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Synthesis of 3-Methoxy-16α-nitro-14,17-ethenoestra-1,3,5(10)-trien-17β-yl Acetate and Fragmentation-Mediated Pathways to 14β,15β-Fused *N*-Heterocycles and 14β-Functionalised Alkyl Derivatives

Alexander V. Baranovsky,*[a] Dmitry A. Bolibrukh,[a] and James R. Bull[b]

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The Diels–Alder reaction of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**) with nitroethylene gives 3-methoxy-16-nitro-14,17-ethenoestra-1,3,5(10)-trien-17β-yl acetate (**2**). Cycloadduct **2** can be reduced with $TiCl_3$, giving oxazine **3** as a result of sigmatropic rearrangement, whereas the treatment of **2** with Lewis acids ($TiCl_4$, $SnCl_4$) leads to a derivative of the cyclic hydroximic acid **10**; the latter is viewed as a product of intramolecular rearrangement. Cycloadduct **2** suffers a weak base-induced cleavage of the C(16)–C(17) bond, releasing the nitrile oxide intermediate, which can be trapped by a dipolarophile or reduced with triphenylphosphane. Thus, the trapping of the nitrile oxide with propargyl alcohol gives the isoxazole **12** in 50% yield, and the reduction of the nitrile oxide with triphenylphosphane gives nitrile **9** in 94% yield.

Introduction

Recent developments in the synthesis of 14,17-ethano-19-norsteroids[1,2] provide the opportunity to explore the potential of cycloaddition methodology for preparing steroids in which ring D is modified in various ways.[3,4] It is envisaged that the primary 14,17-bridge, generated from the reaction of suitably functionalised dienophiles with 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**), can serve as a versatile tool for the introduction of functionalised alkyl chains at C-14. With this objective in mind, we examined the cycloaddition of nitroethylene to the dienyl acetate **1** and the chemistry of the derived cycloadduct.

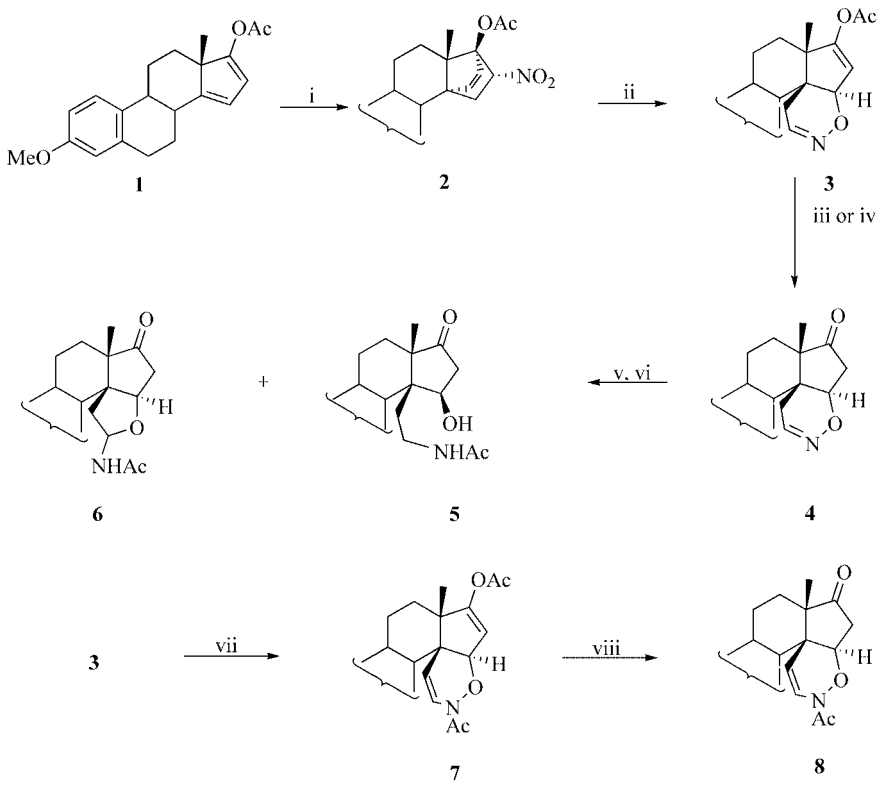
Results and Discussion

The dienyl acetate **1** readily underwent reaction with nitroethylene in refluxing benzene for 6 h to give the expected 16α-nitro cycloadduct **2** as the major product in 86% yield (Scheme 1). The regio- and stereoselectivity of this process was based upon well-established precedent for similar cycloadditions[1–3] and was confirmed with the aid of conclusive spectroscopic data, as well as subsequent reactions.

[a] Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus,
Kuprevich str. 5/2, 220143, Minsk, Belarus
[b] Department of Chemistry, University of Cape Town,
Rondebosch 7701, Cape Town, South Africa

An early objective in this study entailed the exploration of the ethylene and ketene equivalency of nitroethylene in this context. However, the cycloadduct **2** failed to undergo the Nef reaction or its oxidative modifications,[5,6] generally with the recovery of starting material. This result is unsurprising in the light of previous observations.[5,7] On the other hand, the reductive modification of the Nef reaction, employing $TiCl_3$ as a reducing agent[8–10] in a mixture of aqueous acetic acid and THF, resulted in very rapid reaction at room temperature to give a product (71% yield), identified as the 1,2-oxazine **3** and not the expected ketone. The reaction was complete within 20 min under these conditions but was more protracted and less efficient in aqueous THF in the absence of acetic acid.

