A new approach to heterocycle-modified steroids via nitrile oxide intermediates

Alexander V. Baranovsky,[a]* Dmitry A Bolibrukh,[a] Vladimir A. Khripach,[a] and Bernd Schneider[b]

[a]Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, 220143, Minsk, Belarus
[b]Max-Planck-Institute for Chemical Ecology, Beutenberg Campus, Hans Knöll Str. 8, D-07745 Jena, Germany
E-mail: baranovsky@iboch.bas-net.by

The paper is dedicated to Professor Oleg G. Kulinkovich on occasion of his 60th birthday

Abstract
1,3-dipolar cycloaddition of acetylenes and olefins to 3-methoxy-14,17-etheno-16α-nitroestra-1,3,5(10)-trien-17β-yl acetate and its 17^1,17^2-dihydro derivative has been studied. Corresponding 14β-substituted steroids with an isoxazole or isoxazoline ring have been prepared in moderate to good yields. Rationale of the cycloaddition with the secondary nitro compound is viewed as a result of the bridge cleavage of the C16-C17 bond under weakly basic conditions followed by formation of nitrile oxide intermediate.

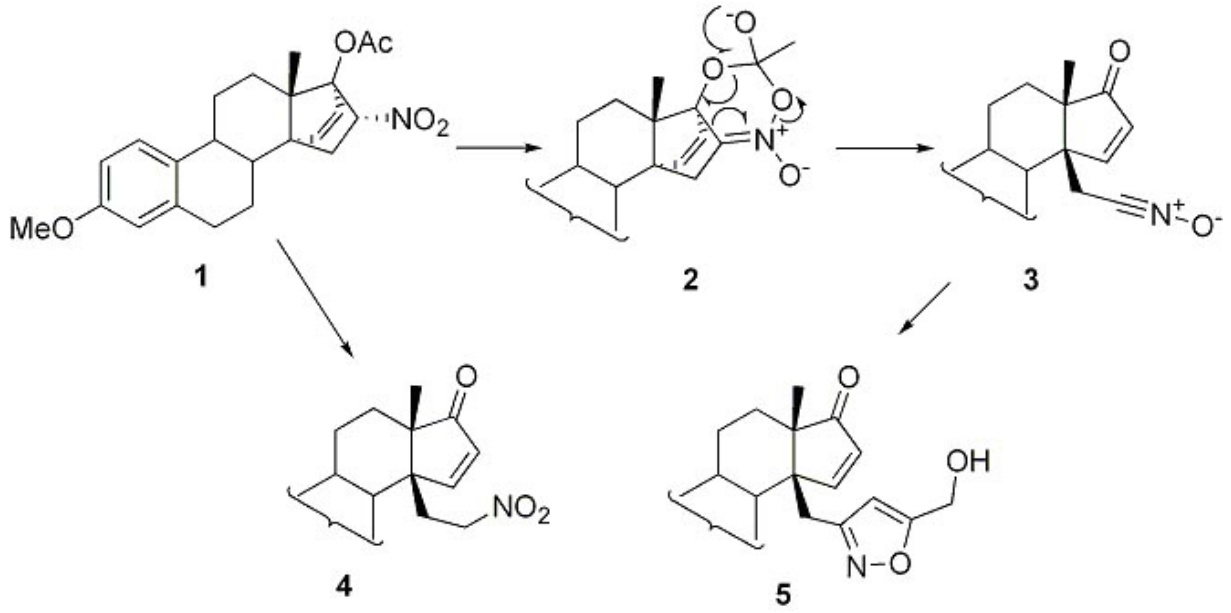
Keywords: Steroid, 1,3-dipolar cycloaddition, nitrile oxide, isoxazole, isoxazoline, nitro, bridgehead cleavage

Introduction

Nitrile oxides have found wide application during several decades in organic synthesis.[1, 2] Isoxazoles and isoxazolines prepared by 1,3-dipolar cycloaddition of nitrile oxides to acetylenes and olefins can be easily transformed via ring cleavage into various bifunctional derivatives like β-ketols, β-aminoalcohols, β-diketones and others.[3-6] The development of stereoselective methods for isoxazoline preparation has increased substantially their synthetic potential.[7-10]

The techniques of nitrile oxide preparation have been constantly improving, but generally, they are based either on dehydrochlorination of hydroximoyl chlorides[11] or on dehydration of primary nitro compounds.[12] It has been shown[13] that in weakly basic conditions, nitro steroid **1** underwent cleavage of the C16-C17 bond. The most probable product of such cleavage is nitrile oxide **3**, resulting from decomposition of the cyclic intermediate **2** (Scheme 1),

which is produced by attack of the aci-form of the nitro group on the 17-acetate carbonyl group. This can be proven by the fact that the product of tertiary alcohol cleavage, nitro ketone **4,** was isolated under more basic conditions. The nitrile oxide was fixed by trapping it with propargyl alcohol. Thus, the reaction of nitro adduct **1** with propargyl alcohol in the presence of sodium hydrocarbonate in ethanol gave isoxazole **5** in 50% yield. Mechanistically, the generation of the nitrile oxide can be considered as an intramolecular version of the Mukaiyama-Hoshino procedure[12] and other closely related methods.[14-17] We have undertaken a present study of the dipolar cycloadditions with several other dipolarophiles to elucidate the scope and application of this transformation for the synthesis of isoxazoles and isoxazolines in steroid series.



