

## Heterocyclic Analogs of Prostaglandins: II.\* Synthesis of 10-Oxaprostanoids with Isoxazole and Isoxazoline Fragments in $\alpha$ - and $\omega$ -Chain

F.S. Pashkovskii<sup>1</sup>, Ya.M. Katok<sup>2</sup>, E.M. Shchukina<sup>1</sup>, E.V. Koroleva<sup>1</sup>, and F.A. Lakhvich<sup>1</sup>

<sup>1</sup>Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, 220141 Belarus  
e-mail: prostan@iboch.bas-net.by

<sup>2</sup>Belarus State Technological University, Minsk, Belarus

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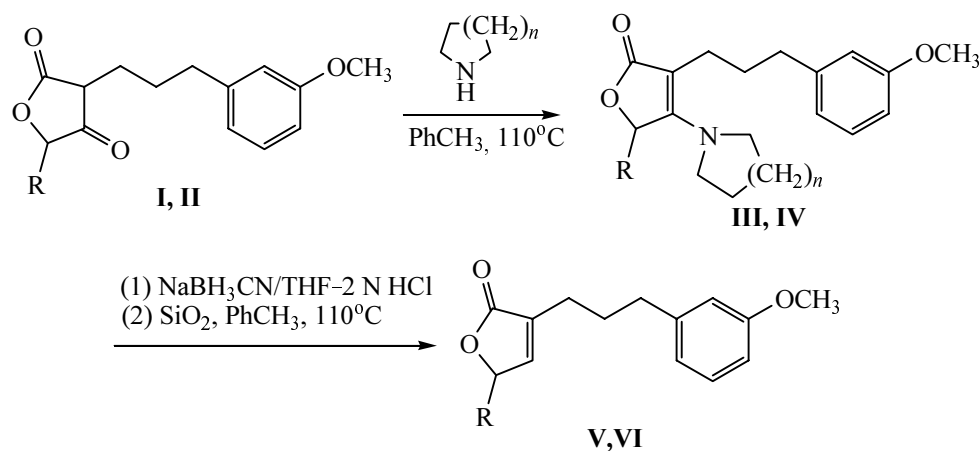
**Abstract**—By the use of “nitrile oxide procedure” from 3-alkyl(arylalkyl)-substituted 2,5-dihydro-2-furanones new 10-oxaprostanoids were prepared containing an isoxazole (isoxazoline) fragment in the  $\alpha$ - or  $\omega$ -prostanoid chain.

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Synthons especially widely applied to the prostanoid synthesis are 2-substituted cyclopentenones that have served for a number of successful prostaglandins syntheses. In [1, 2] we described a new procedure for preparation of 3-alkyl-substituted butenolides which were oxygen-containing analogs of cyclopropanone synthons. The key stages of the procedure consist in cyanoborohydride reduction of a conjugated double bond in 3-alkyl- and 3,5-dialkyl-substituted 4-pyrrolidino-2,5-dihydro-2-furanones obtained from the appropriate tetronic acids and pyrrolidine followed by retromichael elimination of the pyrrolidine moiety from the  $\beta$ -aminolactons formed on reduction.

The initial goal of this study was preparation of enamino derivatives of tetronic acids containing moieties

originating from other cyclic secondary amines, and comparison of the reduction efficiency of the conjugated double bond in the enamino lactons obtained and of the readiness of the amine moiety elimination from the arising  $\beta$ -aminolactons. To this end 2,5-dihydro-2-furanones (alkyltetronic acids) **I** and **II** [3] were brought into a reaction with piperidine. 3-Alkyltetronic acid **I** cleanly reacted with piperidine affording 4-piperidino-2,5-dihydro-2-furanone **III** in a 81% yield. On the contrary, 3,5-dialkyltetronic acid **II** did not form the corresponding enamino derivative even in the presence of a Lewis acid as catalyst, and the reaction ended at the stage of salt formation. However the reaction of tetronic acid **II** with pyrrolidine furnished the corresponding 4-pyrrolidino-2,5-dihydro-2-furanone **IV** in a 88% yield.



R = H (**I**, **III**, **V**), CH<sub>3</sub> (**II**, **IV**, **VI**);  $n = 2$  (**III**), 1 (**IV**).

\* For communication I, see [1].

The reduction of the conjugated double bond in the lacton ring of enamino derivatives **III** and **IV** with sodium cyanoborohydride in methanolic HCl occurred with an equal efficiency, and also similarly proceeded the cleavage of the amine moiety at boiling the reduction products in toluene in the presence of silica gel. The overall yield of the corresponding butenolides **V** and **VI** was 61 and 54% respectively.

Hence, the application of a six-membered secondary cyclic amine to the synthesis of  $\Delta^2$ -butenolides along this procedure is limited to preparation of monosubstituted 2,5-dihydro-2-furanones for the presence of alkyl substituents in positions 3 and 5 of the tetric acid provides a sterical hindrance for the reaction with the secondary amines containing a six-membered ring.

We formerly developed a two-stage isoxazole procedure for building up both the natural and modified prostaglandin  $\omega$ -chain consisting in nitromethane 1,4-addition to a cyclopentenone derivative, and in 1,3-cycloaddition to an alkene or alkyne of a nitrile oxide generated from a nitromethyl derivative [4]. However up till now the "nitrile oxide procedure" was used exclusively in preparation of carbocyclic analogs of 13,15-isoxazolo- and isoxazolinoprostanoids, but isoxazolo(isoxazolino)-prostanoids with a heteroatom in the five-membered ring of the prostanoid skeleton were not yet described.

In extension of research on the synthesis of modified prostaglandins we report here on the preparation of 10-oxa-13,15-isoxazolo(isoxazolino)prostanoids, and also 10-oxa-5,7-isoxazolinoprostanoids proceeding from butenolides **V** and **VI** and formerly described butenolides **VII–X** [1] applying the nitrile oxide (isoxazole) approach to the building up of the side chain of the prostanoid.

For this purpose we brought the named butenolides into the reaction with nitromethane in the presence of tetramethylguanidine as a catalyst. Unlike 2-alkylsubstituted cyclopentenones 3-alkyl substituted 2,5-dihydro-2-furanones are less reactive with respect to nucleophiles [5]. The Michael addition of the nitromethane to compounds **V–X** in methanol solution at room temperature occurs very slowly giving traces of nitromethyl derivatives **XI–XVI**. However the reaction carried out in neat nitromethane afforded target compounds **XI–XVI** in 85–90% yields. The IR spectra of the compounds contain the characteristic bands of nitro group stretching vibrations at 1380–1390 and 1555–1570  $\text{cm}^{-1}$  and those of carbonyl in the saturated lacton at 1770–1795  $\text{cm}^{-1}$ .