The enol acetate **3** was readily hydrolysed to the parent 17-ketone **4** in the presence of bases. This chemical correlation, together with supportive spectroscopic data for **3** and **4** were consistent with all their structural and functional features, and COSY and HETCOR correlations demonstrated the key skeletal connectivities. Thus, the presence of 16-en-17-yl acetate functionality in the primary oxazine **3** was evident from a diagnostic IR absorption at 1764 cm^{-1} for an acetoxy carbonyl group and ^1H NMR singlets for the acetoxy group (δ = 1.18 ppm) and the 15α-H (δ = 5.29 ppm). A doublet for 16-H (δ = 5.67 ppm) and a multiplet for 3′-H (δ = 7.45 ppm) of the oxazine ring, arising from long-range coupling to 15α-H, furnished supporting structural evidence. In the ^1H NMR spectrum of the parent ketone **4**, the signal for 15α-H appears as a triplet, whereas that of 3′-H retains the foregoing multiplet structure. The 17-oxo group gives rise to an IR absorption at 1737 cm^{-1} and a ^{13}C NMR signal at δ = 215.9 ppm.



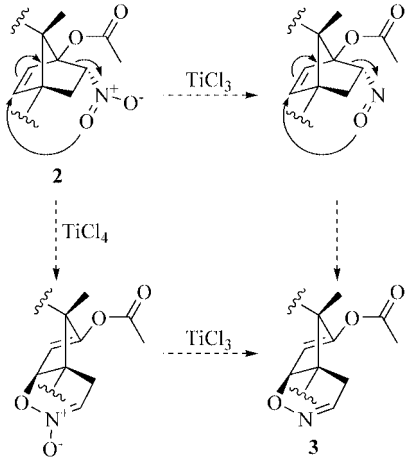
Scheme 1. i: Nitroethylene, PhH, reflux; ii: $TiCl_3$, THF, AcOH, H_2O, NaOAc; iii: $NaHCO_3$, EtOH, H_2O, reflux, 15 min; iv: KOH, MeOH, 15 min; v: Ra/Ni, H_2, AcOH; vi: Ac_2O, AcOH; vii: Ac_2O, reflux; viii: MeOH, H_2O, reflux.

The preservation of a 17-acetoxy group during the formation of **3** is particularly striking, since it clearly excludes any ionic process from engaging the bridgehead oxygen of cycloadduct **2** in oxazine formation. Instead, it offers compelling evidence for a facile [3,3] sigmatropic rearrangement of the 16α-nitroso derivative of **2**, generated as the first obligatory intermediate in the reaction of the nitro group with low-valent titanium.[6,7] Sigmatropic processes of this nature are known for a variety of 5-functionalised born-2-enes,[11–14] and the reported[15] transformation of 5-nitro-7-(*p*-tolyl)bicyclo[2.2.1]hept-2-ene into 3-*p*-tolylpyridine invokes an analogous pathway to a postulated 1,2-oxazine intermediate.

The ready availability of oxazines **3** and **4** invited the consideration of ways in which they could be exploited to gain access to 14β-alkyl-substituted systems of interest. Oxazine **4** underwent reductive cleavage over Raney nickel in the presence of acid but, in contrast to isoxazolines,[16] did not afford the expected hydroxy aldehyde or derived lactol. Instead, the only products isolated after acetylation of the hydrogenolysis mixture were compounds **5** (61% yield) and **6** (31% yield). Evidently, intramolecular cyclisation of the presumed hydroxyimine intermediate and subsequent reduction occur more rapidly than hydrolysis.

The oxazine **3** was found to be rather resistant to Hoffman degradation. Treatment of **3** with neat acetic anhydride at reflux[17] afforded the *N*-acetyl derivative **7**, whereas the additional presence of pyridine in the reaction mixture induced the concomitant slow hydrolysis of the enol acetate **7** to generate the corresponding 17-ketone **8**. However, nitrile **9** (Scheme 3) was obtained in about 50% yield by the action of LDA on the oxazine **3**, in accordance with similar observations for 3-unsubstituted isoxazolines and isoxazoles.[18,19]

