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**SYNTHESIS AND REDUCTIVE CLEAVAGE OF 3-(2-FLUOROPHENYL)-  
AND 3-(4-FLUOROPHENYL)-CYCLOPENT-5-EN[d]ISOXAZOLINES  
BY RANEY NICKEL IN TRIFLUOROACETIC ACID**

3-Fluoro arylcyclopent-5-en[d]isoxazolines have been obtained via the 1,3-dipolar cycloaddition of cyclopentadiene to aromatic nitrile oxides. The reductive cleavage of these isoxazolines by Raney nickel in trifluoroacetic acid led to corresponding acylcyclopentenes along with acylcyclopentanes. The synthesized compounds are the precursors of new prostanoids as well as the analogues of cyclic  $\beta$ -triketones with fluorinated acyl side chain.

**Introduction.** Cyclic  $\beta$ -tri and diketones and widely used in the synthesis of various natural substances including steroids, prostaglandins, etc. [1–3]. There of particular interest is the synthesis of fluorinated analogues as the introduction of possessing high electronegativity fluorine, could cause not only an increase in biological activity, but also in the stability of these compounds [1–6]. This is especially actual for prostaglandins, characterized by high chemical and metabolic instability [7].

The purpose of this work is the development of methods of synthesis of cyclic  $\beta$ -triketones precursors with fluorinated acyl side chain as synthons for preparation of new prostaglandin analogues.

**Main part.** In order to realize the synthetic scheme of new cyclic  $\beta$ -triketones analogs, the condensed fluorinated 3-arylcyclopent-5-en[d]isoxazolines **3 a, b** have been prepared via 1,3-dipolar cycloaddition of unsaturated dipolarophile to the corresponding nitrile oxides. Cyclopentadiene was produced by dicyclopentadiene pyrolysis and served as a dipolarophile. Fluorinated hydroximoyl chlorides **1 a, b** were used as precursors of nitrile oxides.

Compounds **1 a, b** in the reaction conditions used for 1,3-dipolar cycloaddition by the action of triethylamine were converted to nitrile oxides **2 a, b**, which were trapped in situ by cyclopentadiene to form a 3-(2-fluorophenyl- or 3-(4-fluorophenyl)-cyclopent-5-en[d]isoxazolines **3 a, b**, the yield being 40.0 and 58.3%, respectively (Scheme 1).

Cycloaddition reaction was carried out at room temperature with stirring, the products were iso-

lated by column chromatography on silica gel (eluent: ether – light petroleum).

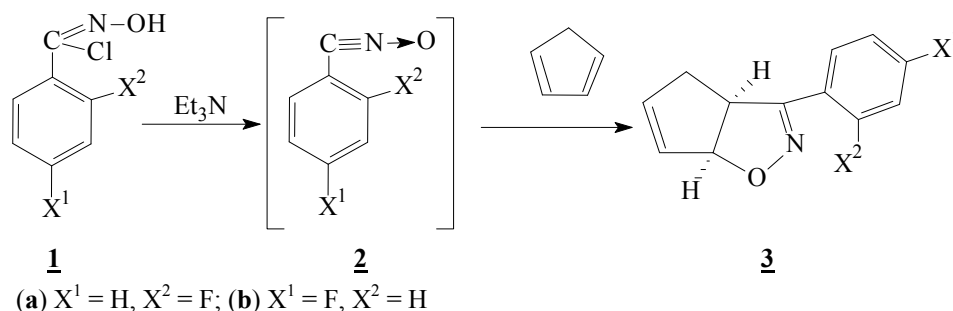
The structure of the prepared products has been proved by the modern physical-chemical methods of organic compounds analysis.

Analysis of H-8 and H-12 signals in the  $^1\text{H}$  NMR spectrum (Fig. 1) as well as that of vinyl protons signals H-10 and H-11 allowed to confirm the isoxazoline **3b** structure (PG numeration of atoms is used to facilitate the spectral characteristics comparison).

