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

Alexander V. Baranovsky, a* Dmitry A Bolibrukh, a Vladimir A. Khripac, 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-nitroestr-1,3,5(10)-trien-17β-yl acetate and its 171,172-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\textsuperscript{12} and other closely related methods.\textsuperscript{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.

\begin{center}
\includegraphics[width=\textwidth]{reaction Scheme}
\end{center}

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.\textsuperscript{13} Earlier, relatively stable steroidal nitrile oxide was prepared in our laboratory and its reactivity toward dipolarophiles was analysed.\textsuperscript{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\textsuperscript{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

a: R = CH$_2$OTHP; b: R=OEt; c: R=OBu; d: R=Ph; e: R=H; f: R=CH(OEt)$_2$; g: R=CH$_2$CH$_2$Cl, h: R=CH$_2$OEt; i: R=CH$_2$Br
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 regioisomers,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 ethers14,21,22 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 1H and 13C 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 1H 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 Massspec 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$_2$SO$_4$. 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$_2$SO$_4$) 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 $\delta$ 1.19 (3H, two s, 18-H), 1.29 (1H, m, 7α-H), 1.31 (1H, m, 11β-H), 1.53 (1H, m, TPH-4H), 1.54 (1H, m, TPH-5H), 1.59 (1H, m, 12α-H), 1.60 (1H, m, TPH-5H), 1.64 (1H, m, TPH-3H), 1.74 (1H, m, TPH-3), 1.82 (1H, m, TPH-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, $\delta_{1/2}$ = 8 Hz, 6-H), 3.06 (1H, two d, $J$ = 15.4 Hz, 14β-H), 3.17 (1H, two d, $J$ = 15.4 Hz, 14β-H), 3.54 (1H, m, TPH-6H), 3.74 (3H, s, 3-CH$_3$O), 3.85 (1H, m, THP-6H), 4.61 (1H, ddd, $J$ = 13.8 Hz, 1.4 Hz, 0.7 Hz, C$_2$H$_2$OTHP), 4.72 (1H, br t, $J$ = 3.4 Hz, TPH-2H), 4.77 (1H, dt, $J$ = 13.8 Hz, 0.7 Hz, C$_2$H$_2$OTHP), 6.15 (1H, s, 14α-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 $\delta$ 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-14I), 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$_2$H$_2$OTHP), 62.27 and 62.31 (THP-6C), 98.34 and 98.41 (THP-2C), 104.31 and 104.39 (C-14I), 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), 164.65 and 164.67 (C-15), 169.58 and 169.60 (C-14IV), 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 $\delta$ 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, 14β-H), 2.17 (1H, dd, $J$ = 4.0, 19.7 Hz, 16β-H) 2.23 (1H, d, $J$ = 17.3 Hz, 14β-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$_3$O), 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 $\delta$ 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-14I), 43.26 (C-16), 43.61 (C-8), 51.16 (C-15), 53.34 (C-14), 53.63 (C-13), 55.22 (3-ISSN 1557-7012 Page 34 ©ARKAT-USA, Inc.)
MeO), 112.41 (C-2), 113.41 (C-4), 127.12 (C-1), 130.46 (C-10), 130.48 (C-4), 132.21 (C-16), 133.24 (C-10), 136.97 (C-5), 157.80 (C-3), 216.86 (C-17). MS m/z: 339 (M+, 90%), 321 (51%), 187 (100%). HRMS: Found: m/z 339.1836. Calcd for C$_2$H$_5$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, isozazole 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$^1$-H), 3.22 (1H, d, $J$ = 15.3 Hz, 14$^4$-H), 3.73 (3H, s, 3-CH$_3$O), 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$^1$), 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$^{III}$), 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$^1$-H), 3.17 (1H, d, $J$ = 15.4 Hz, 14$^4$-H), 3.75 (3H, s, 3-CH$_3$O), 4.45 (1H, m, CH$_2$Br), 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$_2$Br), 23.24 (C-18), 25.06 (C-7), 27.76 (C-11), 28.32 (C-12), 29.94 (C-14$^1$), 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$^{III}$), 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 457.1094. Calcd for C$_{24}$H$_{26}$BrNO$_3$: 455.1096; Found: m/z 457.1090. Calcd for C$_{24}$H$_{26}$BrNO$_3$: 457.1076; isozazole 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, CH$_3$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$^1$-
3.18 (1H, d, J = 15.3 Hz, 14\(^1\)H), 3.69 (2H, q, J = 7.0 Hz, CH\(_2\)CH\(_2\)O), 3.75 (3H, s, 3-CH\(_3\)O), 4.58 (1H, s, CH\(_2\)Br), 6.15 (1H, s, 14\(^{11}\)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). \(^1^C\)-NMR δ 15.19 (CH\(_2\)CH\(_2\)O), 23.32 (C-18), 25.04 (C-7), 27.79 (C-11), 28.22 (C-12), 29.85 (C-14\(^4\)), 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\(_2\)O), 67.00 (CH\(_2\)CH\(_2\)O), 104.15 (C-14\(^{11}\)), 112.55 (C-2), 113.03 (C-4), 128.45 (C-1), 132.18 (C-16), 133.20 (C-3), 147.36 (C-34), 160.66 (C-14\(^{11}\)), 164.63 (C-15), 169.85 (C-14\(^{14}\)), 213.54 (C-17). MS m/z: 439 (M\(^+\), 100%), and isoxazole 5\(^1^3\) (0.064 g, 35%).