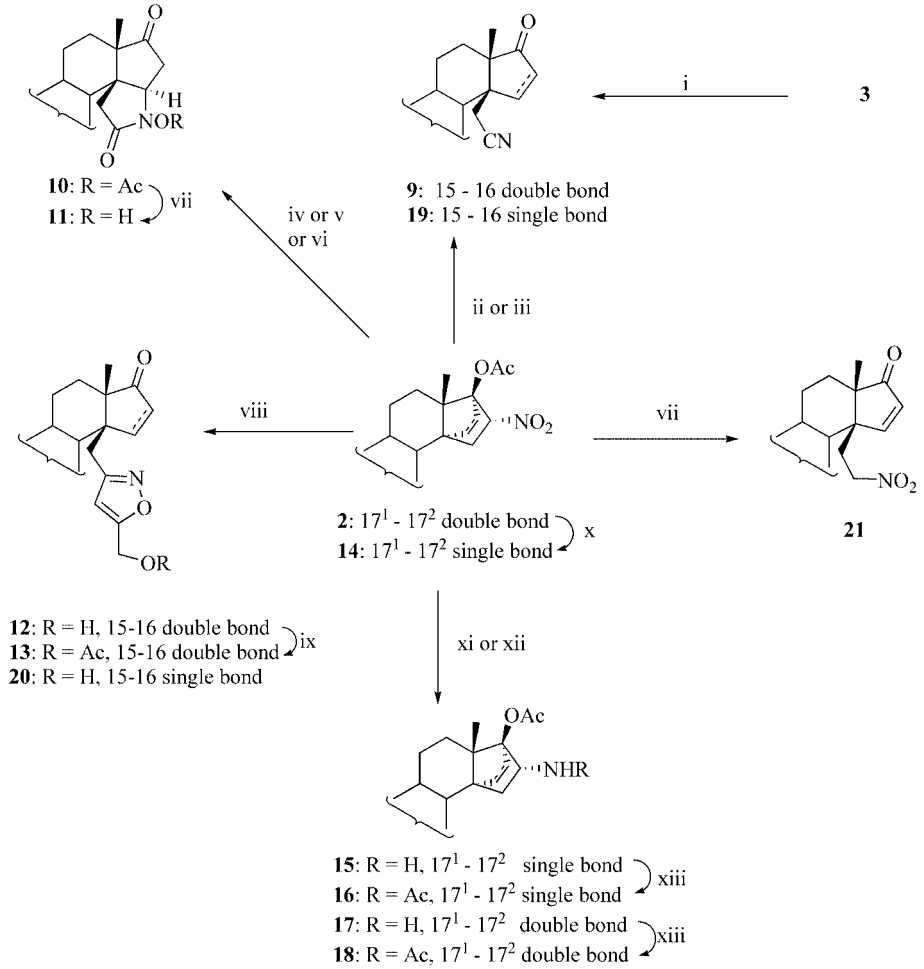
Other possible pathways to oxazine **3** were also considered, and in particular those in which Lewis acids might play a role in triggering the rearrangement of **2**. Lewis acids are known to catalyse various reactions of nitroalkenes. For example, their [4+2] cycloaddition reaction with olefins gives cyclic nitronates.[20] Cyclic nitronates, which may be implicated as intermediates in this study, could then be deoxygenated with $TiCl_3$ to give oxazine **3** (Scheme 2).



Scheme 2.

Our first attempts to induce the Lewis–acid-catalysed rearrangement of nitro compound **2** revealed that rapid reaction occurred in the presence of $TiCl_4$ or $SnCl_4$ in dichloromethane at 0 °C (Scheme 3). At least one equiv. of Lewis acid was required to ensure the complete consumption of starting material, and the addition of more then an equivalent of $TiCl_4$ led to the formation of a yellow precipitate. However, direct attempts to isolate the primary product of these reactions failed, and quenching the reaction with sodium carbonate, triethylamine, *tert*-butyl alcohol or a dipolarophile (methyl propiolate) resulted in the formation of intractable mixtures. The addition of $TiCl_3$ to the reaction mixture failed to give oxazine **3** or **4**.

Instead, acidic hydrolysis proved to be the key to the successful workup of the Lewis-acid-mediated reactions. Thus, standard treatment of **2** with $TiCl_4$, followed by hydrolysis with 1 N HCl for 20 h furnished a single product (65% yield), identified as the *N*-acetoxy lactam **10**. The best result was achieved by quenching the $SnCl_4$-mediated reaction with 50% acetic acid, which gave compound **10** in 83% yield. Alkaline hydrolysis of **10** gave the *N*-hydroxy compound **11**, the integrity of which was evident from the reformation of **10** upon acetylation. Treatment of compound **11** with ethanolic iron(III) chloride gave a dark violet colour, as expected. The structures of the products **10** and **11** were fully supported by extensive spectroscopic analysis. In the first instance, compound **10** has the same molecular mass as the starting material **2**, and the attendant loss of 42 a.m.u. in the hydrolysis product **11** proves the loss of an acetyl group from compound **10**. The mass spectrum of **11** gives a very important structural clue, with an $[M - 16]^+$ ion, which is typical of hydroximic acids.[21] The IR spectrum of **10** exhibits three carbonyl absorption bands at 1800 cm^{-1} (acyl anhydride), 1739 cm^{-1} (17-CO) and 1721 cm^{-1} (lactam). The deacetylated product **11** differs, as expected, since the lactam IR absorption shifts to its typical place at 1682 cm^{-1}, the acyl band disappears, and a broad band appears at 3092 cm^{-1} for the hydroxy group. The ^1H NMR spectra of both compounds display distinctive signals for 15α-H as doublets of doublets at δ = 4.48 ppm and 4.36 ppm and for their 3′-methylene protons. It is notable that the latter signals in **10** appear as an AB multiplet at δ = 1.72 ppm and 1.83 ppm (J = 17.5 Hz) in C_6D_6 solution but coalesce into a two-proton singlet at δ = 2.24 ppm in



Scheme 3. i: LDA, then Ac_2O or aqueous HCl; ii: Ph_3P, $NaHCO_3$, EtOH, H_2O, reflux; iii: NaOAc, Ac_2O, Ph_3P; iv: NaOAc, Ac_2O, then aqueous HCl; v: $TiCl_4$, CH_2Cl_2, then aqueous HCl; vi: $SnCl_4$, CH_2Cl_2, then aqueous AcOH; vii: KOH, MeOH; viii: $NaHCO_3$, propargyl alcohol, EtOH, reflux; ix: Ac_2O, py; x: H_2, Pd/C, EtOH, THF; xi: H_2, Ra/Ni, EtOH, 30 atm; xii: Zn, AcOH, H_2O, reflux; xiii: AcCl, Et_3N, CH_2Cl_2.