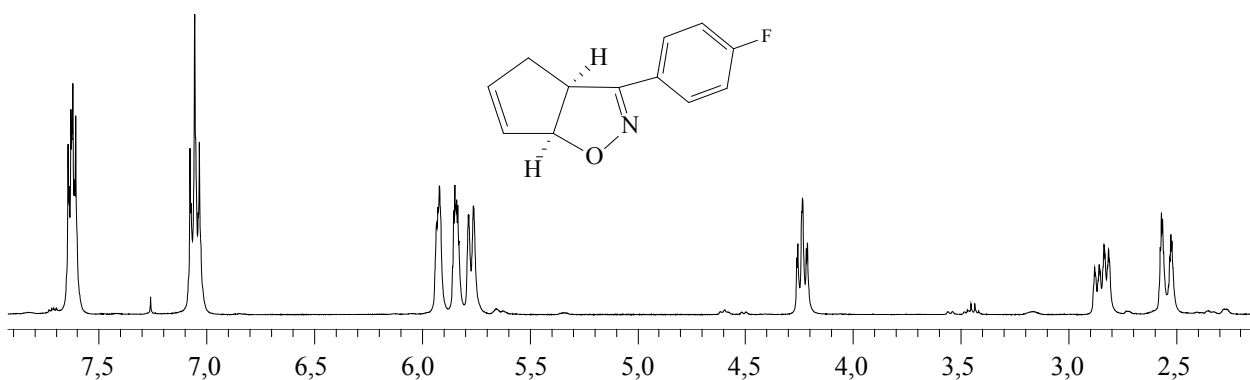
Thus, vinyl protons signals are observed as quite a narrow multiplets with small spin-spin coupling constants (SSCC) in the region of 5.92 ppm (H-11) and 5.84 ppm (H-10). Proton H-8 appears as a triplet of doublets at 4.23 ppm, the shape of this signal is due to H-8 SSC with protons H-12 and two chemically nonequivalent protons  $\text{H}^{\text{A-9}}$  and  $\text{H}^{\text{B-9}}$ . The signal at 5.77 ppm as a doublet of doublets ( $J_1 = 9.2$ ;  $J_2 = 1.0$  Hz), corresponds to the proton H-12 with SSCC  $J = 9.2$  Hz the latter being correlated with a relative *cis*-location of H-12 and H-8.

H-12 signal shift to a weaker field in comparison with H-8 is due to the discreening influence of the isoxazoline oxygen atom. The chemical shifts of all other signals, their multiplicity concern the proposed structure. Similar signals are observed in the compound **3 a**  $^1\text{H}$  NMR spectrum, which correlates to all fragments of the proposed structure.

All signals in the  $^{13}\text{C}$  NMR spectra of the synthesized condensed isoxazolines have been assigned to the corresponding C-atoms present in formula **3**.



Scheme 1

Fig. 1.  $^1\text{H}$  NMR spectrum of 3-(4-fluorophenyl)cyclopent-5-en[d]isoxazoline

The reaction has been ascertained to proceed with a high regio- and stereoselectivity, i.e. regioisomeric as well as stereoisomeric products were not formed.

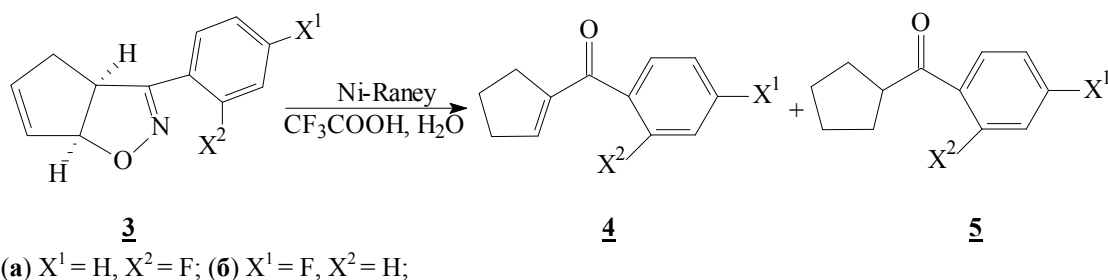
The synthesized by cycloaddition reaction 3-substituted cyclopent-5-en[d]isoxazolines are convenient intermediates in the synthesis of a variety of complex natural and related compounds, they are also of interest as perspective biologically active substances.