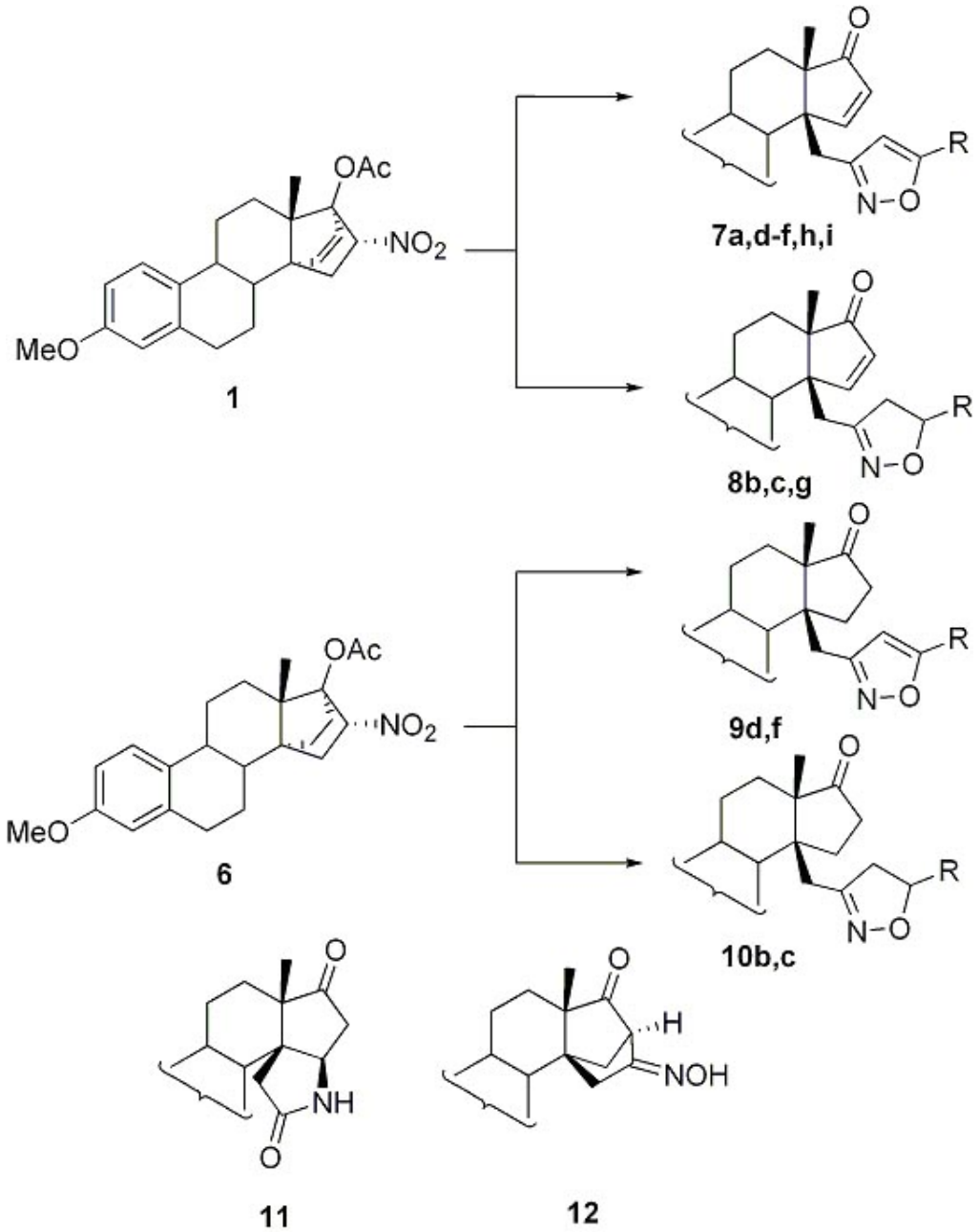
Scheme 1

Results and Discussion

As potential precursors of steroidal nitrile oxides, we used nitro adduct **1** and its dihydro derivative **6**, which had been prepared in accordance with the known methods.[13] Earlier, relatively stable steroidal nitrile oxide was prepared in our laboratory and its reactivity toward dipolarophiles was analysed.[18,19] As far as reactivity and stability of nitrile oxides from nitro steroids **1** and **6** were not known, firstly, we have chosen acetylenes and olefins, which promised to be active enough in cycloaddition.

Thus, we tested the THP-protected propargyl alcohol as dipolarophile to clarify the influence of the free hydroxyl group on the yield of the reaction with nitro compound **1 (**Scheme 2). It was found that the yield of isoxazole **7a** was definitely better (65% versus 50% for the free propargyl alcohol adduct[13] **5**). Quite expectably, isoxazole **7a** was isolated as a mixture of

epimers due to the chiral center in the tetrahydropyranyl group (ratio 1:1 based on the integration curve in the ^{1}H NMR spectrum).



Scheme 2

Further we tried phenyl acetylene as the reagent in reaction with nitro compounds **1, 6**: isoxazoles **7d** and **9d** were isolated in 50% and 68% yields, respectively. In comparison with reaction of steroids **1** and **6** with propargyl alcohol, where yield of products was about 50%, here, the absence of a bridged double bond gave an increase of the yield of isoxazole **9d**.

The reaction of steroid **1** with propargyl bromide was less effective due to substitution of the bromide by nucleophiles, either in propargyl bromide or in the product. Among the isolated products of the reaction, alcohol **5** (35%), its ethoxy derivative **7h** (18%) and bromide **7i** (27%) were found. The principal by-product of the addition of acetylenes to nitro compound **1** was lactam **11**, which is the major product when the reaction is conducted without dipolarophiles in aqueous ethanol. In the case of compound **6**, its hydrolysis in the presence of sodium hydrocarbonate in ethanol gave oxime **12**. However, oxime **12** was not detected when dipolarophile was added to the reaction mixture. The chemical properties and X-ray analysis of compounds **11** and **12** is the subject of a separate paper, which will be published elsewhere.

The results of the cycloaddition of nitro compounds **1** and **6** with 3,3-diethoxypropyne were less encouraging, and desired adducts **7f** and **9f** were isolated only in 28% and 40% yields respectively. Here, the absence of a double bond in nitro steroid **6** gave a certain rise of the yield. Obviously, the competing formation of the lactam **11** reduces the yield of isoxazoles **7** in comparison with isoxazoles **9** prepared from nitro compound **6**.

The reaction of dimethyl acetylenedicarboxylate with steroid **1** was unsuccessful, no isoxazole could be isolated. This result may be connected with low activity of the disubstituted triple bond in cycloaddition. Methyl propiolate as a dipolarophile was also tested, but a complex mixture of products, which included, probably, isoxazole regiomers,[20] was obtained. The major product of these reactions was lactam **11**.

Interesting results have been obtained when olefins were used for the cycloaddition. Although dipolar cycloadditions of nitrile oxides with olefins are considered to be more efficient than with acetylenes,[1,4] the first candidate employed as dipolarophile, allyl alcohol, was completely unreactive in the reaction with nitro compound **1** and only lactam **11** was isolated. However, vinyl ethers[14,21,22] such as ethyl vinyl and butyl vinyl ethers reacted smoothly with both nitro compounds giving the corresponding isoxazolines **8b, 8c, 10b, 10c** as 1 : 1 mixtures of diastereomers at the 5'-position of the heterocyclic ring. The yields of 70-79% were substantially higher in comparison with the isoxazole syntheses. Isoxazole **7e** was detected in 6% yield when the reaction of compound **1** was carried out with ethyl vinyl ether. The formation of **7e** can be explained by elimination of ethanol in the isoxazoline ring. Isoxazole **7e** was found as a major reaction product (45%) of compound **1** with 2-chloroethyl vinyl ether.[21] Interestingly, that in successful synthesis of isoxazolines **8bc**, we failed to isolate lactam **11**, which accompanied isoxazoles in their preparations from nitro compound **1**.

The structure of the adducts was analyzed by 2D NMR spectroscopy and complete assignment of their ^{1}H and ^{13}C NMR spectra was achieved. All spectroscopic data are in full agreement with the proposed structures. All isoxazoles have a single proton peak at 6.15-6.41 ppm depending on the substituent at C-5' in the ^{1}H NMR spectra. A complete set of three carbon

atoms of the isoxazole ring was found in their ^{13}C NMR spectra. The resonances are as following: C-3' at 160-161 ppm, C-4' at 101-104 ppm and C-5' at 169-170 ppm.[2, 23] The presence of the additional chiral center in the THP-group of steroid **7a** affects the nuclei of the atoms nearby and they give a double set of resonances in spectra. Similarly, the NMR spectra of diastereomeric mixtures of isoxazolines have doubled peaks of nuclei around ring D due to the chiral center at C-5' of the isoxazoline ring. The proton resonances of the isoxazoline ring were found at 2.73-2.86 ppm and 3.05-3.10 ppm (4'-H, methylenes) and 5.43-5.47 ppm (5'-H, methynes). Carbon nuclei are more sensitive in relation to the chirality at C-5' and doubled signals were assigned to all carbons except those in the ring A. Peaks of the heterocyclic nuclei in the ^{13}C NMR spectra were at 46-47 ppm (C-4'), 101-102 ppm (C-5') and 156-158 ppm (C-3').

Conclusions

A new approach to heterocycle-modified steroids bearing a substituent (isoxazole or isoxazoline) at C14-position has been developed. It comprises 1,3-dipolar cycloaddition of acetylenes and olefins to steroidal nitrile oxide generated from nitro acetates **1** and **6**. The formation of the nitrile oxide intermediate is a result of the C16-C17 bond cleavage in starting nitro steroid under mild basic conditions. Further transformations[3, 24] of the heterocycle ring of the resulted cycloadducts will open a route to various new steroids bearing a functionalized side chain at C14-position, which is not easy for modification in steroid series.

Experimental Section

General Procedures. Melting points were measured using a Boetius apparatus and are uncorrected. IR spectra were recorded using a UR-20 IR spectrometer. Mass spectra (EI) and accurate mass were recorded on a Micromass Masspec MS002 spectrometer, ratio m/z and relative intensities (%) are indicated for the significant peaks. ^{1}H NMR (500,13 MHz) and ^{13}C NMR (125,75 MHz) spectra were recorded as a $CDCl_3$ solutions using residual signal of solvent (δ 7.26 ppm and 77.16 ppm for ^{1}H and ^{13}C respectively) as an internal secondary standard on a Bruker AVANCE-500 instrument. COSY, HSQC, HMBC and NOESY experiments were carried out with the use of the standard Bruker software package.