$CDCl_3$. Comprehensive analysis of connectivity patterns with the aid of HSQC, HMBC and NOESY spectra for compounds **10** and **11** identified all the key nuclei and facilitated the configurational assignment of the protons, thereby fully supporting the respective structural assignments.

An early objective in this study was to explore the ketene equivalency of nitroethylene cycloaddition by examining the ability of cycloadduct **2** to efficiently undergo the Nef reaction. During this investigation, it was noted that simple treatment of **2** with $NaHCO_3$ in aqueous ethanol gave product mixtures that appeared to contain derivatives of a cyclic hydroxamic acid, one of which was identified as the *N*-hydroxy lactam **11**. The formation of cyclic hydroxamic derivatives (cyclic hydroxamic *O*-esters and cyclic hydroxamic acids) as a result of the abnormal Nef reaction of 5-nitrobicyclo[2.2.1]hept-2-enes has been described several times.[22–24] Similar products have also been observed following the photorearrangement of steroidal nitronates[25] or the treatment of 16-nitro-17-oxosteroids with hydrochloric acid or acetic anhydride.[26] The proposed mechanisms of the rearrangement include either the conventional Nef reaction, leading to cyclisation of the hydroxamic acid, or the more likely outcome,[5] entailing participation of a nitrile oxide intermediate. A third possibility may entail the formation of a cyclic nitronic ester or cyclic intermediate with participation of an acetoxy group and their subsequent decomposition to the nitrile oxide. Therefore, we undertook to study this reaction further in order to clarify its mechanistic aspects and to explore its scope in the potential synthesis of novel 14β-substituted steroids.

It is known[27] that nitrile oxides undergo typical *N*-oxide deoxygenation in the presence of triphenylphosphane (Ph_3P). Consequently, the efficient conversion of **2** into the nitrile **9** (94% yield), in the presence of $NaHCO_3$ and Ph_3P in aqueous ethanol at reflux strongly suggested the intermediacy of a nitrile oxide during fragmentation.

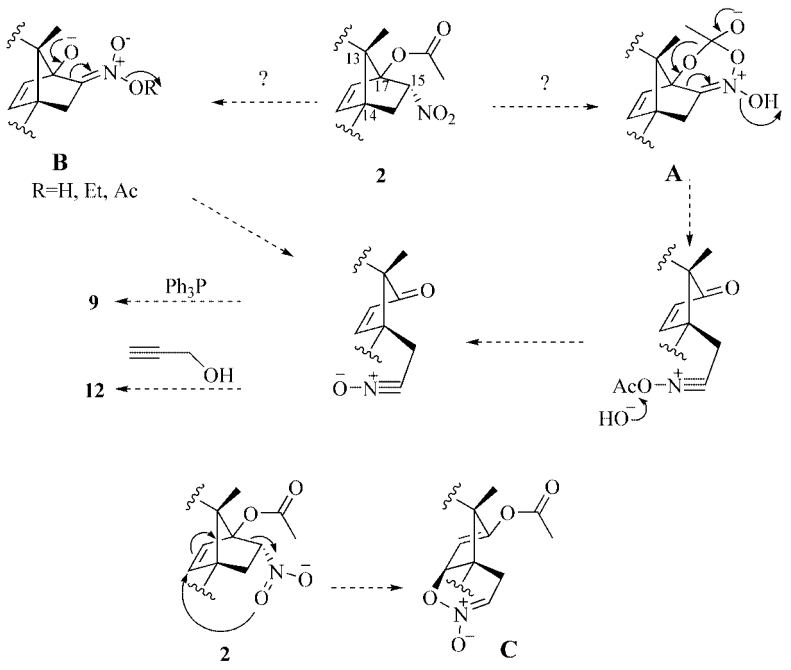
More direct evidence emerged when the reaction was conducted in the presence of a dipolarophile in an attempt to trap any nitrile oxide that might form during the course of fragmentation. Thus, treatment of the steroid **2** with $NaHCO_3$ in absolute ethanol in the presence of propargyl alcohol furnished the expected isoxazole **12** in 50% yield. The structure was confirmed by analytical and spectroscopic data of **12** and the derived acetate **13**. Compound **12** displayed an IR absorption at 3601 cm^{-1} (OH) and 1701 cm^{-1} (cyclopentenone CO) and distinctive AB multiplets at 3.07 ppm and 3.16 ppm (J = 15.44 Hz) and 6.28 ppm and 7.41 ppm (J = 6.01 Hz) in the ^1H NMR spectrum, together with a broad two-proton singlet at δ = 4.75 ppm (CH_2OH). In addition, a singlet at δ = 6.15 ppm for the isoxazole proton was diagnostic for the assigned regiochemistry of the cycloaddition process, since regio-reversed cycloaddition would be expected to have resulted in a significantly downfield signal (to ca. 8.4 ppm) for 5′-H of the alternative isoxazole ring.[28]