The reductive cleavage of cyclopenteneisoxazolines **3** has been studied in order to synthesize new analogues of bioactive cyclic triketones containing fluorine atom in the aromatic substituent (Scheme 2).

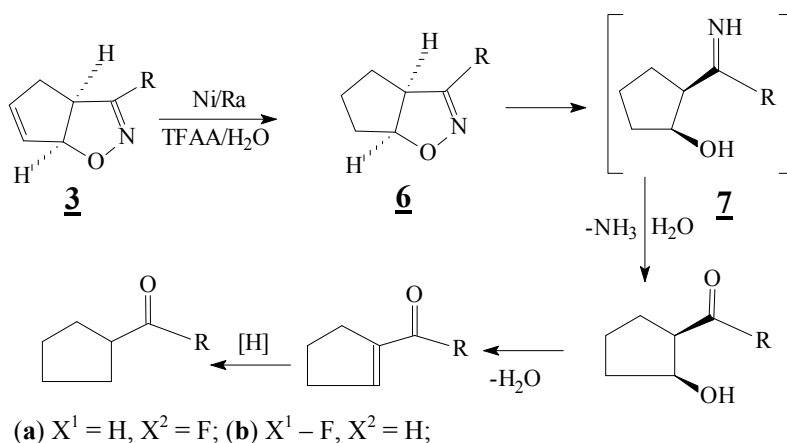
The reductive cleavage of isoxazolines **3 a, b** has been performed by the action of a Raney nickel

in 75% aqueous trifluoroacetic acid at room temperature. The reaction led to the formation of  $\alpha,\beta$ -unsaturated ketones **4 a, b** (the yield 20 and 26%) and ketones **5 a, b**, the yield being 5 and 18% respectively.

This reaction is a complex multistage process proceeding via C=C bond hydrogenation in the cyclopentane ring to form cyclopentanoisoxazoline **6** (Scheme 3), followed by N-O bond cleavage of the isoxazoline heterocycle [8, 9]. The resulting hydroxyimine **7** under reaction conditions was subjected to hydrolysis with the formation of hydroxyketone **8**. The latter by the acid action undergo the intramolecular dehydration to form the target enone **4**. It should be noted that further reduction of enone **4** sometimes occurred, which led to ketone **5**.



Scheme 2



Scheme 3

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy confirmed the structure of the synthesized products. Thus, due to the isoxazoline heterocycle cleavage signal H-8 disappeared in the  $^1\text{H}$  NMR spectrum of the enone **4**, furthermore the H-12 signal moved to a weaker field because the corresponding proton appeared to be vinyl in the structure fragment of  $\alpha,\beta$ -unsaturated ketone. For the compound **4 a**  $^1\text{H}$  NMR spectrum (Fig. 2), H-12 appeared at 6.52 ppm as a narrow signal with SSCC 2.0 Hz, while for the compound **4 b** – at 6.50 ppm as a triplet with spin-spin coupling constant  $J = 1,8$  Hz.

In comparison with the starting isoxazoline, proton signals H-10 and H-11 are shifted to a stronger field and appear at 2.01 ppm (2H-10) and in 2.71 ppm region (2H-11).

In the  $^1\text{H}$  NMR spectrum of the compound **5 a** (Fig. 3), the proton signal H-8 appears as a quintet at 3.64 ppm with the spin-spin coupling constant with protons H-9 and H-12  $J = 8.6$  Hz. The latter become chemically equivalent in ketones **5** due to the symmetry of the structure and are observed at 1.90 ppm. Similarly H-10 and H-11 signals coincide and appear at the 1.66 ppm region.

Several factors affecting the yield and the ratio of the reaction products have also been studied. It has been ascertained that the increase of the reaction time resulted in further reduction of enone **4**

and, consequently, in the increase of ketone **5** yield. The increase of the reaction temperature also stimulated its formation.

Consequently, milder conditions (room temperature and moderate reaction time) mainly lead to the target  $\alpha, \beta$ -unsaturated ketones.

**Experimental part.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of substances solutions in  $\text{CDCl}_3$  with HMDS as an internal standard have been obtained using Bruker AVANCE spectrometer (400 MHz). The progress of the reaction was monitored by TLC on silica gel plates Kieselgel 60 F<sub>254</sub> (Merck), eluent: ether - petroleum ether, developer – iodine vapor or 4% solution of  $\text{KMnO}_4$ . Solvent purification was carried by standard techniques.