The reactions of 1,4-conjugate addition to monosubstituted 2,5-dihydro-2-furanones are known to proceed

non-stereoselectively affording a mixture of the corresponding *cis*- and *trans*-adducts where the relative content of the *trans*-isomers grows with the bulk of substituents [6, 7]. Unlike [6] we failed to isolate *cis*-isomers of the nitromethyl derivatives and to reveal their presence in the reaction mixtures by the  $^1\text{H}$  NMR spectra. The relative orientation of substituents in the positions 8 and 12 of the ring (according to the prostaglandin nomenclature) was assigned using the chemical shift values of proton signals from  $\text{H}^8$  and  $\text{H}^{12}$  in the butyrolacton ring of nitromethyl derivatives **XI–XVI** and the corresponding coupling constants. The proton signals from  $\text{H}^8$  and  $\text{H}^{12}$  in 11-demethyl derivatives **XI**, **XIII**, and **XV** appear in the region 2.34–2.37 and 3.03–3.08 ppm respectively indicating that the compounds are *trans*-isomers [6]. The  $\text{H}^{12}$  proton in nitromethyl derivatives **XII**, **XIV**, and **XVI** suffers shielding from the 11- $\text{CH}_3$  group, and its signal is located upfield (2.54–2.70 ppm) with respect to the analogous signal in the spectra of 11-demethyl derivatives. By contrast, the  $\text{H}^8$  signals in the 11-methyl derivatives are shifted downfield (2.47 ppm) as compared with the corresponding signals in the spectra of 11-demethyl derivatives. Thus in 11-methyl derivatives **XII** and **XVI** the signals of  $\text{H}^{12}$  and  $\text{H}^8$  are brought nearer to each other, and in the spectrum of compound **XIV** they overlap. Inasmuch as in the  $^1\text{H}$  NMR spectra (save in that of compound **XIV**) of nitromethyl derivatives **XI–XIII**, **XV**, and **XVI** the signal of  $\text{H}^8$  does not coincide with other signals and appears in most cases as a doublet of triplets, we have chosen it for estimation of the coupling constant  $J_{8,12}$ . The coupling constant of protons  $\text{H}^8$  and  $\text{H}^{12}$  in 11-demethyl derivatives **XI**, **XIII**, and **XV** equal to 8.0 Hz also indicates the *trans*-orientation of the pseudoaxial protons  $\text{H}^8$  and  $\text{H}^{12}$  and consequently the *trans*-orientation of the pseudoequatorial alkyl (arylalkyl) and nitromethyl substituents in these compounds [7]. Note that the presence of an alkyl substituent in the position 11 causes the increase in the coupling constant of the protons  $\text{H}^8$  and  $\text{H}^{12}$ , and in 11-methyl derivatives **XII**, **XIV**, and **XVI** it amounts to 9.6–10.0 Hz. The coupling constants of protons  $\text{H}^{11}$  and  $\text{H}^{12}$  in 11-methyl derivatives **XII**, **XIV**, and **XVI** equal to 8.0–8.4 Hz evidence the reciprocal *trans*-orientation of the protons and consequently the *trans*-orientation of the methyl and nitromethyl substituents [8].

Thus, the nitromethane addition to butenolides **V–X** occurred stereoselectively giving exclusively *trans*-adducts **XI–XVI**.

The next stage of the “nitrile oxide procedure” involves the conversion effected by phenyl isocyanate of nitromethyl derivatives **XI–XVI** into the corresponding nitrile oxide intermediates **A** that react *in situ* with a terminal alkyne or alkene as a dipolarophile. 1,3-Dipolar cycloadditions of the nitrile oxides proceed regioselectively affording adducts with a 3,5-disubstituted isoxazole (isoxazoline) fragment in keeping with the rule of nitrile oxides addition to the terminal alkynes and alkenes.

The reaction of nitrile oxides obtained from nitromethyl derivatives **XI–XV** with heptyne furnished 13,15-isoxazoloprostanoids **XVII–XXI**. At the same time the reaction of nitrile oxides obtained from nitromethyl derivatives **XI** and **XII** with ethyl 4-pentynoate gave rise to 10,19-dioxa-5,7-isoxazolo-16,17,18-trinor-15,19-inter-*m*-phenylenoprostanoids **XXII** and **XXIII** containing isoxazole moieties in the  $\alpha$ -chain and with 3-arylalkyl substituent playing the part of the  $\omega$ -prostanoid chain.

The addition of nitrile oxides from precursors **XIII–XVI** to 4-vinylpyridine gave rise to a chromatographically inseparable mixture (~1:1) of two cycloadducts, 10-oxa-13,15-isoxazolinoprostanoids **XXIVa–XXVIIa** and **XXIVb–XXVIIb**, with similar but still distinguishable spectral parameters. Both adducts based on their physicochemical characteristics were assigned to 15-epimers originating from non-stereoselective addition of nitrile oxide to the terminal double bond.

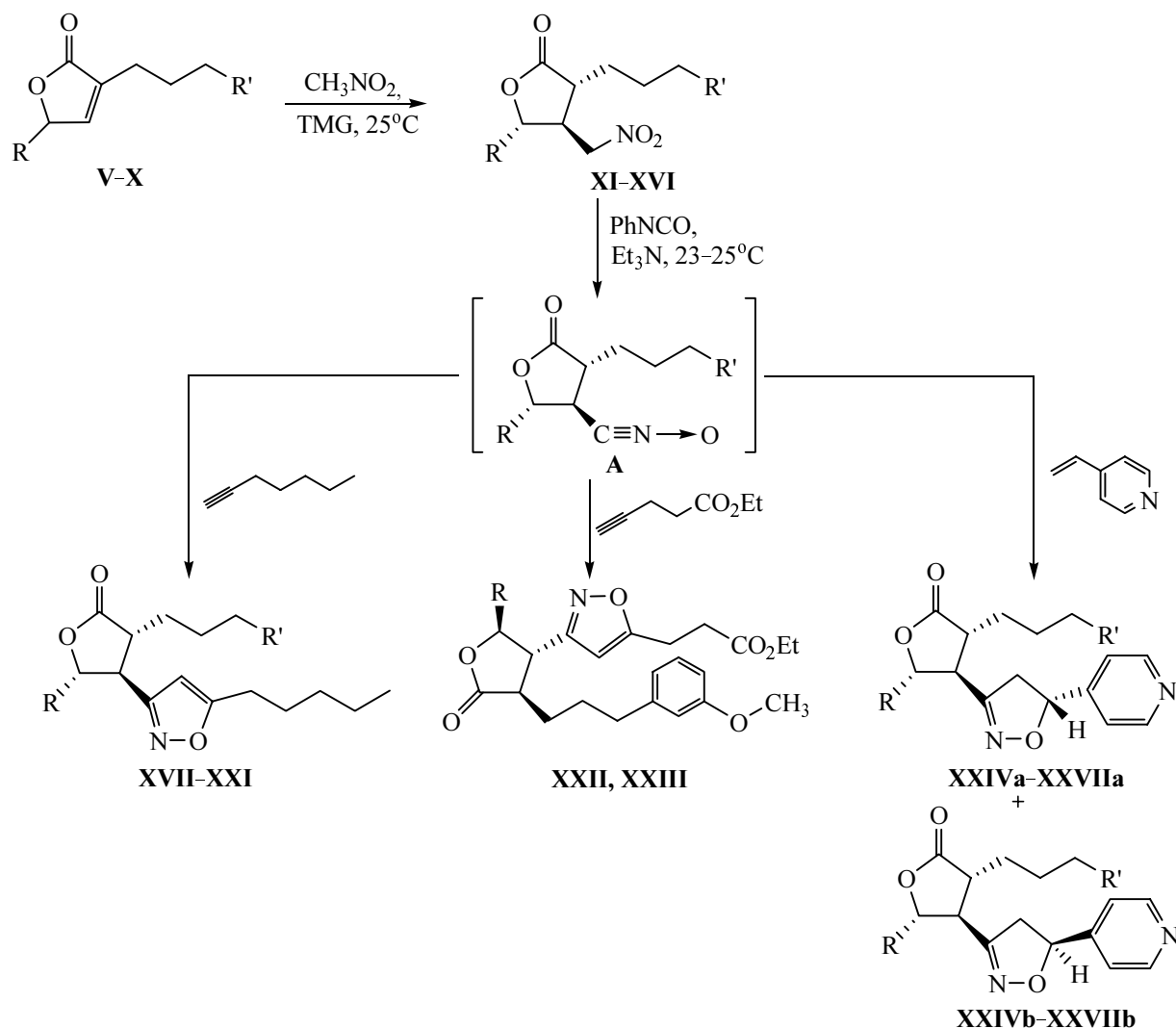
In the IR spectra of heteroprostanoids **XVII–XXVII** alongside the strong band of the stretching vibrations of a carbonyl in the saturated lacton at 1775–1790  $\text{cm}^{-1}$  appeared also a medium band from the absorption of the C=N bond of the heterocycle at 1605–1620  $\text{cm}^{-1}$ .