McKillop et al.[29] obtained isoxazoles from primary nitro compounds by use of acetic anhydride in the presence of sodium acetate and a dipolarophile and considered a mixed nitronic acid anhydride as the possible 1,3-dipole. However, when these conditions were applied to substrate **2**, no isoxazole was detected. The only product obtained upon acidic hydrolysis was compound **10**. It was isolated in 67% yield when the reaction was carried out in the absence of the dipolarophile. Meanwhile, a reaction conducted under the foregoing conditions, but with the addition of Ph_3P gave the nitrile **9**. It was shown recently that activated nitro compounds react with dipolarophiles in the presence of tertiary amines[30] as well as Ph_3P,[31] but the application of these conditions to our substrate did not provide the desired products.

As part of the investigation into mechanistic details of abnormal fragmentation pathways encountered in this study, the cycloadduct **2** was subjected to catalytic hydrogenation to furnish the 17^1,17^2-dihydro compound **14**. Raney nickel hydrogenation of **2** resulted in the saturation of the bridged olefinic bond and the concomitant reduction of the nitro group to give the amine **15**, which was isolated and characterised as the *N*-acetyl derivative **16**. For completeness, it was also demonstrated that the reduction of steroid **2** with zinc in acetic acid gave access to the 16α-amino compound **17**, albeit in modest yield (36%), and thereafter, the *N*-acetyl derivative **18**.

The treatment of dihydro compound **14** with $NaHCO_3$ and Ph_3P in aqueous ethanol at reflux resulted in clean and efficient conversion into the 14β-cyanomethyl 17-ketone **19** (96% yield), whereas the reaction of **14** with $NaHCO_3$ in absolute ethanol in the presence of propargyl alcohol gave rise to the isoxazole **20** (49% yield). These results closely parallel those for the dehydro parent **2**, but treatment of **14** with only $NaHCO_3$ resulted in the consumption of starting material, leading to a hitherto unidentified product, although spectroscopic data favour the formulation of a hydroxamic acid derivative. The dihydro compound **14** was inert to $SnCl_4$ or $TiCl_4$, thereby convincingly implicating the 17^1,17^2-olefinic bond in the analogous reactions carried out on **2**.

The initial part of this study used the starting premise that a weak base might offer more control during the attempted Nef reaction of cycloadduct **2**, but the foregoing results invited the exploration of alternative methodologies to explore the limits of the observed reactivity patterns and to contribute toward understanding the mechanistic pathways. It is particularly revealing that stronger bases change the course of the reaction. Thus, the action of methanolic KOH on **2** gave the 14β-nitroethyl Δ^{15} 17-ketone **21** (88% yield), arising from bridgehead saponification, followed by retro-Henry fragmentation. The structure of **21** was evident from diagnostic analytical and spectroscopic data. Upon treatment with $NaHCO_3$ and Ph_3P, the fragmentation product **21** decomposed slowly over 20 h to give a complex and intractable mixture. Unsurprisingly, there was no evidence of the presence of the 14β-cyanomethyl compound **9**. In another experiment, the treatment of steroid **2** with sodium hydride in refluxing THF also failed to yield any nitrile **9**, even in the presence of Ph_3P. However, when water was added to terminate the reaction, the fragmentation product



Scheme 4.

21 was obtained, accompanied by a trace of the nitrile **9**. Similarly, the treatment of **2** with Ph_3P and DBU in aqueous ethanol also resulted in the formation of **21** as the major product.

The foregoing results provide a basis for interpreting the $NaHCO_3$-induced reaction, as depicted in the Scheme 4. It is proposed that compound **2** first forms a cyclic anhydride (**A**), and it is reasonable to assume that it suffers rapid base-induced cleavage. The nitrile oxide is thereby revealed, the subsequent fate of which is determined by the reaction conditions. Thus, it is reduced to the nitrile in the presence of Ph_3P, trapped in the presence of a dipolarophile or undergoes hydrolysis to hydroxamic acid derivatives.[32] An alternative explanation (**B**), which excludes intramolecular participation by the acetoxy group, is less favourable because of the evidence that the nitro ketone **21**, formed under strongly basic conditions, is not an apparent precursor of the nitrile oxide. Nevertheless, this course of transformation cannot be excluded and could be invoked to account for the formation of the *N*-acetoxy lactam in the reaction of compound **2** with NaOAc and acetic anhydride.[26] The intermediacy of cyclic nitronate (**C**) should be excluded from consideration because transformations analogous to those under discussion also take place in the absence of the bridged olefinic bond.

The mechanism of the Lewis-acid-mediated rearrangement is less clear but may involve a polar species similar to **A**, with binding of a metal ligand to the double bond, nitrogen and oxygen atoms. In conclusion, it is worth emphasising that the cycloadduct **2** undergoes rearrangement only in the presence of a Lewis acid or an inorganic base. Attempts to perform a thermally induced rearrangement in refluxing benzene or toluene led only to the recovery of starting material. A more forcing thermal reaction, performed in xylene in a sealed tube at 200 °C, afforded only the dienyl acetate **1**, arising from a retro-Diels–Alder reaction. Similar results were observed in aqueous ethanol or ethanol-propargyl alcohol mixtures as media.