The following atom numeration was used while discussing spectral data:

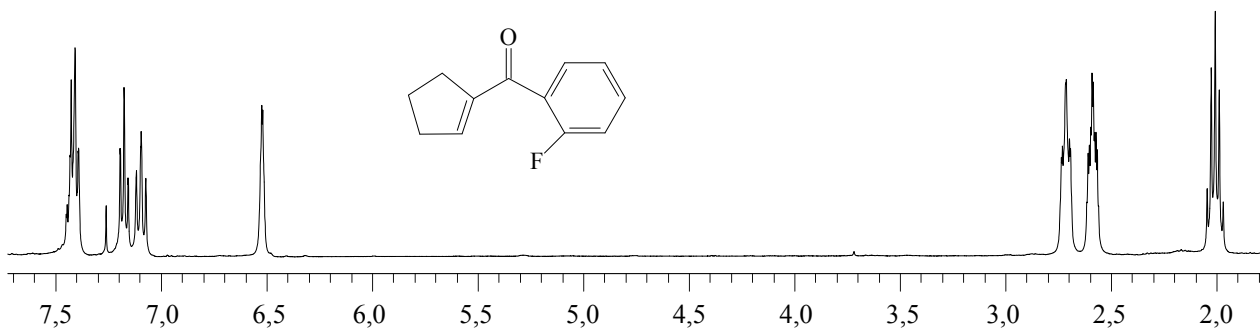
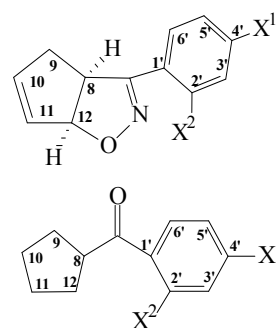


Fig. 2.  $^1\text{H}$  NMR spectrum of (2-fluorophenyl)-(cyclopent-1-enyl)methanone