The estimation of the mutual orientation of the  $\alpha$ - and  $\omega$ -prostanoid chains in isoxazoloprostanoids **XVII–XXI** was also based on the coupling constants  $J_{12,8}$  but unlike the case of nitromethyl derivatives the signal of  $\text{H}^{12}$  proton was used as a reference point. It appeared as a doublet of doublets of doublets at 3.56–3.60 ppm in the spectra of 11-demethylisoxazoloprostanoids **XVII**, **XIX**, and **XXI**, and as a doublet of doublets at 3.07 ppm for 11-methylisoxazoloprostanoids **XVIII** and **XX**. The proton  $\text{H}^{12}$  in the spectra of isoxazoloprostanoids **XVIII** and **XX**, same as in the spectra of the corresponding nitromethyl derivatives, is shielded by the methyl group and its signal appears upfield with respect to the analogous signal in the  $^1\text{H}$  NMR spectra of compounds **XVII**, **XIX**, and **XXI**. The value  $J_{12,8}$  11.0 Hz in the  $^1\text{H}$  NMR spectra of 11-dimethylprostanoids **XVII**, **XIX**, and **XXI**, and the value  $J_{12,8}$  12.0 Hz in the  $^1\text{H}$  NMR spectra of 11-methyl-

prostanoids **XVIII** and **XX** indicate the *trans*-orientation of the  $\alpha$ - and  $\omega$ -prostanoid chains in isoxazoloprostanoids **XVII–XXI**. The *trans*-orientation of the 11-methyl and the  $\omega$ -prostanoid chain is clear from the value of the coupling constant of the methine proton  $\text{H}^{11}$  in the lacton ring adjacent to the methyl group. The doublet of quartets at 4.47 ppm ( $J_{11,12}$  9.5 Hz) testifies to the *trans*-orientation of the 11-methyl substituent and the  $\omega$ -prostanoid chain in compounds **XVIII** and **XX**. The signal of proton  $\text{H}^8$  in the  $^1\text{H}$  NMR spectra of 11-demethylisoxazoloprostanoids **XVII**, **XIX**, and **XXI** appears upfield (2.68–2.89 ppm) with respect to the similar signal in the spectra of 11-methylisoxazoloprostanoids **XVIII** and **XX** (2.87–3.00 ppm).

In the  $^1\text{H}$  NMR spectra of isoxazolinoprostanoids **XXIVa**, **XXIVb–XXVIIa**, **XXVIIb** the presence of a mixture of diastereomers is revealed by doubling or broadening of proton signals from characteristic groups in these compounds. The difference in the chemical shift ( $\Delta\delta$ ) of proton signals from the most corresponding groups in the diastereomers is negligibly small and amounts to 0.01–0.03 ppm. The largest difference in the chemical shifts was observed for the signal from the methine proton  $\text{H}^{11}$  of the lacton ring in 11-methylisoxazolinoprostanoids **XXVa**, **b** and **XXVIIa**, **b**, and it equaled 0.08–0.09 ppm. For the signals of the 11-methyl protons of the lacton ring  $\Delta\delta$  was 0.03–0.04 ppm. In 11-demethylisoxazolinoprostanoids **XXIVa**, **XXIVb** and **XXVIa**, **XXVIb** the largest difference in the chemical shifts was observed for the upfield signal from  $\text{H}_\alpha^{11}$  located in the *trans*-position with respect to  $\text{H}^{12}$  ( $J_{11\alpha,12}$  9.0 Hz), and it amounted to 0.02–0.04 ppm. The difference in the chemical shifts of the signals from  $\text{H}_\beta^{11}$  of the diastereomers either lacked or was negligible (signal broadening).

The difference in the chemical shifts of  $\text{H}^8$  proton signals in the spectra of 11-methyl- and 11-demethylisoxazolinoprostanoids was not revealed due to overlapping with other peaks, first of all, with the resonance of the proton  $\text{H}_\alpha^{14}$ , and in 11-methylisoxazolinoprostanoids **XXVa**, **XXVb** and **XXVIIa**, **XXVIIb** also with that of proton  $\text{H}^{12}$ . Same as in the spectra of nitromethyl derivatives and isoxazoloprostanoids the signal of  $\text{H}^{12}$  suffers shielding by the methyl group in position 11 and therefore it shifts upfield and overlaps with the signal of proton  $\text{H}^8$ . In the 11-demethyl analogs **XXIVa**, **XXIVb** and **XXVIa**, **XXVIb** the signal of proton  $\text{H}^{12}$  is displaced downfield. It overlaps in the spectra of compounds **XXIVa**, **XXIVb** with the signal of  $\text{H}_\beta^{14}$ , and only in the spectra of compounds **XXVIa**, **XXVIb** the overlapping



$R = H, R' =$  (V, XI, XVII), (VII, XIII, XIX, XXIVa, XXIVb),  $(CH_2)_3CO_2CH_3$  (IX, XV, XXI, XXVIa, XXVIIb);

$R = CH_3, R' =$  (VI, XII, XVIII), (VIII, XIV, XX, XXVa, XXVb),  $(CH_2)_3CO_2CH_3$  (X, XVI, XXVIIa, XXVIIIb);

$R = H$  (XXII),  $CH_3$  (XXIII).

is incomplete, and the resonance from  $H^{12}$  appeared as two doublets of doublets. Using the double resonance technique we estimated the coupling constant  $J_{12,8}$  that equaled 10.0 Hz indicating the *trans*-orientation of the  $\alpha$ - and  $\omega$ -prostanoid chains.

The methine proton  $H^{11}$  from the lacton ring gives rise to a resonance at 4.37–4.38 ppm in a form of two doublets of quartets. The coupling constant  $J_{11,12}$  of 9.0 Hz evidences the mutual *trans*-orientation of the 11-methyl group and the  $\omega$ -prostanoid chain in 10-oxa-

11-methylisoxazolinoprostanoids **XXVa**, **XXVb** and **XXVIIa**, **XXVIIb**. The methyl group protons of these compounds are observed as two doublets in the region 1.43–1.44 ppm for one 15-epimer and 1.46–1.48 ppm for another epimer. The signals from the diastereotopic protons of the methylene group in the lacton ring of 11-demethyl analogs **XXIVa**, **XXIVb** and **XXVIa**, **XXVIb** appear in the region 4.11–4.14 ppm ( $H_{\alpha}^{11}$ , *trans* with respect to  $H^{12}$ ,  $J_{11\alpha,12}$  9.0 Hz) as two doublet of doublets, and in the region 4.48–4.49 ppm ( $H_{\beta}^{11}$ , *cis* with



respect to  $H^{12}$ ,  $J_{11\beta,12}$  8.0 Hz) as a slightly broadened doublet of doublets.

The synthesized 10-oxa-13,15- and 10-oxa-5,7-isoxazolo-prostanoids, and also 10-oxa-13,15-isoxazolino-prostanoids are heteroanalogs of 11-desoxyprostaglandines of the *E*-series with an  $\omega$ - or  $\alpha$ -chain modified by several heteroatoms included into one or two heterocycles. These prostanoids are free for further modification using the capability of the functional groups and the latent functionality of the isoxazole (isoxazoline) ring toward reductive transformations [9].