TLC was performed on aluminum backed silica gel 60 F_{254} plates and visualized by UV and/or exposure to $Ce(NH_4)_4(SO_4)_4$ in 8M H_2SO_4. Column chromatography was conducted with Merck Kieselgel 60: 70-230 mesh. Solvents were dried and freshly distilled according to common practice.[25] All reactions were conducted under positive argon pressure.

General procedure for preparation compounds 7-10

$NaHCO_3$ (5 mmol) and dipolarophile (10 mmol) were added to a solution of nitro compound (1 mmol) in absolute ethanol. The mixture was refluxed for 3-19 h and cooled. The solution was evaporated to about 15% of the original volume and then diluted with water (10 mL) and extracted with dichloromethane. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with ethyl acetate/toluene (10:90) as eluent.

3-Methoxy-14β-[(5'-(2-tetrahydropyranyloxymethyl)-isoxazol-3'-ylmethyl]-estra-1,3,5(10),15-tetraen-17-one (7a) and 3-methoxy-2'-oxopyrrolidino-[4',5':14β,15β]-estra-1,3,5(10)-trien-17-one (11). A mixture of $NaHCO_3$ (0.21 g, 2.52 mmol), THP-protected propargyl alcohol (0.71 g, 5.03 mmol) and nitro compound **1** (0.20 g, 0.503 mmol) in absolute ethanol (20 mL) was refluxed for 6 h. After work up and chromatography, the diastereomeric mixture (1:1) of isoxazoles **7a** (0.156 g, 65%) was obtained as a colorless oil. IR (film, cm^{-1}) 1720. ^{1}H-NMR δ 1.19 (3H, two s, 18-H), 1.29 (1H, m, 7α-H), 1.31 (1H, m, 11β-H), 1.53 (1H, m, THP-4H), 1.54 (1H, m, THP-5H), 1.59 (1H, m, 12α-H), 1.60 (1H, m, THP-5H), 1.64 (1H, m, THP-3H), 1.74 (1H, m, THP-3H), 1.82 (1H, m, THP-4H), 1.90 (1H, m, 12β-H), 1.94 (1H, 8β-H), 2.19 (1H, ddd, *J* = 3.3, 5.9, 12.6 Hz, 7β-H), 2.26 (1H, m, 11α-H), 2.27 (1H, m, 9α-H), 2.73 (2H, m, $w_{1/2}$ = 8 Hz, 6-H), 3.06 (1H, two d, *J* = 15.4 Hz, 14^I-H), 3.17 (1H, two d, *J* = 15.4 Hz, 14^I-H), 3.54 (1H, m, THP-6H), 3.74 (3H, s, 3-CH_3O), 3.85 (1H, m, THP-6H), 4.61 (1H, ddd, *J* = 13.8 Hz, 1.4 Hz, 0.7 Hz, C*H*$_2$OTHP), 4.72 (1H, br t, *J* = 3.4 Hz, THP-2H), 4.77 (1H, dt, *J* = 13.8 Hz, 0.7 Hz, C*H*$_2$OTHP), 6.15 (1H, s, 14^{III}-H), 6.28 (1H, d, *J* = 5.9 Hz, 16-H), 6.53 (1H, d, *J* = 2.7 Hz, 4-H), 6.67 (1H, dd, *J* = 2.7 Hz, 8.6 Hz, 2-H), 7.01 (1H, d, *J* = 8.6 Hz, 1-H), 7.41 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 19.10 and 19.13 (THP-4C), 23.35 and 23.37 (C-18), 25.03 (C-7), 25.38 (THP-5C), 27.78 (C-11), 28.16 (C-12), 29.82 (C-14^I), 30.35 and 30.37 (THP-3C), 30.69 (C-6), 33.11 (C-9), 42.16 (C-8), 52.50 (C-13), 54.62 (C-14), 55.33 (3-MeO), 59.77 and 59.80 (*C*H$_2$OTHP), 62.27 and 62.31 (THP-6C), 98.34 and 98.41 (THP-2C), 104.31 and 104.39 (C-14^{III}), 112.52 (C-2), 112.97 (C-4), 128.44 (C-1), 132.15 (C-16), 133.20 (C-10), 136.95 (C-5), 157.34 (C-3), 160.61 (C-14^{II}), 164.65 and 164.67 (C-15), 169.58 and 169.60 (C-14^{IV}), 213.56 (C-17). MS *m/z*: 477 (M^+, 40%), 281 (60%), 187 (100%). HRMS: Found: *m/z* 477.2527. Calcd for $C_{29}H_{35}NO_5$: 477.2515; Found: *m/z* 392.1863. Calcd for $C_{24}H_{26}NO_4$ ($[M-85]^+$): 392.1862. Further elution with ethyl acetate/ethanol (92:8) gave lactam **11** (0.055 g, 31%) as colorless crystals. Mp 141-142 °C ($CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1694, 1732, 3427. ^{1}H-NMR δ 1.12 (3H, s, 18-H), 1.41 (1H, m, 11β-H), 1.54 (1H, m, 12α-H), 1.57 (1H, m, 7α-H), 1.57 (1H, m, 12β-H), 1.60 (1H, m, 8β-H), 1.94 (1H, dq, J = 2.8, 12.4 Hz, 7β-H), 2.09 (1H, d, J = 17.3 Hz, 14^{I}α-H), 2.17 (1H, dd, J = 4.0, 19.7 Hz, 16β-H) 2.23 (1H, d, J = 17.3 Hz, 14^{I}β-H), 2.38 (1H, dq, J = 3.1, 13.1 Hz, 11α-H), 2.68 (1H, td, J = 2.7, 11.6 Hz, 9α-H), 2.87 (2H, m, 6-H), 3.17 (1H, dd, J = 9.4, 19.7 Hz, 16α-H), 3.78 (3H, s, 3-CH_3O), 4.20 (1H, ddd, J = 0.8, 4.0, 9.4 Hz, 15α-H), 6.67 (1H, br s, NH), 6.66 (1H, d, J = 2.7 Hz, 4-H), 6.75 (1H, dd, J = 2.7, 8.6 Hz, 2-H), 7.22 (1H, d, J = 8.6 Hz, 1-H). ^{13}C-NMR δ 15.48 (C-18), 23.87 (C-7), 26.55 (C-11), 30.91 (C-6), 33.03 (C-12), 38.27 (C-9), 40.52 (C-14^I), 43.26 (C-16), 43.61 (C-8), 51.16 (C-15), 53.34 (C-14), 53.63 (C-13), 55.22 (3-

MeO), 112.41 (C-2), 113.41 (C-4), 127.12 (C-1), 130.46 (C-10), 137.21 (C-5), 157.80 (C-3), 176.86 (C-14^{II}), 216.86 (C-17). MS *m/z*: 339 (M^+, 90%), 321 (51%), 187 (100%). HRMS: Found: *m/z* 339.1836. Calcd. for $C_{21}H_{25}NO_3$: 339.1834.