Experimental Section

Melting points were measured with a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter in $CHCl_3$. IR spectra were recorded in $CHCl_3$ with a Perkin–Elmer 983 IR spectrometer. Microanalyses were determined with a Fisons EA 1108 CHNS-O instrument. Mass spectra (EI) were recorded with a VG Micromass 16F spectrometer, and *m*/*z* and relative intensities (%) are indicated for significant peaks. Accurate masses (EI) were obtained with a VG-70E mass spectrometer. ^1H NMR spectra were recorded as $CDCl_3$ solutions with TMS as an internal standard with a Varian VXR-200 (200 MHz) or a Varian Unity (400 MHz) Spectrometer. Coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded with the same instruments at 50 MHz or 100 MHz, respectively.

TLC was performed with aluminum-backed silica gel 60 F_{254} plates and visualized by UV and/or exposure to $Ce(NH_4)_4(SO_4)_4$ in 8 M H_2SO_4. Column chromatography was conducted with Merck Kieselgel 60 [70–230 mesh (gravity) and 230–400 mesh (flash)]. Solvents were dried and freshly distilled according to common practice.[33] All reactions were conducted under positive nitrogen pressure.

3-Methoxy-16α-nitro-14,17-ethenoestra-1,3,5(10)-trien-17β-yl Acetate (2): A solution of dienyl acetate **1** (5.508 g, 17 mmol) and nitroethylene (1.86 g, 25.5 mmol) in dry benzene (25 mL) was refluxed for 2 h, and more nitroethylene (0.336 g, 4.6 mmol) was added. Refluxing was continued for a further 4 h, and the solution was cooled, diluted with dichloromethane and filtered through a Celite plug. The filtrate was evaporated, and the residue was crystallized

from benzene (30 mL) to give adduct **2** (4.64 g) and mother liquor residues (2.28 g). The latter was purified on a silica gel column and underwent crystallisation to afford additional adduct **2** (1.2 g), thus elevating the overall yield to 5.84 g (86%) of **2**. $[\alpha]_D^{20}$ = +169 (*c* = 1.0). M.p. 193–196 °C (from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 3 H, 18 Me), 1.19 (m, 1 H, 12β-H), 1.28 (m, 1 H, 11β-H), 1.42 (td, *J* = 2.6 Hz, *J* = 11.31 Hz, 1 H, 8β-H), 1.68 (m, 1 H, 7α-H), 1.83 (m, 1 H, 7β-H), 2.08 (dd, ^3J = 3.37 Hz, ^2J = 13.14 Hz, 1 H, 15α-H), 2.15 (s, 3 H, OAc), 2.20 (dd, ^3J = 8.41 Hz, ^2J = 13.14 Hz, 1 H, 15β-H), 2.51 (td, *J* = 3.37 Hz, *J* = 11.31 Hz, 1 H, 9α-H), 2.88 (m, 2 H, 6-H), 3.76 (s, 3 H, OMe), 5.38 (dd, *J* = 3.37 Hz, *J* = 8.41 Hz, 1 H, 16β-H), 6.21 (d, *J* = 6.11 Hz, 1 H, 17^1-H), 6.28 (d, *J* = 6.11 Hz, 1 H, 17^2-H), 6.62 (d, ^4J = 2.76 Hz, 1 H, 4-H), 6.70 (dd, ^4J = 2.76 Hz, ^3J = 8.71 Hz, 1 H, 2-H), 7.2 (d, ^3J = 8.71 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (C-18), 21.4 (*C*H$_3$CO), 23.8 (C-7), 26.6 (C-11), 29.1 (C-12), 30.0 (C-6), 34.4 (C-15), 38.8 (C-8), 40.0 (C-9), 55.2 (3-OMe), 55.5 (C-14), 62.2 (C-13), 87.4 (C-16), 95.9 (C-17), 111.9 (C-2), 113.8 (C-4), 126.9 (C-1), 129.6 (C-17^1), 134.4 (C-17^2), 131.6 (C-10), 137.6 (C-5), 157.6 (C-3), 169.7 (CH$_3$*C*O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1744 (OAc), 1547 and 1368 (NO_2) cm^{-1}. MS (EI): *m*/*z* (%) = 397 [M]$^+$ (40). $C_{23}H_{27}NO_5$ (397.46): calcd. C 69.5, H 6.85, N 3.5; found C 69.5, H 6.6, N 3.5.

