ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2009, Vol. 35, No. 1, pp. 111–117. © Pleiades Publishing, Ltd., 2009.
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# Prostaglandin Fluorides in Synthesis of Natural Prostaglandin Derivatives at Carboxyl Group

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Received February 14, 2008; in final form, March 17, 2008

**Abstract**—Methods of synthesis of prostaglandin fluorides were developed and their properties were investigated. These compounds were shown to be convenient synthetic precursors for obtaining esters and amides of natural prostaglandins and their fluorodeoxy analogues.

*Key words: amides, esters, fluorodeoxyprostaglandins, morpholinosulfotrifluoride, prostaglandin fluorides*

**DOI:** 10.1134/S1068162009010142

## INTRODUCTION

Prostaglandin derivatives at carboxyl group are applied to modify the pharmacological profile of natural prostaglandins, which is especially useful if the modifying group itself dispays a biological activity [1, 2].[2] For example, prostaglandin ethanolamides and their 2-glyceric ethers are natural bioregulators in mammals [3].

In addition to carboxyl group, PGs contain in their structures an allyl hydroxyl group in position 15, and PGs of the E, F, and D types, additional one or two hydroxy groups in cyclopentane ring. Because of possible side reactions at these hydroxy groups, PG halides have not drawn attention of chemists as active derivatives for synthesis of PG esters. We had earlier synthesized 15-fluoro-15-deoxyprostaglandins $A_2$ and $E_2$ as free acids and, as intermediate compound, obtained fluoride of 15-fluoro-15-deoxyprostaglandin $A_2$. Without isolation, it was transformed by hydrolysis in a weakly alkaline medium to the corresponding carboxy compound [4]. Continuing these researches, we established that acylfluorides are convenient active derivatives in synthesis of PG esters and amides. In this paper, we for the first time describe methods of obtaining PG fluorides and their chemical properties.

## RESULTS AND DISCUSSION

The treatment of PG $A_2$ (**I**) by MSTF [5, 6] led to 15-fluoro-15-deoxyprostaglandin $A_2$ fluoride (**II**). Its structure was confirmed by NMR spectroscopy and mass spectrometry. Its mass spectrum (direct input, electronic impact) exhibits a molecular ion (*m/z* 338). The intensity of this ion is 38%, while usually the intensity of a molecular ion in mass spectra of such fluorodeoxyprostaglandins does not exceed several percent (see, e.g., [6]). In $^{19}F$ NMR spectrum, there is a singlet signal at –35.5 ppm, which is typical of a signal from fluorine atom of acylfluorides [7].

Unlike PG chlorides, PG fluorides are rather stable at hydrolysis. They can be extracted from water and purified by column chromatography on silica gel. They react with water much slower than with alcohols and amines. For example, the main product of reaction of fluoride (**II**) with 50% water ethanol (up to 80%) was ethyl ester of 15-fluoro-15-deoxyprostaglandin $A_2$ rather than the free acid. At interaction with ammonia, a stronger nucleophile than ethanol, exclusively fluoroprostaglandin amide is formed and there are no products of fluoride hydrolysis.

Examples of synthesis of esters and amides of 15-fluoro-15-deoxyprostaglandin $A_2$ (**III**) are shown in

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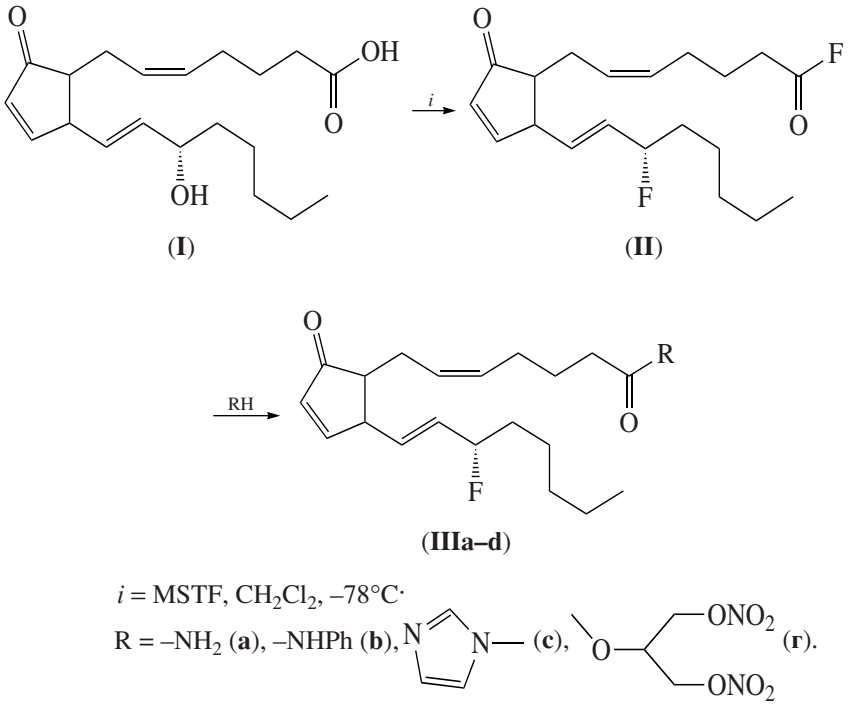
[2] Abbreviations: BDMS, *tert*-butyldimethylsilyl; Mph, morpholin; MSTF, morpholinosulfotrifluoride; PG, prostaglandin; and TMS, trimethylsilyl.