3-Methoxy-14\(^\beta\)-[5\(^\prime\)-diethoxymethyl]-isoxazol-3\(^\prime\)-yethylmethyl)-estra-1,3,5(10),15-tetraena-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\(_2\)CH\(_2\)O), 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, ddm, 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\(^1\)H), 3.18 (1H, d, J = 15.3 Hz, 14\(^2\)H), 3.64 (4H, two q, J = 7.0 Hz, CH\(_2\)CH\(_2\)O), 3.75 (3H, s, 3-CH\(_3\)O), 5.63 (1H, d, J = 0.6 Hz, CH(OCH\(_2\)CH\(_2\)O), 6.24 (1H, d, J = 0.6 Hz, 14\(^{11}\)H), 6.30 (1H, d, J = 5.9 Hz, 16-H), 6.55 (1H, d, J = 2.7 Hz, 4-H), 6.69 (1H, ddm, 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). \(^1^C\)-NMR δ 15.22 (CH\(_2\)CH\(_2\)O), 23.33 (C-18), 25.05 (C-7), 27.79 (C-11), 28.18 (C-12), 30.72 (C-6), 33.15 (C-9), 42.20 (C-8), 52.52 (C-13), 54.63 (C-14), 55.33 (3-MeO), 62.00 and 61.96 (CH\(_2\)CH\(_2\)O), 95.32 (CH(OCH\(_2\)CH\(_2\)O), 104.34 (C-14\(^{11}\)), 128.44 (C-1), 132.20 (C-16), 133.17 (C-10), 136.98 (C-5), 157.36 (C-3), 160.46 (C-14\(^{11}\)), 164.53 (C-15), 169.49 (C-14\(^{14}\)), 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\(_3\): 465.2515.