3-Methoxy-5′,6′-dihydro-4′*H*-1′,2′-oxazino[5′,6′:14β,15β]estra-1,3,5(10),16-tetraen-17-yl Acetate (3): Nitro compound **2** (200 mg, 0.5 mmol) in THF (10 mL) was added to a stirred solution of $TiCl_3$ in aqueous acetic acid, prepared by the addition of $TiCl_3$ (727 mg, 4.7 mmol) to a deoxygenated solution of ammonium acetate (362 mg, 4.7 mmol) in acetic acid (9.2 mL, 70% in water), followed by zinc powder (82 mg, 1.26 mmol). This solution was used within 15 min of preparation. The resulting reaction mixture was stirred for 20 min at room temperature and diluted with $CHCl_3$. The organic phase was extracted with $CHCl_3$ (3×), washed with water and brine, dried ($MgSO_4$), and the solvents were evaporated. The solid residue (190 mg) was chromatographed on a column with silica gel with ethyl acetate/toluene (10:90) as the eluent to afford compound **1** (14 mg) and product **3** (136 mg, 71% yield). $[\alpha]_D^{20}$ = +91 (*c* = 0.8). M.p. 126–129 °C (from methanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, 18 Me), 1.62 (dd, *J* = 3.46 Hz, *J* = 19.47 Hz, 1 H, 4′-H), 2.18 (s, 3 H, OAc), 2.31 (m, 1 H, 11α-H), 2.44 (dd, *J* = 2.46 Hz, *J* = 19.47 Hz, 1 H, 4′-H), 2.78 obsc (m, 1 H, 9α-H), 2.82 (m, 2 H, 6-H), 3.77 (s, 3 H, OMe), 5.29 (br. s, 1 H, 15-H), 5.67 (d, *J* = 1.45 Hz, 1 H, 16-H), 6.62 (d, ^4J = 2.76 Hz, 1 H, 4-H), 6.73 (dd, ^4J = 2.76 Hz, ^3J = 8.74 Hz, 1 H, 2-H), 7.23 (d, ^3J = 8.74 Hz, 1 H, 1-H), 7.45 (m, 1 H, 3′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.7 (C-18), 21.1 (*C*H$_3$CO), 24.4 (C-7), 26.1 (C-11), 28.0 (C-4′), 31.0 (C-6), 36.0 (C-12), 38.1 (C-9), 44.9 (C-8), 45.3 and 49.2 (C-13 and C-14), 55.2 (3-OMe), 78.7 (C-15), 112.1 (C-2), 113.3 (C-4 and C-16), 127.3 (C-1), 131.3 (C-10), 137.6 (C-5), 150.3 (C-3′), 157.6 (C-3), 158.1 (C-17) 168.1 (CH$_3$*C*O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1764 (OAc) cm^{-1}. MS (EI): *m*/*z* (%) = 381 [M]$^+$ (20), 3 2 3 [M – 58]$^+$ (100). $C_{23}H_{27}NO_4$ (381.2): calcd. C 72.42, H 7.13, N 3.65; found C 73.2, H 7.05, N 3.4. HR-MS: *m*/*z* = 381.1939 [M]$^+$, calcd. for $C_{23}H_{27}NO_4$: 381.1939.