3-Methoxy-14β-(5'-phenylisoxazol-3'-ylmethyl)-estra-1,3,5(10),15-tetraen-17-one (7d). A mixture of $NaHCO_3$ (0.20 g, 2.43 mmol), phenyl acetylene (0.53 mL, 4.86 mmol) and nitro compound **1** (0.193 g, 0.486 mmol) in absolute ethanol (20 mL) was refluxed for 11 h. After work up and chromatography, isoxazole **7d** (0.107 g, 50%) was obtained as a colorless oil. IR (film, cm^{-1}) 1720. ^{1}H-NMR δ 1.24 (3H, s, 18-H), 1.32 (1H, m, 7α-H), 1.32 (1H, m, 11β-H), 1.64 (1H, m, 12α-H), 1.93 (1H, m, 12β-H), 2.00 (1H, m, 8β-H), 2.25 (1H, m, 7β-H), 2.28 (1H, m, 11α-H), 2.31 (1H, m, 9α-H), 2.76 (2H, m, $w_{1/2}$ = 13.3 Hz, 6-H), 3.11 (1H, d, *J* = 15.3 Hz, 14^I-H), 3.22 (1H, d, *J* = 15.3 Hz, 14^I-H), 3.73 (3H, s, 3-CH_3O), 6.30 (1H, d, *J* = 5.9 Hz, 16-H), 6.41 (1H, s, 14^{III}-H), 6.53 (1H, d, *J* = 2.7 Hz, 4-H), 6.67 (1H, dd, *J* = 2.7, 8.6 Hz, 2-H), 7.01 (1H, d, *J* = 8.6 Hz, 1-H), 7.43 (1H, d, *J* = 5.9 Hz, 15-H), 7.44 (1H, m, Ph-3H), 7.45 (2H, m, Ph-4,5H), 7.82 (2H, m, Ph-2,6H). ^{13}C-NMR δ 23.48 (C-18), 25.15 (C-7), 27.84 (C-11), 28.25 (C-12), 30.01 (C-14^I), 30.81 (C-6), 33.17 (C-9), 42.27 (C-8), 52.60 (C-13), 54.71 (C-14), 55.36 (3-MeO), 100.94 (C-14^{III}), 112.59 (C-2), 113.05 (C-4), 125.96 (Ph-2C and Ph-6C), 127.36 (Ph-1C), 128.48 (C-1), 129.18 (Ph-3C and Ph-5C) 130.48 (Ph-4C), 132.21 (C-16), 133.24 (C-10), 136.97 (C-5), 157.37 (C-3), 161.33 (C-14^{II}), 164.70 (C-15), 169.97 (C-14^{IV}), 213.58 (C-17). MS *m/z*: 439 (M^+, 100%). Further elution with ethyl acetate/ethanol (92:8) gave lactam **11** (0.034 g, 21%).

3-Methoxy-14β-[(5'-(ethoxymethyl)-isoxazol-3'-ylmethyl]-estra-1,3,5(10),15-tetraen-17-one (7h) and 3-Methoxy-14β-[(5'-(bromomethyl)-isoxazol-3'-ylmethyl]-estra-1,3,5(10),15-tetraen-17-one (7i). A mixture of $NaHCO_3$ (0.19 g, 2.32 mmol), propargyl bromide (0.35 mL, 4.64 mmol) and nitro compound **1** (0.185 g, 0.464 mmol) in absolute ethanol (20 mL) was refluxed for 16 h. Work up and chromatography allowed to isolate in order of elution: bromide **7i** (0.057 g, 27%) as a colorless oil, IR (film, cm^{-1}) 1720. ^{1}H-NMR δ 1.19 (3H, s, 18-H), 1.31 (1H, m, 7α-H), 1.31 (1H, m, 11β-H), 1.58 (1H, m, 12α-H), 1.90 (1H, m, 12β-H), 1.90 (1H, m, 8β-H), 2.16 (1H, m, 7β-H), 2.28 (1H, m, 11α-H), 2.29 (1H, m, 9α-H), 2.74 (2H, m, $w_{1/2}$ = 12.8 Hz, 6-H), 3.07 (1H, d, *J* = 15.4 Hz, 14^I-H), 3.17 (1H, d, *J* = 15.4 Hz, 14^I-H), 3.75 (3H, s, 3-CH_3O), 4.45 (1H, s, CH_2Br), 6.23 (1H, s, 14^{III}-H), 6.30 (1H, d, *J* = 5.9 Hz, 16-H), 6.55 (1H, d, *J* = 2.7 Hz, 4-H), 6.69 (1H, dd, *J* = 2.7 Hz, 8.6 Hz, 2-H), 7.03 (1H, d, *J* = 8.6 Hz, 1-H), 7.41 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 18.59 (CH_2Br), 23.24 (C-18), 25.06 (C-7), 27.76 (C-11), 28.32 (C-12), 29.94 (C-14^I), 30.72 (C-6), 33.26 (C-9), 42.31 (C-8), 52.48 (C-13), 54.62 (C-14), 55.34 (3-MeO), 105.32 (C-14^{III}), 112.59 (C-2), 113.06 (C-4), 128.43 (C-1), 132.26 (C-16), 133.11 (C-10), 136.92 (C-5), 157.41 (C-3), 161.18 (C-14^{II}), 164.33 (C-15), 167.68 (C-14^{IV}), 213.30 (C-17). MS *m/z*: 457 (M^+, 20%), 455 (M^+, 20%), 281 (60%), 187 (100%). HRMS: Found: *m/z* 455.1094. Calcd for $C_{24}H_{26}{}^{79}BrNO_3$: 455.1096; Found: *m/z* 457.1090. Calcd for $C_{24}H_{26}{}^{81}BrNO_3$: 457.1076; isoxazole **7h** (0.035 g, 18%) as a colorless oil, IR (film, cm^{-1}) 1720. ^{1}H-NMR δ 1.20 (3H, s, 18-H), 1.26 (3H, q, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.30 (1H, m, 11β-H), 1.32 (1H, m, 7α-H), 1.60 (1H, m, 12α-H), 1.91 (1H, m, 12β-H), 1.93 (1H, m, 8β-H), 2.20 (1H, dq, *J* = 12.2 Hz, 2.2 Hz, 11α-H), 2.28 (1H, m, 7β-H), 2.30 (1H, m, 9α-H), 2.75 (2H, m, $w_{1/2}$ = 16.5 Hz, 6-H), 3.08 (1H, d, *J* = 15.3 Hz, 14^I-

H), 3.18 (1H, d, *J* = 15.3 Hz, 14^{I}-H), 3.69 (2H, q, *J* = 7.0 Hz, CH_3CH_2O), 3.75 (3H, s, 3-CH_3O), 4.58 (1H, s, CH_2Br), 6.15 (1H, s, 14^{III}-H), 6.30 (1H, d, *J* = 5.9 Hz, 16-H), 6.55 (1H, d, *J* = 2.6 Hz, 4-H), 6.69 (1H, dd, *J* = 2.6 Hz, 8.6 Hz, 2-H), 7.03 (1H, d, *J* = 8.6 Hz, 1-H), 7.42 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 15.19 (CH_3CH_2O), 23.32 (C-18), 25.04 (C-7), 27.79 (C-11), 28.22 (C-12), 29.85 (C-14^{I}), 30.72 (C-6), 33.15 (C-9), 42.20 (C-8), 52.52 (C-13), 54.63 (C-14), 55.34 (3-MeO), 63.66 (CH_2O), 67.00 (CH_3CH_2O), 104.15 (C-14^{III}), 112.55 (C-2), 113.03 (C-4), 128.45 (C-1), 132.18 (C-16), 133.20 (C-10), 136.97 (C-5), 157.36 (C-3), 160.66 (C-14^{II}), 164.63 (C-15), 169.85 (C-14^{IV}), 213.54 (C-17). MS *m/z*: 439 (M^+, 100%); and isoxazole **5**[13] (0.064 g, 35%).