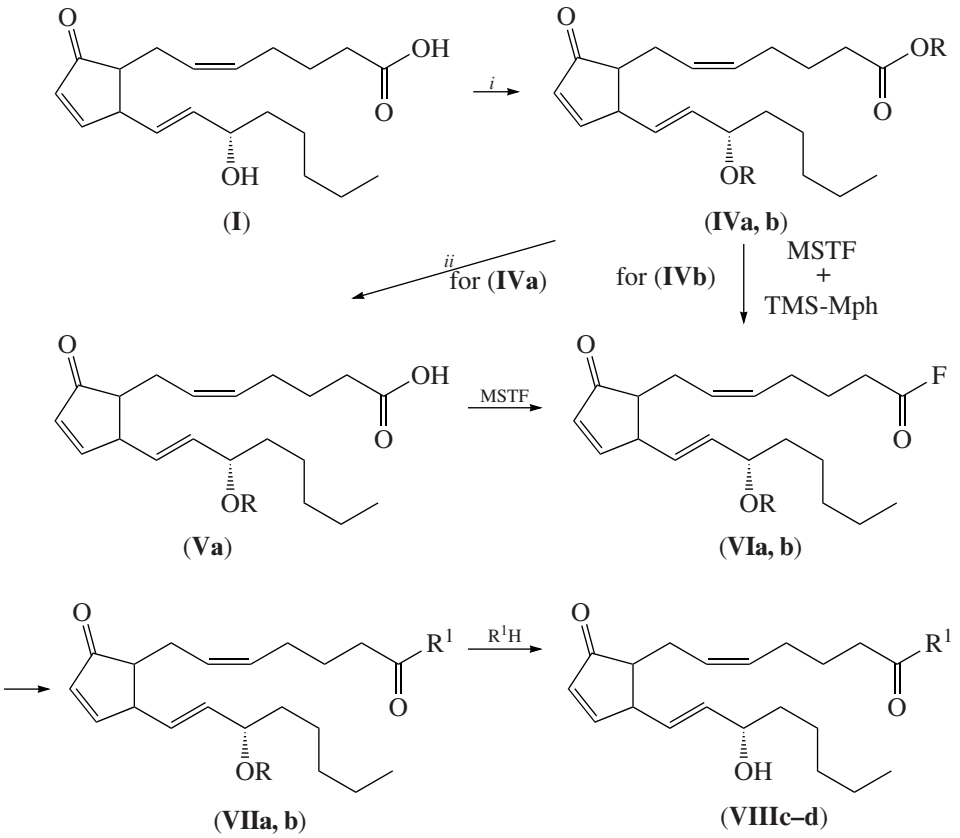
Scheme 1. Hydrogen fluoride splitting off during the reaction was bound with triethylamine (method A in the Experimental section). When obtaining amides, an excess of reacting amine can fulfill this function.

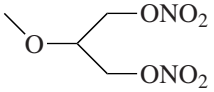



**Scheme 1.**

The obtaining of fluorides of natural PGs is complicated by the presence in their molecules of one or several hydroxy groups, which, along with carboxyl group, are fluorinated by aminotrifluorosulphuranes. To avoid the undesirable reactions of hydroxy groups, we have applied their temporary protection by silyl groupings, such as *tert*-butyldimethylsilyl (BDMS) and trimethylsilyl (TMS), which removed after obtaining the corresponding derivatives at PG carboxyl group (methods B and C in the Experimental section).