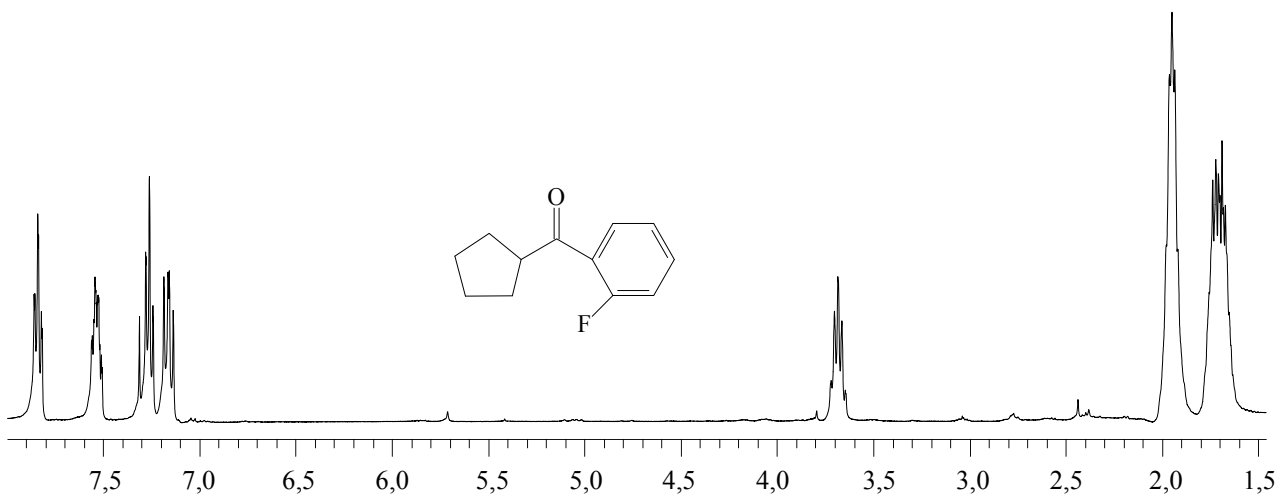


Fig. 3.  $^1\text{H}$  NMR spectrum of (2-fluorophenyl)-(cyclopentyl)methanone

**Synthesis of fluorine containing 3-aryl-cyclopent-5-en[d]isoxazolines.** Solutions of triethylamine (4.44 ml, 0.032 mol) in 20 ml ether and of freshly distilled monomeric cyclopentadiene (3.27 ml, 0.048 mol) in 20 ml ether were added dropwise simultaneously from two dropping funnels to a stirred solution of corresponding hydroximoyl chloride (5.5 g, 0.032 mol) in 20 ml ether. The reaction proceeded while stirring at room temperature until the disappearance of the starting hydroximoyl chloride (TLC analysis). Further, the precipitate of triethylammonium chloride was filtered and washed additionally with ether. The solvent was removed under reduced pressure and the product was isolated from the obtained oil by column chromatography on silica gel using eluent with gradually increasing polarity (ether – hexane).

**3-(2-fluorophenyl)cyclopent-5-en[d]-isoxazoline** was obtained as an oil (40.0% yield).

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 7.78 td (1H; H<sub>ar</sub>-6'; *J* = 7.7; *J* = 1.5); 7.35 m (1H; H<sub>ar</sub>-4'; *J*<sub>1</sub> = 8.2; *J*<sub>2</sub> = 7.2; *J*<sub>3</sub> = 1.8); 7.14 td (1H, H<sub>ar</sub>-5'; *J*<sub>1</sub> = 7.7; *J*<sub>3</sub> = 1.0); 7.08 m (2H; H<sub>ar</sub>-3'; *J*<sub>1</sub> = 8.4; *J*<sub>2</sub> = 1.0); 5.94 m (1H, H-11, *J*<sub>1</sub> = 2.6); 5.82 m (1H, H-10, *J*<sub>1</sub> = 2.6; *J*<sub>2</sub> = 1.5); 5.77 dd (1H, H-12; *J*<sub>1</sub> = 9.5; *J*<sub>2</sub> = 1.0); 4.37 m (1H, H-8; *J*<sub>1</sub> = 9.5; *J*<sub>2</sub> = 4.6; *J*<sub>3</sub> = 2.0); 2.80 dd (1H, H<sup>A</sup>-9; *J*<sub>1</sub> = 17.7; *J*<sub>2</sub> = 8.2; *J*<sub>3</sub> = 2.0); 2.44 dd (1H, H<sup>B</sup>-9, *J*<sub>1</sub> = 17.7; *J*<sub>2</sub> = 2.0).

<sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 159.75 (*J* = 252; C–F); 155.74 (*J* = 3; C=N); 133.76 (C-11); 131.35 (*J* = 9; C-4'); 129.55 (*J* = 4; C-6'), 129.19 (C-10); 124.37 (*J* = 4; C-5'), 117.13 (*J* = 11, C-1'); 116.23 (*J* = 22; C-3'); 90.83 (*J* = 1; C-12); 50.25 (*J* = 6, C-8); 36.84 (*J* = 2, C-9).

The yield of **3-(4-fluorophenyl)cyclopent-5-en[d]isoxazoline** was 53.8%. Crystals. M.p. 69–72 °C.

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 7.63 m (2H; H<sub>ar</sub>-2'+ H<sub>ar</sub>-6'; *J*<sub>1</sub> = 8.9; *J*<sub>2</sub> = 2.0); 7.05 m (2H; H<sub>ar</sub>-3'+ H<sub>ar</sub>-5'; *J*<sub>1</sub> = 8.9; *J*<sub>2</sub> = 2.3); 5.92 m (1H, H-11, *J*<sub>1</sub> = 2.3); 5.84 m (1H, H-10; *J*<sub>1</sub> = 2.3; *J*<sub>2</sub> = 2.0); 5.77 dd (1H, H-12; *J*<sub>1</sub> = 9.2; *J*<sub>2</sub> = 1.0); 4.23 td (1H, H-8; *J*<sub>1</sub> = 9.2; *J*<sub>2</sub> = 2.0), 2.85 m (1H, H<sup>A</sup>-9; *J*<sub>1</sub> = 17.4; *J*<sub>2</sub> = 8.7; *J*<sub>3</sub> = 1.8); 2.54 m (1H, H<sup>B</sup>-9; *J*<sub>1</sub> = 17.4; *J*<sub>2</sub> = 2.0).

<sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 163.27 (*J* = 252; C–F); 157.47 (C=N); 133.445 (C-11); 129.34 (C-10); 128.68 (*J* = 9; C-2' + C-6'); 125.38 (*J* = 3, C-1'); 115.68 (*J* = 22; C-3' + C-5'); 91.15 (C-12), 48.78 (C-8); 37.12 (C-9).

**The reductive cleavage of 3-(2-fluorophenyl)- and 3-(4-fluorophenyl)-cyclopent-5-en[d]isoxazolines by Raney nickel in trifluoroacetic acid.** 3.1 mmol of isoxazoline was dissolved in a solution prepared from 47 ml trifluoroacetic acid and 10 ml water. Raney nickel (4.9 g) was added in small portions to this solution with stirring during 3 hours. The reaction mixture was stirred at ambient temperature until the disappearance of the starting

cyclopentenisoxazoline. The course of the reaction was monitored by analytical TLC. Trifluoroacetic acid was removed by distillation at atmospheric pressure, and the residue was neutralized by saturated sodium carbonate solution. The organic compounds were extracted with ether, the combined organic layers were dried on anhydrous sodium sulfate. The residue obtained after the removal of solvent, was purified by column chromatography on silica gel using eluent with gradually increasing polarity.

**(2-Fluorophenyl)- (cyclopent-1-enyl)-methanone** was obtained as an oil (20.0% yield).

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 7.42 m (2H, H<sub>ar</sub>-4' + H<sub>ar</sub>-6'; *J*<sub>1</sub> = 7.3; *J*<sub>2</sub> = 6.5); 7.18 td (1H, H<sub>ar</sub>-5'; *J*<sub>1</sub> = 7.5; *J*<sub>2</sub> = 0.9); 7.10 m (1H, H<sub>ar</sub>-3'; *J* = 7.9); 6.52 m (1H, H-12, *J*<sub>1</sub> = 2.0); 2.71 m (2H, H<sup>A</sup>-11 + H<sup>B</sup>-11; *J*<sub>1</sub> = 7.9; *J*<sub>2</sub> = 2.0), 2.59 m (2H; H<sup>A</sup>-9 + H<sup>B</sup>-9; *J*<sub>1</sub> = 7.6; *J*<sub>2</sub> = 4.9; *J*<sub>3</sub> = 2.3); 2.01 quintet (2H, H-10; *J* = 7.6).

<sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 190.95 (C = O); 159.37 (*J* = 251, C–F); 149.40 (C-12), 145.70 (C-8); 132.02 (*J* = 9; C<sub>ar</sub>-4'); 129.73 (*J* = 3, C<sub>ar</sub>-6'); 123.87 (*J* = 4; C<sub>ar</sub> 5'); 116.07 (*J* = 22; C<sub>ar</sub>-3'), 34.25 (C-9), 30.59 (C-11), 22.84 (C-10)

**(2-Fluorophenyl)-(cyclopentyl)methanone** was obtained as an oil (5.0% yield).

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 7.79 td (1H, H<sub>ar</sub>-6'; *J*<sub>1</sub> = 7.7; *J*<sub>2</sub> = 1.8); 7.48 m (1H, H<sub>ar</sub>-4'; *J*<sub>1</sub> = 7.2; *J*<sub>2</sub> = 1.8); 7.21 etc. (1H, H<sub>ar</sub>-5'; *J*<sub>1</sub> = 7.7; *J*<sub>2</sub> = 1.0); 7.11 dd (1H, H<sub>ar</sub>-3'; *J*<sub>1</sub> = 8.4; *J*<sub>2</sub> = 1.0); 3.64 quintet (1H, H-8, *J* = 8,6); 1.90 m (4H; 2H-9 + 2H-12), 1.66 m (4H, 2H-10 + 2H-11).

<sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 201.95 (C = O); 161.29 (*J* = 252; C–F); 133.88 (*J* = 9; C<sub>ar</sub>-4'); 130.76 (*J* = 3, C<sub>ar</sub>-6'), 126.27 (*J* = 15; C<sub>ar</sub>-1'); 124.32 (*J* = 3; C<sub>ar</sub>-5'), 116.54 (*J* = 23, C<sub>ar</sub>-3 '); 51.97 (*J* = 6, C-8), 29.20 (C-9 + C-12), 25.97 (C-10 + C-11).

**(4-Fluorophenyl)-(cyclopent-1-enyl)-methanone** was obtained as an oil (26.0% yield).

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 7.75 m (2H, H<sub>ar</sub>-2, H<sub>ar</sub>-6; *J*<sub>1</sub> = 8.7; *J*<sub>2</sub> = 5,6); 7.09 m (2H, H<sub>ar</sub>-3' + H<sub>ar</sub>-5'; *J* = 8.7); 6.50 m (1H, H-12; *J*<sub>1</sub> = 1.8); 2.72 m (2H, H<sup>A</sup>-11 + H<sup>B</sup>-11; *J*<sub>1</sub> = 7,7; *J*<sub>2</sub> = 4.0; *J*<sub>3</sub> = 2.0); 2.60 m (2H; H<sup>A</sup>-9 + H<sup>B</sup>-9; *J*<sub>1</sub> = 7.4; *J*<sub>2</sub> = 4.7; *J*<sub>3</sub> = 2.3); 1.99 quintet (2H, H-10; *J*<sub>1</sub> = 7.6).

<sup>13</sup>C NMR spectrum (δ, ppm, CDCl<sub>3</sub>, *J* Hz): 192.53 (C = O); 164.92 (*J* = 252; C–F); 146.47 (C-12), 144.33 (C-8); 135.06 (*J* = 3, C<sub>ar</sub>-1'); 131.21 (*J* = 9; C<sub>ar</sub>-2' + C<sub>ar</sub>-6'); 115.15 (*J* = 21, C<sub>ar</sub>-3'+ C<sub>ar</sub>-5'), 34.28 (C-9), 31.89 (C-11), 22.67 (C-10).

**(4-Fluorophenyl)-(cyclopentyl)-methanone** was obtained as an oil (18.0% yield).

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm (*J*, Hz): 7.99 m (2H, H<sub>ar</sub>-2', H<sub>ar</sub>-6'; *J* = 8.9); 7.10 m (2H, H<sub>ar</sub>-3'+ H<sub>ar</sub>-5'; *J* = 8.8); 3.66 quintet (1H, H-8, *J* = 7,8); 1.90 m (4 H; 2H-9 + 2H-12), 1.60–1.76 m (4H; 2H-10 + 2H-11; *J*<sub>1</sub> = 7.8).

$^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm ( $J$ , Hz): 201.08 (C=O); 165.45 ( $J = 252$ ; C-F); 133.24 ( $J = 2$ ,  $\text{C}_{\text{ar}}-1'$ ); 130.96 ( $J = 10$ ;  $\text{C}_{\text{ar}}-2' + \text{C}_{\text{ar}}-6'$ ); 115.46 ( $J = 22$ ;  $\text{C}_{\text{ar}}-3' + \text{C}_{\text{ar}}-5'$ ), 46.20 (C-8), 29.89 (C-9 + C-12), 26.21 (C-10 + C-11).

**Conclusion.** The synthesis of isoxazolines has been shown to proceed with high regio- and stereoselectivity.

The transformations of the obtained condensed isoxazolines to analogues of fluorine containing cyclic  $\beta$ -triketones is possible via the realization of latent difunctionality of isoxazoline heterocycle. The reductive cleavage of condensed isoxazolines by Raney nickel in trifluoroacetic acid give the compounds, which are new analogues of fluorine containing acylcyclopentenes. On the one hand, the synthesized compounds are perspective as biologically active substances, on the other hand, they are convenient intermediates in the synthesis of complex natural and other practically useful compounds. Particularly acylcyclopentenes are precursors of fluorine containing prostanoids, the conversion of these synthons into target prostaglandins being possible by both isoxazole [10] and other well-known procedures [7].

The synthesized compounds are precursors of fluorine containing triacylmethane analogues as well as the convenient intermediates in synthesis of fluorine containing prostanoids and other complex natural compounds and their bioactive analogues.

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