Prostanoids **XXIVa**, **XXIVb–XXVIIa**, **XXVIIb** with heterocyclic fragments in the  $\omega$ -chain in their turn constitute convenient intermediates for building up 15-heterocyclic analogs of prostaglandins by selective cleavage of the isoxazoline ring along the routes described for similar semiproducts [10].

## EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from films.  $^1\text{H}$  NMR spectra were registered on spectrometers Bruker AC-200 (200 MHz) and Bruker WM-360 (360 MHz) in  $\text{CDCl}_3$ , internal reference TMS. Mass spectra were measured on a Varian MAT-311 instrument at ionizing electrons energy 70 eV. The column chromatography was carried out on silica gel 40/100  $\mu$  (Czechia), in thin layer chromatography were used Silufol UV-254 (Serva) and Kieselgel 60F<sub>254</sub> (Merck) plates, eluents hexane–ether, 65:35, or chloroform–methanol, 85:15, spots visualized with anisaldehyde. The preparative TLC was performed with the use of glass plates Kieselgel L 5/40  $\mu$ , eluent 5% of methanol in chloroform.

**Reaction of secondary cyclic amines with 3-aryl-alkyltetronic acids I and II.** To a dispersion of 3-alkyltetronic acid (10 mmol) in 30 ml of toluene was added dropwise at stirring 12 mmol of an appropriate amine. The formed salt of the  $\beta$ -dicarbonyl compound was boiled for 5–8 h removing the water arising in the reaction into a Dean-Stark trap. The reaction mixture was filtered, the toluene was distilled off in a vacuum, the residue was subjected to column chromatography on silica gel (eluent chloroform).

**3-[3-(3-Methoxyphenyl)propyl]-4-piperidino-2,5-dihydrofuran-2-one (III).** Oily substance. Yield 81%. IR spectrum,  $\text{cm}^{-1}$ : 1250, 1270, 1325, 1360, 1455 br, 1480, 1500, 1630 max, 1745.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.46–1.69 m (6H,  $3\text{CH}_2$  of piperidine), 1.76 quintet (2H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{Ar}$ ,  $^3J$  7.5 Hz), 2.35 t [2H,  $\text{CH}_2(\text{CH}_2)_2\text{Ar}$ ,  $^3J$  7.5 Hz], 2.65 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.5 Hz), 3.20 narrow m

[4H,  $\text{N}(\text{CH}_2)_2$  of piperidine], 3.80 s (3H,  $\text{OCH}_3$ ), 4.54 s (2H,  $\text{CH}_2$  in lacton ring), 6.66–6.82 m ( $3\text{H}_{\text{arom}}$ ), 7.19 t.d (1 $\text{H}_{\text{arom}}$ ,  $^3J$  7.5,  $^4J$  1.0 Hz). Mass spectrum:  $m/z$  315 [ $M$ ]<sup>+</sup>. Found, %: C 72.37; H 8.06; N 4.48.  $\text{C}_{19}\text{H}_{25}\text{NO}_3$ . Calculated, %: C 72.35; H 7.99; N 4.44.

**5-Methyl-3-[3-(3-methoxyphenyl)propyl]-4-pyrrolidino-2,5-dihydrofuran-2-one (IV).** Oily substance. Yield 88%. IR spectrum,  $\text{cm}^{-1}$ : 1245, 1270, 1345, 1450 sh, 1465, 1500, 1615 max, 1735.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.41 d (3H,  $\text{CH}_3\text{CH}$ ,  $^3J$  6.5 Hz), 1.48–1.72 m (4H,  $2\text{CH}_2$  of pyrrolidine), 1.72–1.90 m (2H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{Ar}$ ), 2.32 t [2H,  $\text{CH}_2(\text{CH}_2)_2\text{Ar}$ ,  $^3J$  8.0 Hz], 2.62 m (2H,  $\text{CH}_2\text{Ar}$ ), 3.21 narrow m [4H,  $\text{N}(\text{CH}_2)_2$  of pyrrolidine], 3.80 s (3H,  $\text{OCH}_3$ ), 4.80 q (1H,  $\text{CH}_3\text{CH}$ ,  $^3J$  6.5 Hz), 6.66–6.82 m ( $3\text{H}_{\text{arom}}$ ), 7.19 t.d (1 $\text{H}_{\text{arom}}$ ,  $^3J$  7.0,  $^4J$  2.0 Hz). Mass spectrum:  $m/z$  315 [ $M$ ]<sup>+</sup>. Found, %: C 72.36; H 7.96; N 4.39.  $\text{C}_{19}\text{H}_{25}\text{NO}_3$ . Calculated, %: C 72.35; H 7.99; N 4.44.

2,5-Dihydrofuran-2-ones **V–X** were obtained by procedure described in [1] and [3].

**3-[3-(3-Methoxyphenyl)propyl]-2,5-dihydrofuran-2-one (V).** Oily substance. Yield 61%. IR spectrum,  $\text{cm}^{-1}$ : 1065, 1085, 1160, 1175, 1210, 1270, 1295, 1325, 1355, 1450, 1460, 1500, 1595, 1610, 1765 max.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.91 quintet (2H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{Ar}$ ,  $^3J$  7.5 Hz), 2.34 t.d [2H,  $\text{CH}_2(\text{CH}_2)_2\text{Ar}$ ,  $^3J$  7.5,  $^4J$  1.8 Hz], 2.66 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.5 Hz), 3.80 s (3H,  $\text{OCH}_3$ ), 4.76 q (2H,  $\text{CH}_2$  in the ring,  $^3J = ^5J = 1.8$  Hz), 6.70–6.82 m ( $3\text{H}_{\text{arom}}$ ), 7.11 quintet (1H vinyl,  $^3J = ^4J = 1.8$  Hz), 7.22 br.t (1 $\text{H}_{\text{arom}}$ ,  $^3J$  8.0 Hz). Mass spectrum:  $m/z$  232 [ $M$ ]<sup>+</sup>. Found, %: C 72.12; H 6.93.  $\text{C}_{14}\text{H}_{16}\text{O}_3$ . Calculated, %: C 72.39; H 6.94.

**5-Methyl-3-[3-(3-methoxyphenyl)propyl]-2,5-dihydrofuran-2-one (VI).** Oily substance. Yield 54%. IR spectrum,  $\text{cm}^{-1}$ : 1025, 1080, 1095, 1120, 1150, 1165, 1200, 1265, 1290, 1320, 1375, 1435, 1455, 1490, 1582, 1600, 1750 max.  $^1\text{H}$  NMR spectrum (360 MHz),  $\delta$ , ppm: 1.40 d (3H,  $\text{CH}_3\text{CH}$ ,  $^3J$  7.2 Hz), 1.89 quintet (2H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{Ar}$ ,  $^3J$  7.8 Hz), 2.32 t.t [2H,  $\text{CH}_2(\text{CH}_2)_2\text{Ar}$ ,  $^3J$  7.8,  $^4J = ^5J = 1.8$  Hz], 2.65 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.8 Hz), 3.81 s (3H,  $\text{OCH}_3$ ), 4.99 q.q (1H,  $\text{CH}_3\text{CH}$ ,  $^3J_1$  7.2,  $^3J_2 = ^5J = 1.8$  Hz), 6.72–6.81 m ( $3\text{H}_{\text{arom}}$ ), 6.99 q (1 $\text{H}_{\text{vinyl}}$ ,  $^3J = ^4J = 1.8$  Hz), 7.21 t.d (1 $\text{H}_{\text{arom}}$ ,  $^3J$  7.2,  $^4J$  1.8 Hz). Mass spectrum:  $m/z$  246 [ $M$ ]<sup>+</sup>. Found, %: C 73.06; H 7.31.  $\text{C}_{15}\text{H}_{18}\text{O}_3$ . Calculated, %: C 73.15; H 7.36.