The use of BDMS protective grouping (method C) implies an exhaustive silylation of PG, e.g., PG $A_2$ (**I**), by BDMS-Cl in the presence of imidazol (Scheme 2). The resulting silyl derivative (**IVa**) was treated with 30% $H_2O_2$ in methanol. Under these conditions, the protective grouping leaves only carboxyl group. A similar result occurs if 1 M HCl in THF is used instead of $H_2O_2$ in methanol. The reaction proceeds much faster, for 1 min, while it requires about 1 h at the use of hydrogen peroxide. However, hydrochloric acid leads to the difficulties with the monitoring of hydrolysis course, as even a small prolongation of the reaction time results in a partial deblocking of hydroxy groups. The silyl derivative with free carboxyl group (**Va**) was fluorinated by MSTF and individual fluoride (**VIa**) was isolated. It was converted into ester or amide and, after removal of protective silyl group by acidic hydrolysis, the required derivatives of PG $A_2$ (**VIIIc**)–(**VIIId**) were obtained.

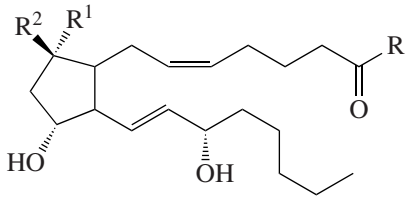



R = BDMS (**a**), TMS (**b**);
$R^1$ = –$NH_2$ (**c**), *t*-BuO– (**d**),  (**e**);

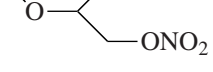
*i* = BDMS-Cl, imidazol, DMF, 25°C, 18 h (**a**);
hexamethyldisilazane, TMS-Cl, THF, 25°C, 2 h (**b**);
*ii* = 30% $H_2O_2$/methanol or 1 M HCl/THF.

**Scheme 2.**

The drawback of this method is the necessity of purification of intermediate silylated prostanoids. Preferable would be such a group that leaves during fluorination reaction of only carboxy groups and would be retained on hydroxy groups. TMS esters are unstable under the conditions of fluorination reaction by MSTF (method A), but there also proceeds a deblocking of hydroxy groups. We found that the use of a mixture of MSTF and TMS-morpholine at a 1 : 1 ratio as a fluorination agent promotes the retaining of protective TMS groupings on hydroxy groups, while it replaces TMS on carboxyl by fluorine with the formation of carboxylic acid fluoride (method B). In this manner, PG $A_2$ was silylated by HMDS in the presence of TMS-Cl (Scheme 2). Bis-trimethylsilyl derivative (**IVb**) was fluorinated without isolation by the above-described mixture, and the resulting fluoride (**VIb**) was transformed in the derivatives (**VIIIc**)–(**VIIIe**) by the reaction with ammonia or alcohols with the subsequent acidic hydrolysis of TMS ester. The amides and esters of natural prostaglandins $E_2$ (**IXa**)–(**IXd**) and $F_{2\alpha}$ (**Xa**)–(**Xd**) were similarly obtained.

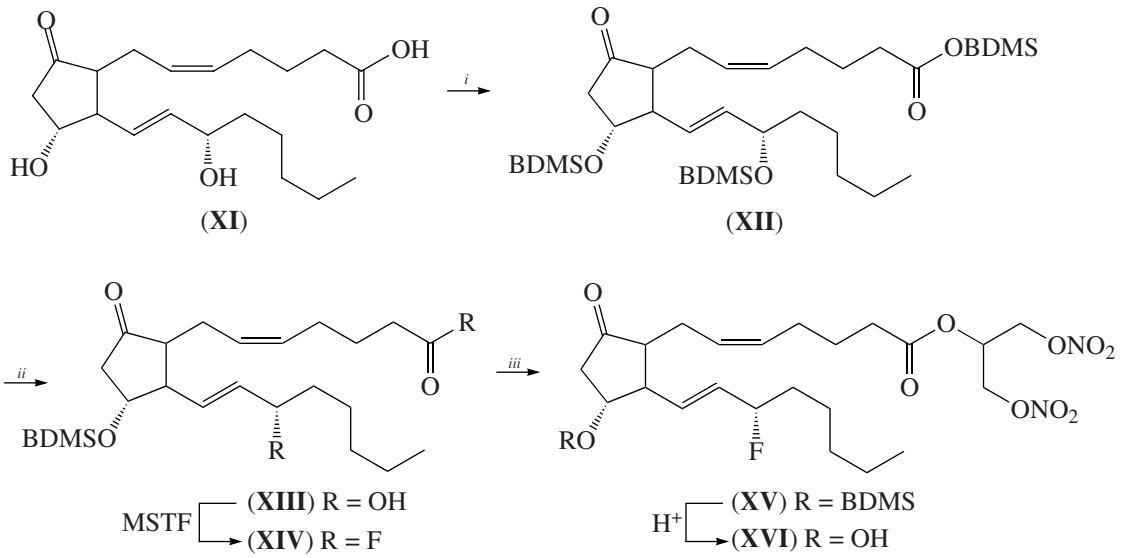


(**IX**), (**Xa–d**)