3-Methoxy-14β-[5'-(diethoxymethyl)-isoxazol-3'-ylmethyl]-estra-1,3,5(10),15-tetraen-17-one (7f). A mixture of $NaHCO_3$ (0.31 g, 3.68 mmol), 3,3-dietoxypropyne (0.52 mL, 4.74 mmol) and nitro compound **1** (0.095 g, 0.237 mmol) in absolute ethanol (15 mL) was refluxed for 7 h. After work up and chromatography, isoxazoline **7f** (0.033 g, 28%) was obtained as a pale-yellow foam. IR (film, cm^{-1}) 1710. ^{1}H-NMR δ 1.19 (3H, s, 18-H), 1.26 (6H, two t, *J* = 7.0 Hz, CH_3CH_2O), 1.28 (1H, m, 7α-H), 1.30 (1H, m, 11β-H), 1.60 (1H, dt, *J* = 14.2, 8.9 Hz, 12α-H), 1.92 (1H, m, 12β-H), 1.94 (1H, m, 8β-H), 2.18 (1H, ddd, *J* = 3.3, 5.6, 12.0 Hz, 7β-H), 2.30 (1H, m, 11α-H), 2.28 (1H, m, 9α-H), 2.74 (2H, m, $w_{1/2}$ = 16.5 Hz, 6-H), 3.07 (1H, d, *J* = 15.3 Hz, 14^{I}-H), 3.18 (1H, d, *J* = 15.3 Hz, 14^{I}-H), 3.64 (4H, two q, *J* = 7.0 Hz, CH_3CH_2O), 3.75 (3H, s, 3-CH_3O), 5.63 (1H, d, *J* = 0.6 Hz, $CH(OCH_2CH_3)_2$), 6.24 (1H, d, *J* = 0.6 Hz, 14^{III}-H), 6.30 (1H, d, *J* = 5.9 Hz, 16-H), 6.55 (1H, d, *J* = 2.7 Hz, 4-H), 6.69 (1H, dd, *J* = 2.7, 8.6 Hz, 2-H), 7.03 (1H, d, *J* = 8.6 Hz, 1-H), 7.42 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 15.22 (CH_3CH_2O), 23.33 (C-18), 25.05 (C-7), 27.79 (C-11), 28.18 (C-12), 29.88 (C-14^{I}), 30.71 (C-6), 33.16 (C-9), 42.26 (C-8), 52.52 (C-13), 54.63 (C-14), 55.33 (3-MeO), 62.00 and 61.96 (CH_3CH_2O), 95.32 ($CH(OCH_2CH_3)_2$), 104.34 (C-14^{III}), 112.55 (C-2), 113.03 (C-4), 128.44 (C-1), 132.20 (C-16), 133.17 (C-10), 136.98 (C-5), 157.36 (C-3), 160.46 (C-14^{II}), 164.53 (C-15), 169.49 (C-14^{IV}), 213.47 (C-17). MS *m/z*: 465 (M^+, 50%), 420 (20%), 362 (25%), 281 (60%), 187 (100%). HRMS: Found: *m/z* 465.2514. Calcd for $C_{28}H_{35}NO_5$: 465.2515.

3-Methoxy-14β-(5'-ethoxyisoxazolin-3'-ylmethyl)-estra-1,3,5(10),15-tetraen-17-one (8b) and 3-Methoxy-14β-(isoxazol-3'-ylmethyl)-estra-1,3,5(10),15-tetraen-17-one (7e). A mixture of $NaHCO_3$ (0.22 g, 2.60 mmol), ethyl vinyl ester (0.50 mL, 5.21 mmol) and nitro compound **1** (0.207 g, 0.521 mmol) in absolute ethanol (20 mL) was refluxed for 4 h. After work up and chromatography, the diastereomeric mixture (1:1) of isoxazolines **8b** (0.153 g, 72%) was obtained as a colorless oil. IR (film, cm^{-1}) 1715. ^{1}H-NMR δ 1.10 (3H, two s, 18-H), 1.17 (3H, two t, *J* = 7.1 Hz, CH_3CH_2O), 1.28 (1H, m, 7α-H), 1.35 (1H, m, 11β-H), 1.78 (1H, m, 12α-H), 1.92 (1H, m, 12β-H), 2.10 (1H, m, 8β-H), 2.15 (1H, m, 7β-H), 2.26 (1H, m, 11α-H), 2.28 (1H, m, 9α-H), 2.73 (1H, d, *J* = 16.3 Hz, 14^{I}-H), 2.77 (2H, m, 6-H), 2.79 (1H, two dd, *J* = 1.0, 8.8 Hz, 14^{III}-H), 2.89 (1H, two d, *J* = 16.3 Hz, 14^{I}-H), 3.08 (1H, two d, *J* = 6.4 Hz, 14^{III}-H), 3.54 (1H, m, CH_3CH_2O), 3.74 (3H, s, 3-CH_3O), 3.84 (1H, m, CH_3CH_2O), 5.47 (1H, td, *J* = 6.4 Hz, 1.0 Hz, 14^{IV}-H), 6.27 (1H, d, *J* = 5.9 Hz, 16-H), 6.53 (1H, d, *J* = 2.6 Hz, 4-H), 6.67 (1H, dd, *J* = 2.6, 8.6 Hz, 2-H), 7.01 (1H, d, *J* = 8.6 Hz, 1-H), 7.38 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 15.13 and 15.16 (CH_3CH_2O), 23.01 and 23.14 (C-18), 25.15 (C-7), 27.81 (C-11), 28.10 and 28.18 (C-12),

30.74 and 30.86 (C-6), 31.37 and 31.45 (C-14^{I}), 33.08 and 33.15 (C-9), 42.14 and 42.31 (C-8), 46.28 (C-14^{III}), 52.31 and 52.33 (C-13), 54.85 and 54.91 (C-14), 55.30 (3-MeO), 63.63 and 63.66 (CH_3CH_2O), 101.73 (C-14^{IV}), 112.48 and 112.50 (C-2), 112.97 (C-4), 128.39 (C-1), 132.03 and 132.07 (C-16), 133.19 and 133.22 (C-10), 136.90 and 136.99 (C-5), 156.67 and 156.75 (C-14^{II}), 157.28 (C-3), 164.61 and 164.63 (C-15), 213.47 (C-17). MS *m/z*: 409 (M^+, 40%), 281 (60%), 187 (100%). HRMS: Found: *m/z* 409.2262. Calcd for $C_{25}H_{31}NO_4$: 409.2253; Found: *m/z* 363.1820. Calcd for $C_{23}H_{25}NO_3$ ([M-46]$^+$). Following elution gave isoxazole **7e** (0.012 g, 6%) as oil. IR (film, cm^{-1}) 1715. ^{1}H-NMR δ 1.20 (3H, s, 18-H), 1.29 (1H, m, 11β-H), 1.31 (1H, m, 7α-H), 1.58 (1H, dt, *J* = 14.2, 8.9 Hz, 12α-H), 1.89 (1H, m, 12β-H), 1.91 (1H, m, 8β-H), 2.19 (1H, m, 7β-H), 2.27 (1H, m, 11α-H), 2.29 (1H, m, 9α-H), 2.73 (2H, m, $w_{1/2}$ = 13.4 Hz, 6-H), 3.12 (1H, d, *J* = 15.3 Hz, 14^{I}-H), 3.22 (1H, d, *J* = 15.3 Hz, 14^{I}-H), 3.74 (3H, s, 3-CH_3O), 6.26 (1H, d, *J* = 1.5 Hz, 14^{III}-H), 6.29 (1H, d, *J* = 5.9 Hz, 16-H), 6.53 (1H, d, *J* = 2.7 Hz, 4-H), 6.68 (1H, dd, *J* = 2.7, 8.6 Hz, 2-H), 7.02 (1H, d, *J* = 8.6 Hz, 1-H), 7.42 (1H, d, *J* = 5.9 Hz, 15-H) 8.37 (1H, d, *J* = 1.5 Hz, 14^{IV}-H). ^{13}C-NMR δ 23.25 (C-18), 25.04 (C-7), 27.79 (C-11), 28.25 (C-12), 29.68 (C-14^{I}), 30.71 (C-6), 33.21 (C-9), 42.23 (C-8), 52.51 (C-13), 54.69 (C-14), 55.34 (3-MeO), 105.99 (C-14^{III}), 112.55 (C-2), 113.05 (C-4), 128.44 (C-1), 132.21 (C-16), 133.18 (C-10), 136.94 (C-5), 157.38 (C-3), 158.43 (C-14^{IV}), 159.63 (C-14^{II}), 164.53 (C-15), 213.47 (C-17). MS *m/z*: 363 (M^+, 50%), 281 (55%), 187 (100%). HRMS: Found: *m/z* 363.1825. Calcd for $C_{23}H_{25}NO_3$: 363.1834; Found: *m/z* 281.1543. Calcd for $C_{19}H_{21}O_2$ ([M-82]$^+$): 281.1542.