**Nitromethane addition to 3-alkyl-substituted 2,5-dihydro-2-furanones V–X.** To a solution of 0.01 mol of 2,5-dihydro-2-furanone **V–X** in 2.1 ml of anhydrous

nitromethane was added 0.002 mol of tetramethylguanidine (TMG), and the reaction mixture was stirred at room temperature till disappearance of the initial furanone (TLC monitoring). On completion of the reaction the mixture was diluted with anhydrous benzene and filtered through a small bed of silica gel. The solvent and nitromethane excess was evaporated, and the residue was subjected to chromatography on silica gel (eluent ether–hexane, 1:3).

**3 $\alpha$ -[3-(3-Methoxyphenyl)propyl]-4 $\beta$ -(nitromethyl)tetrahydrofuran-2-one (XI).** Yield 85%. IR spectrum,  $\text{cm}^{-1}$ : 1035 sh, 1045, 1105, 1160, 1170, 1185 sh, 1265, 1290 sh, 1320, 1385, 1440, 1465, 1490, 1560, 1585, 1605, 1670, 1770 max.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.52–1.98 m [4H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$ ], 2.35 d.t (1H,  $\text{H}^8$ ,  $^3J$  8.0, 6.0 Hz), 2.65 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  6.7 Hz), 3.03 m (1H,  $\text{H}^{12}$ ), 3.80 s (3H,  $\text{OCH}_3$ ), 4.05 d.d (1H,  $\text{H}_\alpha^{II}$  in the ring,  $^2J$  10.0,  $^3J$  7.0 Hz), 4.36–4.61 m (3H,  $\text{H}_\beta^{II}$  in the ring +  $\text{CH}_2\text{NO}_2$ ), 6.68–6.82 m (3H<sub>arom</sub>), 7.22 br.t (1H<sub>arom</sub>,  $^3J$  7.5 Hz). Mass spectrum:  $m/z$  293 [ $M$ ]<sup>+</sup>. Found, %: C 61.53; H 6.55.  $\text{C}_{15}\text{H}_{19}\text{NO}_5$ . Calculated, %: C 61.42; H 6.53.

**5 $\alpha$ -Methyl-3 $\alpha$ -[3-(3-methoxyphenyl)propyl]-4 $\beta$ -(nitromethyl)tetrahydrofuran-2-one (XII).** Yield 87%. IR spectrum,  $\text{cm}^{-1}$ : 1040 br, 1110, 1150, 1165, 1190, 1260, 1315, 1380, 1435, 1455, 1490, 1555 max, 1580, 1600, 1770.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.44 d (3H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  6.0 Hz), 1.66–1.91 m [4H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$ ], 2.47 d.t (1H,  $\text{H}^8$ ,  $^3J$  9.6, 5.4 Hz), 2.56 m (1H,  $\text{H}^{12}$ ), 2.64 m (2H,  $\text{CH}_2\text{Ar}$ ), 3.81 s (3H,  $\text{OCH}_3$ ), 4.34 d.q (1H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  8.4, 6.0 Hz), 4.49 d (2H,  $\text{CH}_2\text{NO}_2$ ,  $J$  6.0 Hz), 6.72–6.81 m (3H<sub>arom</sub>), 7.21 br.t (1H<sub>arom</sub>,  $^3J$  7.8 Hz). Mass spectrum:  $m/z$  307 [ $M$ ]<sup>+</sup>. Found, %: C 62.39; H 6.92.  $\text{C}_{16}\text{H}_{21}\text{NO}_5$ . Calculated, %: C 62.53; H 6.89.

**Methyl 4-[3-(4 $\beta$ -nitromethyl-2-oxotetrahydrofuran-3 $\alpha$ -yl)propyl]benzoate (XIII).** Yield 90%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1115, 1185, 1290 max, 1320, 1390, 1443, 1565, 1620, 1725, 1780.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.56–2.00 m [4H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$ ], 2.37 d.t (1H,  $\text{H}^8$ ,  $^3J$  8.0, 6.0 Hz), 2.72 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  6.5 Hz), 3.03 m (1H,  $\text{H}^{12}$ ), 3.90 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.06 d.d (1H,  $\text{H}_\alpha^{II}$  in the ring,  $^2J$  10.0,  $^3J$  7.0 Hz), 4.41–4.63 m (3H,  $\text{H}_\beta^{II}$  in the ring +  $\text{CH}_2\text{NO}_2$ ), 7.25 d (2H<sub>arom</sub>,  $^3J$  8.0 Hz), 7.96 d (2H<sub>arom</sub>,  $^3J$  8.0 Hz). Mass spectrum:  $m/z$  321 [ $M$ ]<sup>+</sup>. Found, %: C 59.90; H 5.95.  $\text{C}_{16}\text{H}_{19}\text{NO}_6$ . Calculated, %: C 59.81; H 5.96.

**Methyl 4-[3-(5 $\alpha$ -methyl-4 $\beta$ -nitromethyl-2-oxotetrahydrofuran-3 $\alpha$ -yl)propyl]benzoate (XIV).** Yield 87%. IR spectrum,  $\text{cm}^{-1}$ : 1025, 1060, 1120, 1190, 1290 max, 1315, 1385, 1440, 1560, 1615, 1720, 1780.  $^1\text{H}$  NMR

spectrum,  $\delta$ , ppm: 1.45 d (3H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  6.0 Hz), 1.62–2.00 m [4H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$ ], 2.44–2.65 m (2H,  $\text{H}^8 + \text{H}^{12}$ ), 2.72 m (2H,  $\text{CH}_2\text{Ar}$ ), 3.90 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.34 d.q (1H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  8.0, 6.0 Hz), 4.51 d (2H,  $\text{CH}_2\text{NO}_2$ ,  $J$  5.5 Hz), 7.26 d (2H<sub>arom</sub>,  $^3J$  8.0 Hz), 7.97 d (2H<sub>arom</sub>,  $^3J$  8.0 Hz). Mass spectrum:  $m/z$  335 [ $M$ ]<sup>+</sup>. Found, %: C 60.75; H 6.27.  $\text{C}_{17}\text{H}_{21}\text{NO}_6$ . Calculated, %: C 60.88; H 6.31.

**Methyl 7-(4 $\beta$ -nitromethyl-2-oxotetrahydrofuran-3 $\alpha$ -yl)heptanoate (XV).** Yield 85%. IR spectrum,  $\text{cm}^{-1}$ : 1035, 1115, 1185, 1210, 1265 sh, 1340, 1390, 1450, 1475, 1570, 1750, 1795.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.23–1.54 m (6H, 3 $\text{CH}_2$   $\alpha$ -chain), 1.54–1.90 m (4H,  $\text{CH}_2$  at the ring +  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$ ), 2.26–2.42 m (1H,  $\text{H}^8$ ), 2.32 t (2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $^3J$  7.5 Hz), 3.08 m (1H,  $\text{H}^{12}$ ), 3.68 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.10 d.d (1H,  $\text{H}_\alpha^{II}$  in the ring,  $^2J$  10.0,  $^3J$  7.0 Hz), 4.42–4.70 m (3H,  $\text{H}_\beta^{II}$  in the ring +  $\text{CH}_2\text{NO}_2$ ). Mass spectrum:  $m/z$  287 [ $M$ ]<sup>+</sup>. Found, %: C 54.37; H 7.37.  $\text{C}_{13}\text{H}_{21}\text{NO}_6$ . Calculated, %: C 54.34; H 7.37.