(**IX**) $R^1 + R^2$ = O;
(**X**) $R^1$ = OH, $R^2$ = H;
R = –$NH_2$ (**a**), –$NMe_2$ (**b**), *t*-BuO– (**c**),  (**d**)

Our studies showed that, for the preparation of natural PG derivatives at carboxyl group, the preference

should be given to the use of TMS protective group, whereas BDMS protection is better for the synthesis of fluorodeoxy analogues. In this case, it is possible to remove BDMS protective grouping from hydroxy groups (mainly 15-OH) simultaneously with the carboxy group deprotection. Then, in the reaction of monosilylated prostanoid with MSTF, the formation of carboxyl fluoride occurs at simultaneous fluorination of hydroxy group. By this method, PG $E_2$ (**XI**) was particularly transformed in the 1,3-bis(nitrooxy)prop-2-yl ester of 15-fluoro-15-deoxyprostaglandin $E_2$ (**XVI**) (Scheme 3). Silyl derivative (**XII**) was transformed by partial acidic hydrolysis into a mixture of 11- and 15-BDMS-ethers, which were separated by chromatography. The fluorination of individual 11-BDMS-ether (**XIII**) by the action of MSTF led to acid fluoride (**XIV**), which reacted with glycerol 1,3-dinitrate to form the corresponding ester (**XV**) by method D and, after removal of silyl groupings by acidic hydrolysis, to the target prostanoid (**XVI**).




*i* = BDMS-Cl, imidazol, DMF, 25°C, 18 h;
*ii* = 1 M HCl/THF, 5 min;
*iii* = acetone, glycerol-1,3-dinitrate, $Et_3N$, 25°C.

**Scheme 3.**

Cyanure fluoride is also possible to use as a reagent for the synthesis of carboxyl fluorides; it reacts exclusively with carboxyl group rather than with hydroxy groups [8]. However, this reaction proceeds in the presence of pyridine as a base. Therefore, at the synthesis of PG acid fluorides with the use of cyanure fluoride, a pyridine-catalyzed reaction of the resulting fluoride partially proceeds with free hydroxy groups. It leads to the difficultly identified products of both intermolecular and intramolecular condensation and decreases yields of target products.

Thus, we suggested a convenient way of synthesis of PG amides and esters and their fluorodeoxyanalogues through intermediate acid fluorides. The developed procedure can find application for the synthesis of derivatives at carboxy group and other hydroxycaboxylic acids.

## EXPERIMENTAL

Prostaglandin $A_2$ was isolated from corals of Caribbean sea (*Plexaura homomalla*). PG $A_2$ and $F_{2\alpha}$ were obtained from an experimental plant of Institute of Chemistry (Tallinn, Estonia). MSTF was synthesized as described earlier [4]. UV spectra were registered on a Specord UV VIS device (Germany). Mass spectra were registered on a Varian MAT 44C (Varian, Germany) mass spectrometer at electron impact ionization (energy of electrons 70 eV, input from the emitter) (EI) or at chemical ionization by ammonia (CI)[3] $^{19}F$ NMR spectra were recorded down on a Bruker CPX200 spectrometer (Bruker, Germany). TLC was carried out on Silufol UV 254 plates (Kavalier, Czechia), detection by 5% solution of phospho-molybdic acid in alcohol. Column chromatography was carried out with the use of

[3] At the description of mass spectra, the putative structures of ions and relative intensity in % are given.

silica gel L (Chemapol, Czechia); the course of separation was monitored by TLC. Evaporation of solutions was carried out on a rotary evaporator in a vacuum of a water-jet pump at a bath temperature not above 30°C.

**Fluorination of prostaglandins (Method A).** MSTF (1.5 equiv per one fluorinated group) was dissolved in 3 ml $CH_2Cl_2$ in an atmosphere of argon. The mixture was stirred and cooled at –78°C. A solution of PG to be fluorinated in $CH_2Cl_2$ was dropwise added to the mixture, and it was stirred until the termination of reaction (TLC monitoring). Then saturated water solution of ammonium chloride (3 ml) was added to the reaction mixture, and the mixture allowed warming up to room temperature. The mixture was diluted with 5 ml of water, the organic layer was separated, and the water layer was extracted with chloroform (3 × 10 ml). Organic extracts were combined, washed with water, the saturated water solution of sodium chloride, dried by anhydrous $Na_2SO_4$, and evaporated. The residue was purified by column chromatography on silica gel.