3-Methoxy-14β-(5'-butoxyisoxazolin-3'-ylmethyl)-estra-1,3,5(10),15-tetraen-17-one (8c). A mixture of $NaHCO_3$ (0.328 g, 3.90 mmol), butyl vinyl ester (0.50 mL, 3.90 mmol) and nitro compound **1** (0.155 g, 0.39 mmol) in absolute ethanol (20 mL) was refluxed for 6 h. After work up and chromatography, the diastereomeric mixture (1:1.2) of isoxazolines **8c** (0.133 g, 78%) was obtained as a white foam. IR (film, cm^{-1}) 1710. ^{1}H-NMR δ 0.85 (3H, visible q, *J* = 7.2 Hz, C*H*$_3$CH$_2$CH$_2$), 1.12 (3H, two s, 18-H), 1.28 (1H, m, 7α-H), 1.30 (2H, m, CH$_3$C*H*$_2$CH$_2$), 1.36 (1H, m, 11β-H), 1.50 (2H, m, C*H*$_2$CH$_2$O), 1.79 (1H, m, 12α-H), 1.93 (1H, m, 12β-H), 2.10 (1H, m, 8β-H), 2.18 (1H, m, 7β-H), 2.28 (1H, m, 11α-H), 2.29 (1H, m, 9α-H), 2.74 (1H, d, *J* = 16.9 Hz, 14^{I}-H), 2.76 (2H, m, 6-H), 2.81 (1H, two d, *J* = 17.4 Hz, 14^{III}-H), 2.92 (1H, two d, *J* = 16.9 Hz, 14^{I}-H), 3.08 (1H, two dd, *J* = 6.2, 17.4 Hz, 14^{III}-H), 3.48 (1H, dt, *J* = 9.4, 6.5 Hz, CH$_2$C*H*$_2$O), 3.75 (3H, s, 3-CH$_3$O), 3.80 (1H, two dt, *J* = 9.4, 6.5 Hz, CH$_2$C*H*$_2$O), 5.47 (1H, two dd, *J* = 6.5 Hz, 1.3 Hz, 14^{IV}-H), 6.29 (1H, d, *J* = 5.9 Hz, 16-H), 6.54 (1H, d, *J* = 2.6 Hz, 4-H), 6.69 (1H, dd, *J* = 2.6, 8.6 Hz, 2-H), 7.03 (1H, d, *J* = 8.6 Hz, 1-H), 7.39 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 13.89 (*C*H$_3$CH$_2$CH$_2$), 19.35 (CH$_3$*C*H$_2$CH$_2$), 23.12 and 23.27 (C-18), 25.12 and 25.20 (C-7), 27.83 and 27.84 (C-11), 27.99 and 28.14 (C-12), 30.74 and 30.87 (C-6), 31.22 and 31.39 (C-14^{I}), 31.68 and 31.70 (*C*H$_2$CH$_2$O), 32.99 and 33.07 (C-9), 42.11 and 42.21 (C-8), 46.24 and 46.31 (C-14^{III}), 52.32 and 52.39 (C-13), 54.88 and 54.99 (C-14), 55.34 (3-MeO), 67.95 and 67.92 (CH$_2$*C*H$_2$O), 101.97 and 101.93 (C-14^{IV}), 112.51 and 112.49 (C-2), 112.99 (C-4), 128.45 (C-1), 132.13 and 132.06 (C-16), 133.28 and 133.25 (C-10), 136.97 and 136.95 (C-5), 156.78 (C-14^{II}), 157.30 (C-3), 164.76 and 164.70 (C-15), 213.58 (C-17). MS *m/z*: 437 (M^+, 35%), 281 (80%), 187 (100%). HRMS: Found: *m/z* 437.2551. Calcd for $C_{27}H_{35}NO_4$: 437.2566.

3-Methoxy-14β-[5'-(2-chloroethoxy)-isoxazolin-3'-ylmethyl]-estra-1,3,5(10),15-tetraen-17-one (8g). A mixture of $NaHCO_3$ (0.14 g, 1.70 mmol), 2-chloroethyl vinyl ester (0.36 mL, 3.40 mmol) and nitro compound **1** (0.135 g, 0.340 mmol) in absolute ethanol (20 mL) was refluxed for 19 h. After work up and chromatography, isoxazole **7e** (0.056 g, 45%) was isolated followed by a diastereomeric mixture (1:1.2) of isoxazolines **8g** (0.056 g, 16%). IR (film, cm^{-1}) 1715. ^{1}H-NMR δ 1.10 (3H, two s, 18-H), 1.33 (1H, m, 7α-H), 1.37 (1H, m, 11β-H), 1.78 (1H, m, 12α-H), 1.93 (1H, m, 12β-H), 2.09 (1H, td, *J* = 11.7, 1.7 Hz, 8β-H), 2.16 (1H, m, 7β-H), 2.28 (m, 1H, 11α-H), 2.29 (m, 1H, 9α-H), 2.73 obsc (1H, d, *J* = 16.3 Hz, 14^{I}-H), 2.76 (2H, m, 6-H), 2.86 (0.45H, dd, *J* = 0.8, 7.3 Hz, 14^{III}-H), 2.89 (1H, two d, *J* = 16.3 Hz, 14^{I}-H), 2.90 (0.55H, dd, *J* = 0.9, 7.3 Hz, 14^{III}-H), 3.10 (0.55H, t, *J* = 6.2 Hz, 14^{III}-H), 3.14 (0.45H, t, *J* = 6.2 Hz, 14^{III}-H), 3.60 (2H, m, ClC*H*$_2$CH$_2$O) 3.74 (3H, s, 3-CH$_3$O), 3.76 (1H, m, ClCH$_2$C*H*$_2$O), 4.04 (1H, m, ClCH$_2$C*H*$_2$O), 5.53 (1H, td, *J* = 6.2, 0.9 Hz, 14^{IV}-H), 6.28 (1H, two d, *J* = 5.9 Hz, 16-H), 6.54 (1H, d, *J* = 2.6 Hz, 4-H), 6.68 (1H, dd, *J* = 2.6, 8.7 Hz, 2-H), 7.02 (1H, d, *J* = 8.7 Hz, 1-H), 7.38 (1H, d, *J* = 5.9 Hz, 15-H). ^{13}C-NMR δ 22.87 and 23.16 (C-18), 25.17 and 25.19 (C-7), 27.78 and 27.83 (C-11), 28.14 and 28.44 (C-12), 30.78 and 30.88 (C-6), 31.31 and 31.43 (C-14^{I}), 33.08 and 33.34 (C-9), 42.20 and 42.32 (C-8), 42.93 and 42.96 (Cl*C*H$_2$CH$_2$O), 46.50 (C-14^{III}), 52.34 (C-13), 54.90 and 54.95 (C-14), 55.34 (3-MeO), 68.08 (ClCH$_2$*C*H$_2$O), 102.02 (C-14^{IV}), 112.55 (C-2), 113.00 (C-4), 128.44 (C-1), 132.22 (C-16), 133.16 and 133.21 (C-10), 136.90 and 136.95 (C-5), 157.09 (C-14^{II}), 157.33 (C-3), 164.34 and 164.52 (C-15), 213.38 and 213.43 (C-17). MS *m/z* : 444 (M$^+$, 100%).