**Methyl 7-(5 $\alpha$ -methyl-4 $\beta$ -nitromethyl-2-oxotetrahydrofuran-3 $\alpha$ -yl)heptanoate (XVI).** Yield 89%. IR spectrum,  $\text{cm}^{-1}$ : 1035 sh, 1065, 1100, 1120, 1195, 1260, 1355 sh, 1370, 1390, 1445, 1460 sh, 1565, 1670, 1745, 1785 max.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.20–1.43 m (6H, 3 $\text{CH}_2$   $\alpha$ -chain), 1.46 d (3H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  6.0 Hz), 1.50–1.82 m (4H,  $\text{CH}_2$  at the ring +  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$ ), 2.32 t (2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $^3J$  7.5 Hz), 2.47 d.t (1H,  $\text{H}^8$ ,  $^3J$  10.0, 5.5 Hz), 2.54–2.70 m (1H,  $\text{H}^{12}$ ), 3.68 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.36 d.q (1H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  8.0, 6.0 Hz), 4.54 d (2H,  $\text{CH}_2\text{NO}_2$ ,  $J$  6.5 Hz). Mass spectrum:  $m/z$  301 [ $M$ ]<sup>+</sup>. Found, %: C 55.90; H 7.74.  $\text{C}_{14}\text{H}_{23}\text{NO}_6$ . Calculated, %: C 55.80; H 7.69.

**10-Oxa-13,15(5,7)-isoxazolo- XVII–XXIII and 10-oxa-13,15-isoxazolinoprostanoids XXIVa, XXIVb–XXVIIa, XXVIIab.** In 15 ml of anhydrous benzene was dissolved 0.001 mol of nitromethyl derivative XI–XVI, excess of an appropriate alkyne or alkene was added (0.002–0.003 mol) and 0.004 mol of phenyl isocyanate. After adding several drops of triethylamine (till precipitation of diphenylurea started) the reaction mixture was stirred at room temperature for 24–48 h preventing moisture penetration till disappearance of the initial nitro compound (TLC monitoring). The reaction mixture was filtered through aluminum oxide, and the retained residue of product was eluted with a hexane–ether mixture. The target compound was isolated by chromatography on silica gel at gradient elution with a mixture hexane–ether or chloroform–methanol.

**3 $\alpha$ -[3-(3-Methoxyphenyl)propyl]-4 $\beta$ -(5-pentylisoxazol-3-yl)tetrahydrofuran-2-one (XVII).** Yield 45%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1040, 1090, 1120, 1160, 1185, 1240, 1285, 1320, 1385, 1445, 1510, 1535, 1605, 1785.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.90 t (3H,  $\text{CH}_3$ ,  $^3J$  6.5 Hz), 1.20–1.44 m (4H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.56–1.98 m [6H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$  + isoxazolyl- $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$ ], 2.59 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.0 Hz), 2.72 t (2H, isoxazolyl- $\text{CH}_2$ ,  $^3J$  7.5 Hz), 2.77–2.90 m (1H,  $\text{H}^8$ ), 3.56 d.d.d (1H,  $\text{H}^{1/2}$ ,  $^3J$  11.0, 9.0, 8.0 Hz), 3.80 s (3H,  $\text{OCH}_3$ ), 4.19 d.d (1H,  $\text{H}_\alpha^{II}$  in lacton ring,  $^2J$  9.0,  $^3J$  9.0 Hz), 4.54 d.d (1H,  $\text{H}_\beta^{II}$  in lacton ring,  $^2J$  9.0,  $^3J$  8.0 Hz), 5.85 s ( $1\text{H}_{\text{isoxazol}}$ ), 6.68–6.82 m ( $3\text{H}_{\text{arom}}$ ), 7.22 br.t ( $1\text{H}_{\text{arom}}$ ,  $^3J$  7.5 Hz). Mass spectrum:  $m/z$  371 [ $M$ ] $^+$ . Found, %: C 71.08; H 7.91.  $\text{C}_{22}\text{H}_{29}\text{NO}_4$ . Calculated, %: C 71.13; H 7.87.

**5 $\alpha$ -Methyl-3 $\alpha$ -[3-(3-methoxyphenyl)propyl]-4 $\beta$ -(5-pentylisoxazol-3-yl)tetrahydrofuran-2-one (XVIII).** Yield 50%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1040, 1090, 1120, 1160, 1185, 1240, 1285, 1320, 1385, 1445, 1510, 1535, 1605, 1785.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.90 t (3H,  $\text{CH}_3$ ,  $^3J$  6.5 Hz), 1.20–1.44 m (4H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.46 d (3H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  6.0 Hz), 1.56–1.98 m [6H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$  + isoxazolyl- $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$ ], 2.59 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.0 Hz), 2.72 t (2H, isoxazolyl- $\text{CH}_2$ ,  $^3J$  7.5 Hz), 2.87–3.00 m (1H,  $\text{H}^8$ ), 3.07 d.d (1H,  $\text{H}^{1/2}$ ,  $^3J$  12.0, 9.5 Hz), 3.80 s (3H,  $\text{OCH}_3$ ), 4.47 d.q (1H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  9.5, 6.0 Hz), 5.88 s ( $1\text{H}_{\text{isoxazole}}$ ), 6.68–6.82 m ( $3\text{H}_{\text{arom}}$ ), 7.22 br.t ( $1\text{H}_{\text{arom}}$ ,  $^3J$  7.5 Hz). Mass spectrum:  $m/z$  385 [ $M$ ] $^+$ . Found, %: C 71.52; H 8.09.  $\text{C}_{23}\text{H}_{31}\text{NO}_4$ . Calculated, %: C 71.66; H 8.10.

**Methyl 4-{3-[2-oxo-4 $\beta$ -(5-pentylisoxazol-3-yl)tetrahydrofuran-3 $\alpha$ -yl]propyl}benzoate (XIX).** Yield 48%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1040, 1090, 1120, 1160, 1185, 1240, 1285, 1320, 1385, 1445, 1510, 1535, 1605, 1725 max, 1785.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.90 t (3H,  $\text{CH}_3$ ,  $^3J$  6.5 Hz), 1.20–1.42 m (4H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.55–1.98 m [6H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$  + isoxazolyl- $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$ ], 2.67 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.0 Hz), 2.73 t (2H, isoxazolyl- $\text{CH}_2$ ,  $^3J$  7.5 Hz), 2.77–2.89 m (1H,  $\text{H}^8$ ), 3.57 d.d.d (1H,  $\text{H}^{1/2}$ ,  $^3J$  11.0, 9.0, 8.0 Hz), 3.90 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.19 d.d (1H,  $\text{H}_\alpha^{II}$  in lacton ring,  $^2J$  9.0,  $^3J$  9.0 Hz), 4.57 d.d (1H,  $\text{H}_\beta^{II}$  in lacton ring,  $^2J$  9.0,  $^3J$  8.0 Hz), 5.88 s ( $1\text{H}_{\text{isoxazole}}$ ), 7.20 d ( $2\text{H}_{\text{arom}}$ ,  $^3J$  8.0 Hz), 7.94 d ( $2\text{H}_{\text{arom}}$ ,  $^3J$  8.0 Hz). Mass spectrum:  $m/z$  399 [ $M$ ] $^+$ . Found, %: C 69.00; H 7.30.  $\text{C}_{23}\text{H}_{29}\text{NO}_5$ . Calculated, %: C 69.15; H 7.32.