**Synthesis of carboxyl group derivatives of natural PG $A_2$, $E_2$, and $F_{2\alpha}$ with the use of TMS-protection (Method B).** PG (50 mg) was dissolved in 2 ml THF, hexamethyldisilazane (150 μl) and trimethylchlorosilane (50 μl) was added, and the reaction mixture was stirred for 2 h at room temperature. Then solvent was evaporated, and the residue was dissolved in $CH_2Cl_2$ (0.5 ml, solution A). MSTF (150 mg) was dissolved in $CH_2Cl_2$ (2 ml) in an atmosphere of argon at –78°C and *N*-trimethylsilylmorpholine (150 mg) was added. The reaction mixture was left to be spontaneously heated up to room temperature and stirred for 30 min (solution B). It was cooled to –78°C, a solution A was added and stirred for 1 h. After the termination of the fluorination reaction (TLC monitoring), a saturated aqueous $NH_4Cl$ was added (3 ml) to the reaction mixture, it was left to be heated up to room temperature, diluted with 5 ml of water, the organic layer was separated, and the water was extracted with chloroform (3 × 10 ml). Organic extracts were combined and washed with water up to pH 6.5–7.0 with saturated water solution of NaCl, dried with anhydrous $Na_2SO_4$, filtered, and filtrate was evaporated. The obtained acid fluoride was dissolved in 2 ml of absolute acetone and the corresponding alcohol or amine (1.5 equiv) and triethylamine (2 equiv) was added. The reaction mixture was stirred at room temperature before the termination of reaction (TLC monitoring), evaporated, and the residue was dissolved in 2 ml methanol and 1 N HCl (100 μl) was added. After 20 min, the mixture was diluted with water and extracted with ethyl acetate (3 × 10 ml). The combined extract was washed with water, saturated water solution of NaCl, dried with anhydrous $Na_2SO_4$, the drier was filtered, and the filtrate was evaporated. The derivative was purified by column chromatography on silica gel.

***tert*-Butyldimethylsilyl derivatives of prostaglandins (Method C).** *tert*-Butyldimethylchlorosilane and imidazol (1.5 equiv per each group to be silylated) were added to a stirred solution of 100 mg of PG to be silylated in 1 ml DMF. The reaction mixture was kept for 18 h at room temperature, diluted with 5 ml of water and 5 ml of ether. The ether layer was separated, and the water layer was extracted with ether (3 × 10 ml). The combined ether extracts were washed with the water, saturated water solution of NaCl, dried with anhydrous $Na_2SO_4$, filtered, and filtrate was evaporated.

**15-Fluoro-15-deoxyprostaglandin $A_2$ fluoride (II)** was synthesized from PG $A_2$ (**I**) (100 mg) by the method A, yield 70 mg (70%), weak-yellow viscous oil, $R_f$ 0.62 (7 : 1 benzene–ethyl acetate); UV-spectrum ($\lambda_{max}$ 217 nm, ε 6000 $M^{-1}$ $cm^{-1}$ (ethanol); MS (EI), *m/z*: 338 ($[M]^+$, 38), 318 ($[M - HF]^+$, 45), 310 ($[M - CO]^+$, 10), 298 ($[M - 2HF]^+$, 30), 190 (100). $^{19}F$ NMR spectrum ($CDCl_3$) (δ, ppm, relative $CCl_3F$): 171.8 (1 F, d, 15-F), –35.5 (1 F, s, 1-F).

**Carboxyl group derivatives of 15-fluoro-15-deoxyprostaglandin $A_2$ (IIIa)–(IIId) (method D).** 15-Fluoro-15-deoxyprostaglandin $A_2$ fluoride (**II**) was dissolved in absolute acetone (2 ml) and 1.5 equiv of the corresponding alcohol or amine and 2 equiv of triethylamine were added. The mixture was stirred at room temperature before the termination of reaction (TLC). The mixture was diluted with water and extracted with ethyl acetate (3 × 10 ml). The combined extract was washed with water, saturated water solution of NaCl, dried with anhydrous $Na_2SO_4$, filtered, and evaporated. The obtained derivative was purified with column chromatography on silica gel.