3-Methoxy-14\(^\beta\)-(5\(^\prime\)-ethoxyisoxazolin-3\(^\prime\)-yethylmethyl)-estra-1,3,5(10),15-tetraena-17-one (8b) and 3-Methoxy-14\(^\beta\)-(isoxazol-3\(^\prime\)-yethylmethyl)-estra-1,3,5(10),15-tetraena-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\(_2\)CH\(_2\)O), 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\(^2\)H), 2.77 (2H, m, 6-H), 2.79 (1H, two dd, J = 1.0, 8.8 Hz, 14\(^{11}\)H), 2.89 (1H, two d, J = 16.3 Hz, 14\(^1\)H), 3.08 (1H, two d, J = 6.4 Hz, 14\(^{11}\)H), 3.54 (1H, m, CH\(_2\)CH\(_2\)O), 3.74 (3H, s, 3-CH\(_3\)O), 3.84 (1H, m, CH\(_2\)CH\(_2\)O), 5.47 (1H, td, J = 6.4 Hz, 1.0 Hz, 14\(^{14}\)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). \(^1^C\)-NMR δ 15.13 and 15.16 (CH\(_3\)CH\(_2\)O), 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), 33.08 and 33.15 (C-9), 42.14 and 42.31 (C-8), 46.28 (C-14), 52.31 and 52.33 (C-13), 54.85 and 54.91 (C-14), 55.30 (3-MeO), 63.63 and 63.66 (CH$_3$CH$_2$O), 101.73 (C-14IV), 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-14II), 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$_2$H$_3$NO$_4$: 409.2253; Found: m/z 363.1820. Calcd for C$_2$H$_3$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, d, 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$_3$O), 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$^II$-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), 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-14IV), 159.63 (C-14II), 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$_2$H$_3$NO$_3$: 363.1834; Found: m/z 281.1543. Calcd for C$_3$H$_2$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 8e (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, CH$_3$CH$_2$CH$_2$), 1.12 (3H, two s, 18-H), 1.28 (1H, m, 7α-H), 1.30 (2H, m, CH$_2$CH$_2$CH$_2$), 1.36 (1H, m, 11β-H), 1.50 (2H, m, CH$_2$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$^II$-H), 3.08 (1H, two dd, J = 6.2, 17.4 Hz, 14$^II$-H), 3.48 (1H, dt, J = 9.4, 6.5 Hz, CH$_2$CH$_2$O), 3.75 (3H, s, 3-CH$_3$O), 3.80 (1H, two dt, J = 9.4, 6.5 Hz, CH$_2$CH$_2$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 (CH$_3$CH$_2$CH$_2$), 19.35 (CH$_3$CH$_2$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), 31.68 and 31.70 (CH$_2$CH$_2$O), 32.99 and 33.07 (C-9), 42.11 and 42.21 (C-8), 46.24 and 46.31 (C-14)$^I$, 52.32 and 52.39 (C-13), 54.88 and 54.99 (C-14), 55.34 (3-MeO), 67.95 and 67.92 (CH$_2$CH$_2$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$_2$H$_3$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 NaHCO₃ (0.14 g, 1.70 mmol), 2-chloroethyl vinyl ester (0.36 mL, 3.40 mmol) and nitro compound I (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. ¹H-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, 14I-H), 2.76 (2H, m, 6-H), 2.86 (0.45H, dd, J = 0.8, 7.3 Hz, 14III-H), 2.89 (1H, two d, J = 16.3 Hz, 14I⁻H), 2.90 (0.55H, dd, J = 0.9, 7.3 Hz, 14III⁻H), 3.10 (0.55H, t, J = 6.2 Hz, 14I⁻II), 3.14 (0.45H, t, J = 6.2 Hz, 14III⁻II), 3.60 (2H, m, ClCH₂CH₂O) 3.74 (3H, s, 3-CH₃O), 3.76 (1H, m, ClCH₂CH₂O), 4.04 (1H, m, ClCH₂CH₂O), 5.53 (1H, td, J = 6.2, 0.9 Hz, 14IV-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). ¹³C-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), 33.08 and 33.34 (C-9), 42.20 and 42.32 (C-8), 42.93 and 42.96 (ClCH₂CH₂O), 46.50 (C-14III), 52.34 (C-13), 54.90 and 54.95 (C-14), 55.34 (3-MeO), 68.08 (ClCH₂CH₂O), 102.02 (C-14IV), 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-14III), 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)-triien-17-one (9d). A mixture of NaHCO₃ (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. ¹H-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, 14I-H), 2.69 (1H, m, 9α-H), 2.90 (2H, m, 6-H), 2.95 (1H, d, J = 14.6 Hz, 14I⁻H), 3.79 (3H, s, 3-CH₃O), 6.37 (1H, s, 14III⁻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-4H, 5H), 7.75 (2H, m, Ph-2H, 6H). ¹³C-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), 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-14III), 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-14II, 169.72 (C-14IV), 221.59 (C-17). MS m/z: 441 (M⁺, 45%), 399 (30%), 370 (25%), 283 (40%), 159 (100%). HRMS: Found: m/z 441.2315. Caled for C₂₉H₃₁N₂O₃: 441.2304.