3-Methoxy-14β-(5'-phenylisoxazol-3'-ylmethyl)-estra-1,3,5(10)-trien-17-one (9d). A mixture of $NaHCO_3$ (0.10 g, 1.185 mmol), phenyl acetylene (0.52 mL, 4.74 mmol) and nitro compound **6** (0.095 g, 0.237 mmol) in absolute ethanol (15 mL) was refluxed for 3 h. After work up and chromatography, isoxazole **9d** (0.071 g, 68%) was obtained as a colorless oil. IR (film, cm^{-1}) 1730. ^{1}H-NMR δ 1.23 (3H, s, 18-H), 1.41 (1H, m, 12β-H), 1.42 (1H, m, 11β-H), 1.56 (1H, ddt, *J* = 12.7, 11.0, 6.2 Hz, 7α-H), 1.64 (1H, dd, *J* = 3.5, 14.1 Hz, 12α-H), 1.68 (1H, td, *J* = 11.5, 2.4 Hz, 8β-H), 1.98 (1H, m, 15β-H), 2.18 (1H, dqui, *J* = 2.9, 12.7 Hz, 7β-H), 2.26 (1H, m, 15α-H), 2.27 (1H, m, 16β-H), 2.34 (1H, dq, *J* = 12.4, 3.5 Hz, 11α-H), 2.45 (1H, ddd, *J* = 4.8, 9.7, 18.1 Hz, 16α-H), 2.68 (1H, d, *J* = 14.6 Hz, 14^{I}-H), 2.69 (1H, m, 9α-H), 2.90 (2H, m, 6-H), 2.95 (1H, d, *J* = 14.6 Hz, 14^{I}-H), 3.79 (3H, s, 3-CH$_3$O), 6.37 (1H, s, 14^{III}-H), 6.66 (1H, d, *J* = 2.7 Hz, 4-H), 6.74 (1H, dd, *J* = 2.7, 8.6 Hz, 2-H), 7.22 (1H, d, *J* = 8.6 Hz, 1-H), 7.43 (1H, m, Ph-3H), 7.44 (2H, m, Ph-4,5H), 7.75 (2H, m, Ph-2,6H). ^{13}C-NMR δ 15.97 (C-18), 24.24 (C-15), 24.38 (C-7), 25.25 (C-11), 30.48 (C-6), 33.25 (C-12), 33.33 (C-14^{I}), 33.61 (C-16), 38.47 (C-9), 42.63 (C-8), 48.72 (C-14), 53.10 (C-13), 55.34 (3-MeO), 101.22 (C-14^{III}), 111.81 (C-2), 113.64 (C-4), 125.92 (Ph-2C and Ph-6C), 126.44 (C-1), 127.39 (Ph-1C), 129.07 (Ph-3C and Ph-5C), 130.30 (Ph-4C), 132.37 (C-10), 137.94 (C-5), 157.81 (C-3), 161.77 (C-14^{II}), 169.72 (C-14^{IV}), 221.59 (C-17). MS *m/z*: 441 (M$^+$, 45%), 399 (30%), 370 (25%), 283 (40%), 159 (100%). HRMS: Found: *m/z* 441.2315. Calcd for $C_{29}H_{31}NO_3$: 441.2304.

3-Methoxy-14β-[5'-(diethoxymethyl)-isoxazol-3'-ylmethyl]-estra-1,3,5(10)-trien-17-one (9f). A mixture of $NaHCO_3$ (0.105 g, 1.25 mmol), 3,3-dietoxypropyne (0.18 mL, 1.25 mmol) and

nitro compound **6** (0.050 g, 0.125 mmol) in absolute ethanol (5 mL) was refluxed for 3 h. After work up and chromatography, isoxazole **9f** (0.023 g, 40%) was obtained as a pale-yellow foam. IR (film, cm^{-1}) 1735. ^{1}H-NMR δ 1.18 (3H, s, 18-H), 1.26 (6H, two t, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.40 (1H, m, 12β-H), 1.41 (1H, m, 11β-H), 1.53 (1H, m, 7α-H), 1.65 (1H, m, 12α-H), 1.65 (1H, m, 8β-H), 1.92 (1H, m, 16β-H), 1.96 (1H, m, 15β-H), 2.11 (1H, m, 7β-H), 2.24 (1H, m, 15α-H), 2.34 (1H, m, 11α-H), 2.45 (1H, m, 16α-H), 2.63 (1H, d, *J* = 14.7 Hz, 14^{I}-H), 2.69 (1H, td, *J* = 11.4, 3.1 Hz, 9α-H), 2.88 (2H, m, 6-H), 2.92 (1H, d, *J* = 14.7 Hz, 14^{I}-H), 3.62 (4H, q, *J* = 7.1 Hz, CH$_3$C*H*$_2$O), 3.80 (3H, s, 3-CH$_3$O), 5.61 (1H, d, *J* = 0.6 Hz, C*H*(OCH$_2$CH$_3$)$_2$), 6.20 (1H, d, *J* = 0.6 Hz, 14^{III}-H), 6.66 (1H, d, *J* = 2.7 Hz, 4-H), 6.75 (1H, dd, *J* = 2.7, 8.6 Hz, 2-H), 7.22 (1H, d, *J* = 8.6 Hz, 1-H). ^{13}C-NMR δ 15.21 (*C*H$_3$CH$_2$O), 15.90 (C-18), 24.23 (C-15), 24.32 (C-7), 25.29 (C-11), 30.44 (C-6), 33.28 (C-12), 33.32 (C-14^{I}), 33.57 (C-16), 38.47 (C-9), 42.61 (C-8), 49.30 (C-14), 53.15 (C-13), 55.36 (3-MeO), 61.73 and 61.90 (CH$_3$*C*H$_2$O), 95.23 (*C*H(OCH$_2$CH$_3$)$_2$), 104.71 (C-14^{III}), 111.83 (C-2), 113.67 (C-4), 126.45 (C-1), 132.38 (C-10), 137.97 (C-5), 157.85 (C-3), 160.93 (C-14^{II}), 169.25 (C-14^{IV}), 221.40 (C-17). MS *m/z*: 467 (M$^+$, 40%), 422 (25%), 364 (35%), 283 (35%), 185 (100%). HRMS: Found: *m/z* 467.2676. Calcd for $C_{28}H_{37}NO_5$: 467.2672.

3-Methoxy-14β-(5'-ethoxyisoxazolin-3'-ylmethyl)-estra-1,3,5(10)-trien-17-one (10b). A mixture of $NaHCO_3$ (0.088 g, 1.05 mmol), ethyl vinyl ester (0.40 mL, 4.20 mmol) and nitro compound **6** (0.084 g, 0.210 mmol) in absolute ethanol (15 mL) was refluxed for 14 h. After work up and chromatography, a diastereomeric mixture (1 : 1.1) of isoxazolines **10b** (0.068 g, 79%) was obtained as a colorless oil. IR (film, cm^{-1}) 1730. MS *m/z* : 411 (M$^+$, 100%), 283 (M$^+$-128, 90%), 365 (M$^+$-46, 30%). HRMS Calcd. $C_{25}H_{33}NO_4$: 411.2410. Found: 411.2417. The mixture of isoxazolines **10b** was re-chromatographed on silica gel with ethyl acetate/toluene (5 : 95) to afford a less polar isomer of isoxazolines **10b** (0.007 g) as oil. ^{1}H-NMR δ 1.12 (3H, s, 18-H), 1.18 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.39 (1H, m, 11β-H), 1.40 (1H, m, 12β-H), 1.54 (1H, ddt, *J* = 12.8, 11.0, 6.5 Hz, 7α-H), 1.65 (1H, m, 12α-H), 1.66 (1H, m, 8β-H), 1.95 (1H, m, 15β-H), 2.08 (1H, m, 7β-H), 2.24 (1H, m, 15α-H), 2.27 (1H, m, 16β-H), 2.34 (1H, m, 11α-H), 2.35 (1H, d, *J* = 14.8 Hz, 14^{I}-H), 2.50 (1H, m, 16α-H), 2.59 (1H, d, *J* = 14.8 Hz, 14^{I}-H), 2.67 (1H, td, *J* = 11.7, 3.0 Hz, 9α-H), 2.71 (1H, dd, *J* = 1.2, 17.5 Hz, 14^{III}-H), 2.88 (2H, m, 6-H), 3.05 (1H, dd, *J* = 6.5, 17.5 Hz, 14^{III}-H), 3.52 (1H, dq, *J* = 9.4, 7.1 Hz, CH$_3$C*H*$_2$O), 3.78 (3H, s, 3-CH$_3$O), 3.84 (1H, dd, *J* = 9.4, 7.1 Hz, CH$_3$C*H*$_2$O), 5.43 (1H, dd, *J* = 1.2, 6.5 Hz, 14^{IV}-H), 6.64 (1H, d, *J* = 2.8 Hz, 4-H), 6.73 (1H, dd, *J* = 2.8, 8.6 Hz, 2-H), 7.20 (1H, d, *J* = 8.6 Hz, 1-H). ^{13}C-NMR δ 15.13 (*C*H$_3$CH$_2$O), 15.81 (C-18), 24.18 (C-15), 24.52 (C-7), 25.30 (C-11), 30.55 (C-6), 33.01 (C-12), 33.44 (C-16), 34.46 (C-14^{I}), 38.48 (C-9), 42.56 (C-8), 46.54 (C-14^{III}), 49.28 (C-14), 53.10 (C-13), 55.37 (3-MeO), 63.53 (CH$_3$*C*H$_2$O), 101.73 (C-14^{IV}), 111.83 (C-2), 113.65 (C-4), 126.48 (C-1), 132.33 (C-10), 137.93 (C-5), 157.08 (C-14^{II}), 157.84 (C-3), 221.74 (C-17).