**15-Fluoro-15-deoxyprostaglandin $A_2$ amide (IIIa)** was synthesized from 50 mg of fluoride (**II**) by the method D with yield of 47.4 mg (95%); slight yellow viscous oil, $R_f$ 0.53 (100 : 10 : 1 chloroform–methanol–ammonia); mass spectrum (EI), *m/z*: 316 ($[M - F]^+$, 56), 298 ($[M - HF - NH_3]^+$, 21) 270 ($[M - HF - NH_3 - CO]^+$, 9).

**15-Fluoro-15-deoxyprostaglandin $A_2$ anilide (IIIb)** was synthesized from 100 mg of fluoride (**II**) by method D; yield 59.5 mg (81%); slight yellow viscous oil, $R_f$ 0.24 (7 : 1 benzene–ethyl acetate); mass spectrum (EI), *m/z*: 411 ($[M]^+$, 3.6), 391 ($[M - HF]^+$, 13.6), 298 ($[M - HF - C_6H_7N]^+$, 6.8), 270 ($[M - HF - C_6H_7N - CO]^+$, 3), 202 (100).

**15-Fluoro-15-deoxyprostaglandin $A_2$ imidazolide (IIIc)** was synthesized from fluoride (**II**) (40 mg) by method D; yield 36.3 mg (79%); slight yellow viscous oil, $R_f$ 0.47(100 : 10 : 1 chlorofom–methanol–ammonia); mass spectrum (EI), *m/z*: 386 ($[M]^+$, 63.3), 366 ($[M - HF]^+$, 33.6), 318 ($[M - C_3H_4N_2]^+$, 30), 298 ($[M - HF - C_3H_4N_2]^+$, 21).

**15-Fluoro-15-deoxyprostaglandin $A_2$ 1,3-bis(nitrooxy)prop-2-yl ester (IIId)** was synthesized from 100 mg of fluoride (**II**) by the method D; yield 119 mg (80%); slight yellow viscous oil, $R_f$ 0.7 (5 : 1 benzene–ethyl acetate); mass spectrum (EI), *m/z*: 500 ($[M]^+$, 3.6), 480 ($[M - HF]^+$, 2.8), 434 ($[M–HF–NO_2]^+$, 1.1),

389 ([$M$ – HF – 2 × $NO_2$]$^+$, 3.8), 391 ([$M$ – 2 × $NO_2$–OH]$^+$, 2.6), 371 ([$M$ – HF – 2 × $NO_2$ – OH]$^+$, 2.9), 343 ([$M$ – F – $CH_2ONO_2$ – $ONO_2$]$^+$, 3.9), 318 ([$M$ – $(CH_2ONO_2)_2COH$]$^+$, 13.4), 315 ([$M$ – $(CH_2ONO_2)_2C$–HF]$^+$, 37), 298 ([$M$ – $(CH_2ONO_2)_2COH$ – HF]$^+$, 22.3), 190 (100).

**15-(*tert*-Butyldimethyl)silyloxyprostaglandin $A_2$ *tert*-butyldimethylsilyl ester (IVa)** was synthesized from 100 mg of prostaglandin $A_2$ (**I**); yield of prostanoid (**IVa**) 151.8 mg (89%), colorless viscous oil, $R_f$ 0.75 (7 : 1 benzene–ethyl acetate); UV-spectrum: $\lambda_{max}$ 217 nm (ethanol); mass spectrum (EI), *m/z*: 562 ([$M$]$^+$, 20), 547 ([$M$ – $CH_3$]$^+$, 4), 505 ([$M$ – $C_4H_9$]$^+$, 100), 491 ([$M$ – $C_5H_{11}$]$^+$, 5.5), 430 ([$M$ – $C_6H_{15}SiOH$]$^+$, 16), 373 ([$M$ – $C_6H_{15}SiOH$ – *t*-$C_4H_9$]$^+$, 70), 299 ([$M$ – $C_6H_{15}SiOH$ – $C_6H_{15}SiO$]$^+$, 54).