3-Methoxy-14β-[5'-(diethoxymethyl)-isoxazol-3'-ylmethyl]-estra-1,3,5(10)-triien-17-one (9f). A mixture of NaHCO₃ (0.105 g, 1.25 mmol), 3,3-dietyoxypropyne (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. ¹H-NMR δ 1.22 (3H, s, 18-H), 1.26 (6H, two t, J = 7.1 Hz, CH₃CH₂O), 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, 14β-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, 14α-H), 3.62 (4H, q, J = 7.1 Hz, CH₃CH₂O), 3.80 (3H, s, 3-CH₃O), 5.61 (1H, d, J = 0.6 Hz, CH(OCH₂CH₃)), 6.20 (1H, d, J = 0.6 Hz, 14III-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). ¹³C-NMR δ 15.21 (CH₃CH₂O), 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-14I), 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 (CH₃CH₂O), 95.23 (CH(OCH₂CH₃)), 104.71 (C-14III), 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-14II), 169.25 (C-14IV), 221.40 (C-17). MS m/z: 467 (M⁺, 40%), 422 (25%), 364 (35%), 283 (35%), 185 (100%). HRMS: Found: m/z 467.2676. Caled for C₂₃H₃₇NO₅: 467.2672.

3-Methoxy-14β-(5′-ethoxyisoxazolin-3′-ylmethyl)-estra-1,3,5(10)-trien-17-one (10b). A mixture of NaHCO₃ (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) 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: Caled: C₂₅H₃₅N_O₅. Found: 411.2417.

The mixture of isoxazolines 10b was re-chromatographed on silica gel with ethyl acetate/toluene (5:1) to afford a less polar isomer of isoxazolines 10b (0.007 g) as oil. ¹H-NMR δ 1.22 (3H, s, 18-H), 1.18 (3H, t, J = 7.1 Hz, CH₃CH₂O), 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, 14β-H), 2.50 (1H, m, 16α-H), 2.59 (1H, d, J = 14.8 Hz, 14α-H), 2.67 (1H, td, J = 11.7, 3.0 Hz, 9α-H), 2.71 (1H, dd, J = 1.2, 17.5 Hz, 14III-H), 2.88 (2H, m, 6-H), 3.05 (1H, dd, J = 6.5, 17.5 Hz, 14III-H), 3.52 (1H, dq, J = 9.4, 7.1 Hz, CH₃CH₂O), 3.78 (3H, s, 3-CH₃O), 3.84 (1H, dd, J = 9.4, 7.1 Hz, CH₃CH₂O), 5.43 (1H, dd, J = 1.2, 6.5 Hz, 14IV-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). ¹³C-NMR δ 15.13 (CH₃CH₂O), 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-14I), 38.48 (C-9), 42.56 (C-8), 46.54 (C-14III), 49.28 (C-14), 53.10 (C-13), 55.37 (3-MeO), 63.53 (CH₃CH₂O), 101.73 (C-14IV), 111.83 (C-2), 113.65 (C-4), 126.48 (C-1), 132.33 (C-10), 137.93 (C-5), 157.08 (C-14II), 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 NaHCO₃ (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%). ¹H-NMR δ 0.91 (3H, t, J = 7.4 Hz, CH₃CH₂CH₂), 1.13 (3H, s, 18-H), 1.34 (2H, m,
13C NMR δ 13.96 (CH3CH2), 15.84 (C-18), 19.34 (CH3CH2), 24.15 (C-15), 24.56 (C-7), 25.32 (C-11), 30.57 (C-6), 31.69 (CH3CH2), 32.98 (C-12), 33.44 (C-16), 34.45 (C-14I), 38.49 (C-9), 42.51 (C-8), 46.55 (C-14III), 49.30 (C-14), 53.15 (C-13), 55.38 (3-MeO), 67.89 (CH2CH2O), 101.93 (C-14IV), 111.82 (C-2), 113.66 (C-4), 126.49 (C-1), 132.33 (C-10), 137.94 (C-5), 157.06 (C-14II), 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 C27H37NO4: 439.2723.

**Supplementary Information Available**

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

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**References and Notes**