3-Methoxy-14β-(5'-butoxyisoxazolin-3'-ylmethyl)-estra-1,3,5(10)-trien-17-one (10c). A mixture of $NaHCO_3$ (0.14 g, 1.66 mmol), butyl vinyl ester (0.21 mL, 1.66 mmol) and nitro compound **6** (0.066 g, 0.166 mmol) in absolute ethanol (10 mL) was refluxed for 6 h. After work up and chromatography, a less polar isomer of isoxazolines **10c** was isolated (0.008 g, 11%). ^{1}H-NMR δ 0.91 (3H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$CH$_2$), 1.13 (3H, s, 18-H), 1.34 (2H, m,

$CH_3CH_2CH_2$),1.39 (1H, m, 11β-H), 1.42 (1H, m, 12β-H), 1.53 (1H, m, 7α-H), 1.54 (2H, m, CH_2CH_2O), 1.67 (1H, m, 8β-H), 1.68 (1H, m, 12α-H), 1.97 (1H, m, 15β-H), 2.08 (1H, m, 7β-H), 2.25 (1H, m, 15α-H), 2.28 (1H, m, 16β-H), 2.35 (1H, m, 11α-H), 2.37 (1H, d, *J* = 14.8 Hz, 14^{I}-H), 2.50 (1H, m, 16α-H), 2.57 (1H, d, *J* = 14.8 Hz, 14^{I}-H), 2.68 (1H, td, *J* = 11.5, 3.2 Hz, 9α-H), 2.73 (1H, dd, *J* = 1.2, 17.5 Hz, 14^{III}-H), 2.88 (2H, m, 6-H), 3.06 (1H, dd, *J* = 6.5, 17.5 Hz, 14^{III}-H), 3.46 (1H, dt, *J* = 9.4, 6.6 Hz, CH_2CH_2O), 3.80 (3H, s, 3-CH_3O), 3.80 (1H, dt, *J* = 9.4, 6.6 Hz, CH_2CH_2O), 5.43 (1H, dd, *J* = 1.2, 6.5 Hz, 14^{IV}-H), 6.66 (1H, d, *J* = 2.8 Hz, 4-H), 6.74 (1H, dd, *J* = 2.8, 8.6 Hz, 2-H), 7.22 (1H, d, *J* = 8.6 Hz, 1-H). ^{13}C-NMR δ 13.96 ($CH_3CH_2CH_2$), 15.84 (C-18), 19.34 ($CH_3CH_2CH_2$), 24.15 (C-15), 24.56 (C-7), 25.32 (C-11), 30.57 (C-6), 31.69 (CH_2CH_2O), 32.98 (C-12), 33.44 (C-16), 34.45 (C-14^{I}), 38.49 (C-9), 42.51 (C-8), 46.55 (C-14^{III}), 49.30 (C-14), 53.15 (C-13), 55.38 (3-MeO), 67.89 (CH_2CH_2O), 101.93 (C-14^{IV}), 111.82 (C-2), 113.66 (C-4), 126.49 (C-1), 132.33 (C-10), 137.94 (C-5), 157.06 (C-14^{II}), 157.82 (C-3), 221.80 (C-17). Further elution gave a diastereomeric mixture (1 : 1) of isoxazolines **10c** (0.042 g, 58%) as oil. IR (film, cm^{-1}) 1733. MS *m/z*: 439 (M^+, 30%), 365 (20%), 283 (40%). HRMS: Found: *m/z* 439.2715. Calcd for $C_{27}H_{37}NO_4$: 439.2723.

Supplementary Information Available

^{13}C NMR spectra of the synthesized compounds **7a-10c** are available as supplementary information.

Acknowledgements

This work was carried out as a part of the research projects of International Science and Technology Center, Grant No. B-1332; INTAS, Grant, No 06-1000014-5620, and the State Program of Focused Fundamental Research, State registration No 20052814. The high resolution mass measurements were kindly performed by Sybille Lorenz.

The authors are thankful to Prof. J. R. Bull and Prof. Ae de Groot for their assistance in the development of this work.

References and Notes

1. Grundmann, Ch.; Grunanger P. *The Nitrile Oxides*, Springer-Verlag: New York, 1971.
2. Torssel, K. B. G. *Nitrile Oxides,Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988.
3. Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17,* 410.

4. Padwa, A.; Pearson, W. H. *Synthetic Application of 1,3-Dipolar Cycloaddition toward Heterocycles and Natural Products,* John Wiley & Sons: New York, 2002.
5. Khripach, V.; Litvinovskaya, R.; Baranovsky, A.; Drach, S. *Tetrahedron Lett.* **1990**, *31*, 7065.
6. Baranovsky, A. V.; Groen, M. B.; de Groot, Ae.; Litvinovskaya, R. P.; Khripach, V. A. *Collect. Czech. Chem. Commun*. **1998**, *63,* 1564.
7. Kanemasa, S. *Synlett* **2002**, 1371.
8. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev*. **1998**, *98*, 863.
9. Litvinovskaya, R. P.; Khripach, V. A. *Russ. Chem. Rev*. **2001,** *70*, 405.
10. Pellissier, H. *Tetrahedron* **2007,** *63,* 3235.
11. Huisgen, R.; Mack, W. *Tetrahedron Lett.* **1961,** 583.
12. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339;
13. Baranovsky, A. V.; Bolibrukh, D. A.; Bull, J. R. *Eur. J. Org. Chem.* **2007**, 445.
14. McKillop, A.; Kobylecki, R. J. *Tetrahedron* **1974**, *30*, 1365.
15. Das, N. B.; Torssel, K. B. G. *Tetrahedron* **1983**, *39*, 2247.
16. Basel, Y.; Hassner, A. *Synthesis* **1997,** 309.
17. Cecchi, L.; De Sarlo, F.; Machetti, F.*Tetrahedron Lett.* **2005**, *46*, 7877.
18. Khripach, V. A.; Zhabinskii, V. N.; Kotyatkina, A. I. *Zhurn. Org. Khim.* **1993**, *29*, 1569.
19. Khripach, V. A.; Zhabinskii, V. N.; Kotyatkina, A. I. *Zhurn. Org. Khim.* **1993**, *29*, 1573.
20. Hu, Y.; Houk, K. N. *Tetrahedron* **2000,** *56,* 8239.
21. Jimenez, R.; Perez, L.; Tamariz, J.; Salgado, H. *Heterocycles* **1993**, *35,* 591.
22. Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993,** *58,* 3857.
23. Martins, M. A. P.; Martins, A. C. L. *Magn. Reson. Chem.* **1994**, *32*, 614.
24. Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001,** *123,* 3611.
25. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th Edn.; Pergamon: Oxford, 2003.