**Methyl 4-{3-[5 $\alpha$ -methyl-2-oxo-4 $\beta$ -(5-pentylisoxazol-3-yl)tetrahydrofuran-3 $\alpha$ -yl]propyl}benzoate (XX).** Yield 40%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1080,

1120, 1185, 1235, 1285 max, 1320, 1395, 1445, 1510, 1530, 1565 sh, 1610, 1730, 1785.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.90 t (3H,  $\text{CH}_3$ ,  $^3J$  6.5 Hz), 1.26–1.41 m (4H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.46 d (3H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  6.0 Hz), 1.57–1.80 m [4H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{Ar}$  + isoxazolyl- $\text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3$ ], 1.80–2.00 m [2H,  $\text{CH}_2(\text{CH}_2)_2\text{Ar}$ ], 2.64 t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.5 Hz), 2.74 t (2H, isoxazolyl- $\text{CH}_2$ ,  $^3J$  7.5 Hz), 2.87–3.00 m (1H,  $\text{H}^8$ ), 3.07 d.d (1H,  $\text{H}^{1/2}$ ,  $^3J$  12.0, 9.5 Hz), 3.90 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.47 d.q (1H,  $\text{CH}_3\text{CH}^{II}$ ,  $^3J$  9.5, 6.0 Hz), 5.88 s ( $1\text{H}_{\text{isoxazole}}$ ), 7.18 d ( $2\text{H}_{\text{arom}}$ ,  $^3J$  8.0 Hz), 7.94 d ( $2\text{H}_{\text{arom}}$ ,  $^3J$  8.0 Hz). Mass spectrum:  $m/z$  413 [ $M$ ] $^+$ . Found, %: C 69.69; H 7.60.  $\text{C}_{24}\text{H}_{31}\text{NO}_5$ . Calculated, %: C 69.71; H 7.55.

**Methyl 7-[2-oxo-4 $\beta$ -(5-pentylisoxazol-3-yl)tetrahydrofuran-3 $\alpha$ -yl]heptanoate (XXI).** Yield 49%. IR spectrum,  $\text{cm}^{-1}$ : 1035, 1080, 1105, 1180, 1235, 1275, 1325, 1385, 1450, 1505 sh, 1510, 1525, 1565, 1610, 1745, 1790.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.92 t (3H,  $\text{CH}_3$ ,  $^3J$  6.5 Hz), 1.14–1.48 m (10H,  $3\text{CH}_2$   $\alpha$ -chain +  $2\text{CH}_2$   $\omega$ -chain), 1.48–1.78 m (6H,  $\text{CH}_2$  at the ring +  $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$  +  $\text{CH}_2$   $\omega$ -chain), 2.29 t (2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $^3J$  7.5 Hz), 2.68–2.85 m (1H,  $\text{H}^8$ ), 2.74 t (2H, isoxazolyl- $\text{CH}_2$ ,  $^3J$  7.5 Hz), 3.60 d.d.d (1H,  $\text{H}^{1/2}$ ,  $^3J$  11.0, 9.0, 8.0 Hz), 3.67 s (3H,  $\text{CO}_2\text{CH}_3$ ), 4.20 d.d (1H,  $\text{H}_\alpha^{II}$  in lacton ring,  $^2J$  9.0,  $^3J$  9.0 Hz), 4.57 d.d (1H,  $\text{H}_\beta^{II}$  in lacton ring,  $^2J$  9.0,  $^3J$  8.0 Hz), 5.92 s ( $1\text{H}_{\text{isoxazole}}$ ). Mass spectrum:  $m/z$  365 [ $M$ ] $^+$ . Found, %: C 65.87; H 8.53.  $\text{C}_{20}\text{H}_{31}\text{NO}_5$ . Calculated, %: C 65.73; H 8.55.

**Ethyl 3-{3-(4 $\beta$ -[3-(3-methoxyphenyl)propyl]-5-oxotetrahydrofuran-3 $\alpha$ -yl)isoxazol-5-yl}propanoate (XXII).** Yield 52%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1040, 1090, 1120, 1160, 1185, 1240, 1285, 1320, 1385, 1445, 1510, 1535, 1605, 1740 max, 1785.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.27 t (3H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $^3J$  7.0 Hz), 1.50–2.11 m [4H,  $(\text{CH}_2)_2\text{CH}_2\text{Ar}$ ], 2.60 br.t (2H,  $\text{CH}_2\text{Ar}$ ,  $^3J$  7.0 Hz), 2.72 t (2H, isoxazolyl- $\text{CH}_2$ ,  $^3J$  7.5 Hz), 2.78–2.98 m (1H,  $\text{H}^{1/2}$ ), 3.10 t (2H,  $\text{CH}_2\text{CO}_2\text{Et}$ ,  $^3J$  7.5 Hz), 3.57 d.d.d (1H,  $\text{H}^8$ ,  $^3J$  11.0, 9.0, 8.0 Hz), 3.80 s (3H,  $\text{OCH}_3$ ), 4.10–4.30 m (3H,  $\text{CO}_2\text{CH}_2\text{CH}_3$  +  $\text{H}_\alpha^9$  in lacton ring), 4.56 d.d (1H,  $\text{H}_\beta^9$  in lacton ring,  $^2J$  9.0,  $^3J$  8.0 Hz), 5.94 s ( $1\text{H}_{\text{isoxazole}}$ ), 6.68–6.82 m ( $3\text{H}_{\text{arom}}$ ), 7.22 br.t ( $1\text{H}_{\text{arom}}$ ,  $^3J$  7.5 Hz). Mass spectrum:  $m/z$  401 [ $M$ ] $^+$ . Found, %: C 65.73; H 6.74.  $\text{C}_{22}\text{H}_{27}\text{NO}_6$ . Calculated, %: C 65.82; H 6.78.

**Ethyl 3-{3-(2 $\beta$ -methyl-4 $\beta$ -[3-(3-methoxyphenyl)propyl]-5-oxotetrahydrofuran-3 $\alpha$ -yl)isoxazol-5-yl}propanoate (XXIII).** Yield 41%. IR spectrum,  $\text{cm}^{-1}$ : 1030, 1040, 1090, 1120, 1160, 1185, 1240, 1285, 1320, 1385, 1445, 1510, 1535, 1605, 1740 max, 1785.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.27 t (3H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $^3J$  7.0 Hz),



1.46 d (3H, CH<sub>3</sub>CH<sup>II</sup>, <sup>3</sup>J 6.0 Hz), 1.50–2.11 m [4H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>Ar], 2.60 br.t (2H, CH<sub>2</sub>Ar, <sup>3</sup>J 7.0 Hz), 2.72 t (2H, isoxazolyl-CH<sub>2</sub>, <sup>3</sup>J 7.5 Hz), 2.87–3.00 m (1H, H<sup>I2</sup>), 3.07 d.d (1H, H<sup>8</sup>, <sup>3</sup>J 12.0, 9.5 Hz), 3.10 t (2H, CH<sub>2</sub>CO<sub>2</sub>Et, <sup>3</sup>J 7.5 Hz), 3.80 s (3H, OCH<sub>3</sub>), 4.20 q (2H, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, <sup>3</sup>J 7.0 Hz), 4.47 d.q (1H, CH<sub>3</sub>CH<sup>II</sup>, <sup>3</sup>J 9.5, 6.0 Hz), 5.94 s (1H<sub>isoxazole</sub>), 6.68–6.82 m (3H<sub>arom</sub>), 7.22 br.t (1H<sub>arom</sub>, <sup>3</sup>J 7.5 Hz). Mass spectrum: *m/z* 415 [M]<sup>+</sup>. Found, %: C 66.54; H 6.98. C<sub>23</sub>H<sub>29</sub>NO<sub>6</sub>. Calculated, %: C 66.49; H 7.04.