**15-(*tert*-Butyldimethyl)silyloxyprostaglandin $A_2$ (Va).** 1 M HCl (150 μl) was added to a solution of disilyl derivative (**IVa**) (100 mg) in 1 ml THF and stirred for 1.5 min at room temperature. The reaction mixture was poured out in a mixture of chloroform of 4 ml and 2 ml of saturated water solution of $NaHCO_3$. The organic layer was separated, water acidified with 1 M HCl to pH 3–4 and extracted with chloroform (3 × 10 ml). The extract was washed with water, saturated NaCl, dried by anhydrous $Na_2SO_4$, filtered, and filtrate was evaporated. The residue was purified by column chromatography on silica gel in a gradient system benzene–ethyl acetate. Prostaglandin (**Va**) was obtained; yield 71.5 mg (89%), colorless viscous oil, $R_f$ 0.55 (3 : 1 benzene–ethyl acetate); mass spectrum of methyl ester (EI), *m/z*: 431 ([$M$ – $OCH_3$]$^+$, 7), 405 ([$M$ – $C_4H_9$]$^+$, 100), 391 ([$M$ – $C_5H_{11}$]$^+$, 34), 373 ([$M$ –$C_4H_9$ – $OCH_3$]$^+$, 40).

**15-(*tert*-Butyldimethyl)silyloxyprostaglandin $A_2$ fluoride (VIa)** was synthesized from 70 mg of prostanoid (**Va**) by the method A; yield 64.6 mg (85%); colorless viscous oil; $R_f$ 0.77 (7 : 1 benzene–ethyl acetate); mass spectrum (EI), *m/z*: 450 ([$M$]$^+$, 20), 430 ([$M$ – HF]$^+$, 18), 393 ([$M$ – $C_4H_9$]$^+$, 100), 379 ([$M$ – $C_5H_{11}$]$^+$, 28), 393 ([$M$ – $C_4H_9$ – HF]$^+$, 31).

**Prostaglandin $A_2$ amide (VIIIc)** was synthesized from 100 mg of prostaglandin $A_2$ (**I**) by the method B; yield 91.2 mg (92%); slight yellow viscous oil, $R_f$ 0.29 (100 : 10 : 1 chloroform–methanol–ammonia), $\lambda_{max}$ 217 nm, ε 7800 (ethanol); mass spectrum (CI), *m/z*: 334 ([$M$ + H]$^+$), 316 ([$M$ + H – $H_2O$]$^+$).

**Prostaglandin $A_2$ *tert*-butyl ester (VIIId).** Fluoride (**VIa**) (50 mg) was dissolved in acetone (1 ml) *tert*-butanol (100 μl) was added, and mixture was stirred for 5 h at room temperature. Solvent was evaporated, and the oily residue was dissolved in 0.5 ml THF, added 1 ml of 67% aqueous acetic acid and 10 μl of 1 M hydrochloric acid were added and the mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with water and extracted with etyl acetate (3 × 5 ml). The extract was washed with water, saturated water solution of NaCl, dried with anhydrous $Na_2SO_4$, filtered, and filtrate was evaporated. The resulting derivative was purified by column chromatography on silica gel; yield 31.4 mg (73%); slight yellow viscous oil; $R_f$ 0.68 (100 : 10 : 1 chloroform–methanol–ammonia); UV-spectrum: $\lambda_{max}$ 217 nm, ε 7200 (ethanol); mass spectrum (CI), *m/z*: 390 ([$M$]$^+$), 372 ([$M$ – $H_2O$]$^+$).

**Prostaglandin $A_2$ 1,3-bis(nitrooxy)prop-2-yl ester (VIIIe)** was synthesized from 100 mg of PG $A_2$ (**I**) by the method B; yield 123.8 mg (83%); viscous yellow oil, $R_f$ 0.65 (40 : 10 : 1 benzene–dioxane–acetic acid); UV-spectrum: $\lambda_{max}$ 218 nm, ε 7140 (ethanol); mass spectrum (CI), *m/z*: 499 ([$M$ + H]$^+$), 481 ([$M$ + H–$H_2O$]$^+$).

**Prostaglandin $E_2$ amide (IXa)** was synthesized from 40 mg of PG $E_2$ by the method B; yield 36.3 mg (91%); colorless viscous oil, $R_f$ 0.1 (1 : 1 chloroform–aceton); mass spectrum of trimethylsilyl derivative (EI), *m/z*: 568 ([$M$ + H]$^+$, 0.9), 553 ([$M$ + H –$CH_3$]$^+$, 1.4), 523 ([$M$ + H – $(CH_3)_3$]$^+$, 0.9), 495 ([$M$ + H –$(CH_3)_3Si$]$^+$, 12), 480 ([$M$ + H–$(CH_3)_3Si$–NH]$^+$, 12), 424 ([$M$ + H – $(CH_3)_3Si$ – $C_5H_{11}$]$^+$, 67), 405 ([$M$–$(CH_3)_3Si$ – $(CH_3)_3SiOH$]$^+$, 58), 390 ([$M$ – $CH_3$ – $(CH_3)_3Si$ – $(CH_3)_3SiOH$]$^+$, 22), 334 ([$M$ – $((CH_3)_3Si)_3$ – H]$^+$, 100).

