (1H, H^9), 2.95 d.d (0.7H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 14.60, $^3J_{14,15}$ 5.50), 3.04 br.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.00), 3.11 d.d (0.3H, $H^{14\text{-}1}_B$, $^2J_{14,14}$ 14.00, $^3J_{14,15}$ 6.00), 3.28 t.d (1H, H^8_{exo}), 3.34 d.d (0.3H, $H^{14\text{-}2}_B$, $^2J_{14,14}$ 18.00, $^3J_{14,15}$ 8.20), 3.60 d.d (0.7H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.20, $^3J_{14,15}$ 8.90), 3.67 s (3H, CH_3O), 4.39 two d.d (1H, H^{15}), 7.12 d.d (1H, C_5H_5N, $H^{5'}$, $^3J_{5',6'}$ 5.00, $^3J_{5',4'}$ 7.10), 7.32 br.d (1H, C_5H_5N, $H^{3'}$, $^3J_{3',4'}$ 7.00), 7.62 t.t (1H, C_5H_5N, $H^{4'}$, $^3J_{4',5'(3')}$ 7.90), 8.50 br.d (1H, C_5H_5N, $H^{6'}$, $^3J_{6',5'}$ 5.00). Mass spectrum, *m/z*: 459 $[M]^+$.

Methyl 7,13-dioxo-15-(2-pyridyl)-16-thia-16-phenyl-9,11-ethano-1,17,18,19,20-pentanorprostanate (XXXII). We obtained 0.19 g of thiaprostanoid **XXXII** as viscous oily substance (yield 95%). IR spectrum, cm^{-1}: 1459 [δ(CH_2 sciss.)], 1718 [ν(C=O)], 1749 [ν(CO_2CH_3)], 2880 [$\nu_s(CH_2)$], 2962 [$\nu_{as}(CH_2)$]. ^1H NMR spectrum (400 MHz), δ, ppm: 0.82–0.90 m (1H, $H^{11'}_{endo}$), 0.98–1.43 m (5H: 1H, $H^{9'}_{endo}$; 1H, H^{10}_{anti}; 1H, $H^{9'}_{exo}$; 1H, H^{10}_{syn}; 1H, $H^{11'}_{exo}$), 1.58 m (4H, $2CH_2$, α-chain), 2.30 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 7.10), 2.39 m [2H, $CH_2CO(O)$], 2.48 br.d (0.6H, H^{11}, $^3J_{11,11'}$ 3.98), 2.50 br.d (0.4H, H^{11}, $^3J_{11,11'}$ 3.99), 2.58 br.s (0.6H, H^9), 2.61 br.s (0.4H, H^9), 2.95 d.d (0.6H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 17.36, $^3J_{14,15}$ 5.05), 3.00 br.d (0.6H, H^{12}_{endo}, $^3J_{12,8}$ 5.21), 3.02 br.d (0.4H, H^{12}_{endo}, $^3J_{12,8}$ 5.37), 3.11 d.d (0.4H, $H^{14\text{-}1}_B$, $^2J_{14,14}$ 17.34, $^3J_{14,15}$ 5.73), 3.21 t.d (0.4H, H^8_{exo}, $^3J_{8,12}$ 4.8, $^3J_{8,9'}$ 1.56), 3.25 t.d (0.6H, H^8_{exo}, $^3J_{8,12}$ 4.54, $^3J_{8,9'}$ 1.8), 3.41 d.d (0.4H, $H^{14\text{-}2}_B$, $^2J_{14,14}$ 17.13, $^3J_{14,15}$ 8.64), 3.66 s (3H, CH_3O), 3.68 d.d (0.6H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.77, $^3J_{14,15}$ 9.35), 4.78 d.d (0.6H, H^{15}, $^3J_{15,14}$ 5.38), 4.80 d.d (0.4H, H^{15}, $^3J_{15,14}$ 5.63), 7.09 two t.d (0.4H, C_5H_5N, $H^{5'}$, $^3J_{5',6'}$ 4.79, $^3J_{5',3'}$ 1.01; 0.6H, C_5H_5N, $H^{5'}$, $^3J_{5',6'}$ 4.82, $^3J_{5',3'}$ 1.24), 7.15 br.t (1H, C_5H_5N, $H^{3'}$, $^3J_{3',4'}$ 7.93), 7.23 m (3H, C_6H_5, $H^{3''}$, $H^{4''}$, $H^{5''}$), 7.30 m (2H, C_6H_5, $H^{2''}$, $H^{6''}$), 7.50 m (1H, C_5H_5N, $H^{4'}$), 8.50 m (1H, C_5H_5N, $H^{6'}$). Mass spectrum, *m/z*: 479 $[M]^+$.

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