**Methyl 4-{3-(2-oxo-4β-[5α,β-(pyridin-4-yl)-4,5-dihydroisoxazol-3-yl]tetrahydrofuran-3α-yl)propyl}benzoate (XXIVa, b).** Yield 80%. IR spectrum, cm<sup>-1</sup>: 1010, 1030, 1050 sh, 1060, 1120, 1175, 1185, 1205, 1260, 1290, 1320, 1345, 1390, 1445, 1495, 1550, 1620, 1640, 1725, 1775. <sup>1</sup>H NMR spectrum, δ, ppm: 1.56–2.00 m [4H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>Ar], 2.60–2.90 m (4H, H<sup>8</sup> + H<sup>I4</sup> + CH<sub>2</sub>Ar), 3.23–3.47 m (2H, H<sup>I2</sup> + H<sup>I4</sup>), 3.90 s (3H, CO<sub>2</sub>CH<sub>3</sub>), 4.11 2 d.d (1H, H<sup>II</sup> in lacton ring, <sup>2</sup>J 9.0, <sup>3</sup>J 9.0 Hz), 4.48 br.d.d (1H, H<sup>II</sup> in lacton ring, <sup>2</sup>J 9.0, <sup>3</sup>J 8.0 Hz), 5.64 br.d.d (1H, CHPy, <sup>3</sup>J 11.0, 7.0 Hz), 7.22 narrow m (4H, 2H<sub>ph</sub> + 2H<sub>py</sub>), 7.96 br.d (2H<sub>ph</sub>, <sup>3</sup>J 7.5 Hz), 8.60 narrow m (2H<sub>py</sub>). Mass spectrum: *m/z* 408 [M]<sup>+</sup>. Found, %: C 67.52; H 5.89. C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>. Calculated, %: C 67.63; H 5.92.

**Methyl 4-{3-(5α-methyl-2-oxo-4β-[5α,β-(pyridin-4-yl)-4,5-dihydroisoxazol-3-yl]tetrahydrofuran-3α-yl)propyl}benzoate (XXVa, XXVb).** Yield 82%. IR spectrum, cm<sup>-1</sup>: 1030, 1055 sh, 1080, 1120, 1190, 1240, 1290 max, 1315, 1350, 1395, 1420, 1440, 1610, 1725, 1785. <sup>1</sup>H NMR spectrum, δ, ppm: 1.43 d, 1.46 d (3H, CH<sub>3</sub>CH<sup>II</sup>, <sup>3</sup>J 6.0 Hz), 1.58–1.96 m [4H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>Ar], 2.66 t, 2.69 t (2H, CH<sub>2</sub>Ar, <sup>3</sup>J 7.5 Hz), 2.71–2.97 m (3H, H<sup>8</sup> + H<sup>I2</sup> + H<sup>I4</sup>), 3.42 2 d.d (1H, H<sup>I4</sup>, <sup>2</sup>J 17.0, <sup>3</sup>J 11.0 Hz), 3.90 s (3H, CO<sub>2</sub>CH<sub>3</sub>), 4.37 2 d.q (1H, CH<sub>3</sub>CH<sup>II</sup>, <sup>3</sup>J 9.0, 6.0 Hz), 5.64 br.d.d (1H, CHPy, <sup>3</sup>J 11.0, 7.0 Hz), 7.22 narrow m (4H, 2H<sub>ph</sub> + 2H<sub>py</sub>), 7.96 2 d (2H<sub>ph</sub>, <sup>3</sup>J 8.0 Hz), 8.60 narrow m (2H<sub>py</sub>). Mass spectrum: *m/z* 422 [M]<sup>+</sup>. Found, %: C 68.33; H 6.18. C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>. Calculated, %: C 68.23; H 6.20.

**Methyl 7-{2-oxo-4β-[5α,β-(pyridin-4-yl)-4,5-dihydroisoxazol-3-yl]tetrahydrofuran-3α-yl}-heptanoate (XXVIa, b).** Yield 85%. IR spectrum, cm<sup>-1</sup>: 1000, 1030, 1080, 1120, 1190, 1225 sh, 1240 sh, 1270, 1320, 1350, 1395, 1420, 1450, 1470, 1610, 1745, 1785 max <sup>1</sup>H NMR spectrum, δ, ppm: 1.12–1.50 m (6H, 3CH<sub>2</sub> α-chain), 1.50–1.71 m (3H, 1H from CH<sub>2</sub> at the ring + CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me), 1.71–1.92 m (1H from CH<sub>2</sub> at the ring), 2.31 t (2H, CH<sub>2</sub>CO<sub>2</sub>Me, <sup>3</sup>J 7.5 Hz), 2.62–2.80 m

(1H, H<sup>8</sup>), 2.80–3.00 d.d (2.90 d.d) (1H, H<sup>I4</sup>, <sup>2</sup>J 17.0, <sup>3</sup>J 7.0 Hz), 3.28–3.45 d.d.d (3.37 d.d.d) (1H, H<sup>I2</sup>, <sup>3</sup>J 10.0, 9.0, 8.0 Hz), 3.41–3.61 d.d (3.51 d.d) (1H, H<sup>I4</sup>, <sup>2</sup>J 17.0, <sup>3</sup>J 11.0 Hz), 3.67 s (3H, CO<sub>2</sub>CH<sub>3</sub>), 4.14 2 d.d (1H, H<sup>II</sup> in lacton ring, <sup>2</sup>J 9.0, <sup>3</sup>J 9.0 Hz), 4.49 d.d (1H, H<sup>II</sup> in lacton ring, <sup>2</sup>J 9.0, <sup>3</sup>J 8.0 Hz), 5.68 br.d.d (1H, CHPy, <sup>3</sup>J 11.0, 7.0 Hz), 7.26 d (2H<sub>py</sub>, <sup>3</sup>J 5.0 Hz), 8.63 br.d (2H<sub>py</sub>, <sup>3</sup>J 5.0 Hz). Mass spectrum: *m/z* 374 [M]<sup>+</sup>. Found, %: C 64.23; H 6.94. C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>. Calculated, %: C 64.15; H 7.00.

**Methyl 7-{5α-methyl-2-oxo-4β-[5α,β-(pyridin-4-yl)-4,5-dihydroisoxazol-3-yl]tetrahydrofuran-3α-yl}heptanoate (XXVIIa, b).** Yield 80%. IR spectrum, cm<sup>-1</sup>: 1000, 1030, 1080, 1120, 1190, 1225 sh, 1240 sh, 1270, 1320, 1350, 1395, 1420, 1450, 1470, 1610, 1745, 1785 max <sup>1</sup>H NMR spectrum, δ, ppm: 1.12–1.40 m (6H, 3CH<sub>2</sub> α-chain), 1.44 d, 1.48 d (3H, CH<sub>3</sub>CH<sup>II</sup>, <sup>3</sup>J 6.0 Hz), 1.52–1.70 m (3H, 1H from CH<sub>2</sub> at the ring + CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me), 1.72–1.91 m (1H from CH<sub>2</sub> at the ring), 2.30 2 t (2H, CH<sub>2</sub>CO<sub>2</sub>Me, <sup>3</sup>J 7.0 Hz), 2.63–3.00 m (3H, H<sup>8</sup> + H<sup>I2</sup> + H<sup>I4</sup>), 3.50 2 d.d (1H, H<sup>I4</sup>, <sup>2</sup>J 17.0, <sup>3</sup>J 11.0 Hz), 3.68 s (3H, CO<sub>2</sub>CH<sub>3</sub>), 4.38 2 d.q (1H, CH<sub>3</sub>CH<sup>II</sup>, <sup>3</sup>J 9.0, 6.0 Hz), 5.68 2 d.d (1H, CHPy, <sup>3</sup>J 11.0, 7.0 Hz), 7.26 d (2H<sub>py</sub>, <sup>3</sup>J 5.0 Hz), 8.64 narrow m (2H<sub>py</sub>). Mass spectrum: *m/z* 388 [M]<sup>+</sup>. Found, %: C 64.84; H 7.24. C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>. Calculated, %: C 64.93; H 7.27.

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