**Prostaglandin $E_2$ *tert*-butyl ester (IXc)** was synthesized from 30 mg of PG $E_2$ by the method B; yield 24.1 mg (72%); colorless viscous oil, $R_f$ 0.68 (2 : 1 benzene–ethyl acetate); mass spectrum (CI), *m/z*: 408 ([$M$]$^+$), 390 ([$M$ – $H_2O$]$^+$).

**Prostaglandin $E_2$ 1,3-bis(nitrooxy)prop-2-yl ester (IXd)** was synthesized from 100 mg of PG $E_2$ by method B; yield 108.5 mg (74%); colorless viscous oil; $R_f$ 0.39 (40 : 10 : 1 benzene–dioxane–acetic acid); mass spectrum (CI), *m/z*: 517 ([$M$ + H]$^+$).

**Prostaglandin $F_{2\alpha}$ dimethylamide (Xb)** was synthesized from 40 mg of PG $F_{2\alpha}$ by method B; yield 34.9 mg (81%); colorless viscous oil; $R_f$ 0.31 (2 : 1 benzene–ethyl acetate); mass spectrum (CI), *m/z*: 381 ([$M$]$^+$), 363 ([$M$ – $H_2O$]$^+$).

**Prostaglandin $F_{2\alpha}$ *tert*-butyl ester (Xc)** was synthesized from 35 mg of PG $F_{2\alpha}$ by method B; yield 26.4 mg (65%); colorless viscous oil; $R_f$ 0.54 (2 : 1 benzene–ethyl acetate); mass spectrum (CI), *m/z* : 410 ([$M$]$^+$), 392 ([$M$ – $H_2O$]$^+$).

**Prostaglandin $F_{2\alpha}$ 1,3-bis(nitrooxy)prop-2-yl ester (Xd)** was synthesized from 100 mg of prostaglandin $F_{2\alpha}$ by the method B; yield 115.6 mg (79%); colorless viscous oil; $R_f$ 0.25 (40 : 10 : 1 benzene–dioxane–acetic acid); mass spectrum (CI), *m/z*: 519 ([$M$ + H]$^+$), 501 ([$M$ + H – $H_2O$]$^+$).

**15-Fluoro-15 deoxyprostaglandin $E_2$ 1,3-bis(nitrooxy)prop-2-yl ester (XVI).** Prostaglandin $E_2$ (**XI**) (100 mg) was silylated by the method C. The trissilyl derivative (**XII**) was dissolved in THF (2 ml), 1 M HCl (300 μl) was added and the mixture was stirred at room temperature for 5 min. The reaction mixture was treated as described for prostanoid (**Va**). The mixture of 11- and 15-monosilyl derivatives of PG $E_2$ was separated by column chromatography on silica gel in gradient system benzene–ethyl acetate. The resulting 11-BDMS derivative (**XIII**) was fluorinated by the

method A with the formation of bisfluoride (**XIV**) and converted into ester (**XV**) by method D. Then the ester (**XV**) was dissolved in THF (2 ml) and added 0.3 ml of 50% hydrofluoric acid. The reaction mixture was stirred for 1 h at room temperature, poured out in the saturated water solution of sodium bicarbonate (5 ml) and extracted with ethyl acetate ($3 \times 10$ ml). The combined extracts were washed the water, saturated water solution of NaCl, dried with anhydrous $Na_2SO_4$, filtered, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel in a gradient system benzene–ethyl acetate. Yield of the ester 47.1 mg (32% from PG $E_2$); colorless viscous oil; $R_f$ 0.7 (40 : 10 : 1 benzene–dioxane–acetic acid); mass spectrum (EI), *m*/*z*: 519 ($[M + H]^+$, 0.3), 498 ($[M - HF]^+$, 22), 480 ($[M - HF - H_2O]^+$, 8.6), 472 ($[M - NO_2]^+$, 0.25), 452 ($[M - HF - NO_2]^+$, 13), 427 ($[M - HF - C_5H_{11}]^+$, 72), 353 ($[M - (CH_2ONO_2)_2C]^+$, 2.5), 316 ($[M - (CH_2ONO_2)_2COH - HF]^+$, 10), 298 ($[M - (CH_2ONO_2)_2COH - HF - H_2O]^+$, 6).

## ACKNOWLEDGMENTS

We thank V.E. Pashinnik (Institute of Organic Chemistry, Kiev, Ukraine) for the help in synthesis of MSTF.

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