Cleavage of the Oxazine 4 by Raney Nickel: Methanolic KOH (2 M, 0.3 mL) was added to the oxazine **3** (207 mg, 0.54 mmol) in methanol (15 mL) at ambient temperature. The solution was stirred for 10 min, and dry ice was added. The solvent was evaporated without heating, water was added, and the organic material was extracted with ethyl acetate (3 × 15 mL). The organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated to give **3-methoxy-5′,6′-dihydro-4*H*-1′,2′-oxazino[5′,6′:14β,15β]estra-1,3,5(10)-trien-17-one** (**4**, 182 mg, 99% yield). $[\alpha]_D^{20}$ = +37.7 (*c* = 1.0). M.p. 164–165 °C (from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, 18 Me), 1.90 (d, *J* = 2.9 Hz, 2 H, 4′-H), 2.30 (dd, *J* = 9.02 Hz, *J* = 19.72 Hz, 1 H, 16α-H), 2.40 (m, 1 H, 11α-H), 2.82 (m, 3 H, 9α-H and 6-H), 2.86 obsc (dd, *J* = 8.72 Hz, *J* = 19.72 Hz, 1 H, 16β-H), 3.76 (s, 3 H, OMe), 5.24 (br. t, *J* = 8.72 Hz, 1 H, 15α-H), 6.61 (d, ^4J = 2.75 Hz, 1 H, 4-H), 6.73 (dd, ^4J = 2.75 Hz, ^3J = 8.72 Hz, 1 H, 2-H), 7.2 (d, ^3J = 8.72 Hz, 1 H, 1-H), 7.48 (m, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1 (C-18), 23.3 (C-7), 26.3 (C-11), 27.2 (C-4′), 29.6 (C-12), 30.9 (C-6), 37.0 (C-9), 38.4 (C-16), 43.8 (C-8), 40.1 and 55.8 (C-13 and C-14), 55.2 (3-OMe), 71.6 (C-15), 112.2 (C-2), 113.6 (C-4), 127.0 (C-1), 130.9 (C-10), 137.5 (C-5), 148.3 (C-3′), 157.7 (C-3), 215.9 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1737 (CO) cm^{-1}. MS (EI): *m*/*z* (%) = 339 [M]$^+$ (20). $C_{21}H_{25}NO_3$ (339): calcd. C 74.31, H 7.42, N 4.13; found C 74.26, H 7.43, N 4.14. Crude oxazine **4** (140 mg, 0.36 mmol) was dissolved in acetic acid (4 mL). Raney nickel was added, and the resulting mixture was stirred under hydrogen (1 atm) for 6 h, at which time acetic anhydride (0.2 mL) and some crystals of DMAP were added under nitrogen. After 24 h, the solvent was evaporated under high vacuum, the residue was diluted with $CHCl_3$ (20 mL), and the catalyst was filtered off. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The residual oil was separated on silica gel column with ethyl acetate as the eluent affording **2′ξ-(acetylamino)-3-methoxy-tetrahydrofurano[4′,5′:14β,15β]estra-1,3,5(10)-trien-17-one** (**5**, 84 mg, 61% yield). $[\alpha]_D^{20}$ = +71.4 (*c* = 0.8). M.p. 229–230 °C (from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 18 Me), 1.96 (s, 3 H, NAc), 2.32 obsc (dd, ^3J = 3.98 Hz, ^2J = 20.33 Hz, 1 H, 16α-H), 2.64 (m, 1 H, 9α-H), 2.89 (m, 2 H, 6-H), 3.17 (dd, ^3J = 9.33 Hz, ^2J = 20.33 Hz, 1 H, 16β-H), 3.77 (s, 3 H, OMe), 4.82 (dd, *J* = 3.98 Hz, *J* = 9.33 Hz, 1 H, 15α-H), 5.96 (dd, *J* = 7.33 Hz, *J* = 15.59 Hz, 1 H, 2′-H), 6.38 (br. d, *J* = 8.41 Hz, 1 H, NH), 6.63 (d, ^4J = 2.76 Hz, 1 H, 4-H), 6.73 (dd, ^4J = 2.76 Hz, ^3J = 8.56 Hz, 1 H, 2-H), 7.19 (d, ^3J = 8.56 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (C-18), 23.4 (*C*H$_3$CO), 24.1 (C-7), 26.4 (C-11), 30.6 (C-6), 33.8 (C-12), 39.0 (C-9), 42.4 (C-8), 43.4 and 43.8 (C-16 and C-3′), 55.2 (3-OMe), 55.4 and 59.2 (C-13 and C-14), 76.4 (C-15), 82.3 (C-2′), 112.3 (C-2), 113.4 (C-4), 126.9 (C-1), 130.7 (C-10), 137.4 (C-5), 157.8 (C-3), 170.4 (CH$_3$*C*O), 218.7 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3431 (NH), 1729 (CO), 1683 (amide) cm^{-1}. MS (EI): *m*/*z* (%) = 383 [M]$^+$ (40), 324 [M – 59]$^+$ (40). $C_{23}H_{29}NO_4$ (383): calcd. C 72.04, H 7.62, N 3.65; found C 71.77, H 7.83, N 3.73. Subsequent elution with ethyl acetate/ethanol (95:5) gave **14β-(2-acetylaminoethyl)-15β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one** (**6**, 43 mg, 31% yield). $[\alpha]_D^{20}$ = +100.3 (*c* = 0.7). M.p. 186–187 °C (from acetone). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (s, 3 H, 18 Me), 1.97 (s, 3 H, NAc), 2.29 obsc (dd, *J* = 7.74 Hz, *J* = 20.01 Hz, 1 H, 16α-H), 2.74 (m, 1 H, 9α-H), 2.88 (m, 2 H, 6-H), 3.17 obsc (dd, *J* = 9.6 Hz, *J* = 20.01 Hz, 1 H, 16β-H), 3.18 (m, 2 H, 1′-H), 3.78 (s, 3 H, OMe), 4.92 (br. t, *J* = 8.86 Hz, 1 H, 15α-H), 5.92 (m, 1 H, NH), 6.63 (d, *J* = 2.67 Hz, 1 H, 4-H), 6.73 (dd, *J* = 2.67 Hz, *J* = 8.8 Hz, 1 H, 2-H), 7.21 (d, *J* = 8.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7 (C-18), 23.0 (*C*H$_3$CO), 25.0 (t), 25.9 (t), 31.0 (t), 31.3 (t), 33.0 (t), 36.2 (t), 38.3 (t), 42.6 and 43.6 (C-8 and C-9), 50.0 and 54.8 (C-13 and C-14), 55.2 (3-OMe), 111.9 (C-2), 113.5 (C-4), 126.7 (C-1), 131.8 (C-10), 137.6 (C-5), 157.7 (C-3), 170.5 (CH$_3$*C*O), 218.0 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3616 (OH), 3450, (NH), 1729(CO), 1660 (amide) cm^{-1}. MS (EI): *m*/*z* (%) = 385 [M]$^+$ (5), 367 [M – 18]$^+$ (40). $C_{23}H_{31}NO_4$ (385): calcd. C 71.66, H 8.11, N 3.63; found C 71.59, H 8.17, N 3.54.

***N*-Acetyl-3-methoxy-5′,6′-dihydro-2*H*-1′,2′-oxazino[5′,6′:14β,15β]-estra-1,3,5(10),16-tetraen-17-yl Acetate (7) and *N*-Acetyl-3-meth-**

oxy-5′,6′-dihydro-2*H*-1′,2′-oxazino[5′,6′:14β,15β]estra-1,3,5(10)-trien-17-one (8): Oxazine **3** (94 mg, 0.25 mmol) was dissolved in acetic anhydride (4 mL) and refluxed under nitrogen for 20 min and then cooled. The solvent was evaporated under reduced pressure, and the crystalline residue was purified by flash chromatography on a short silica gel column with ethyl acetate/toluene (5:95) as the eluent to give acetate **7** (96 mg, 91% yield). $[\alpha]_D^{20}$ = +302.7 (*c* = 1.1). M.p. 172–174 °C (from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 18 Me), 1.28 (qd, *J* = 2.95 Hz, *J* = 11.6 Hz, 1 H, 11-H), 1.58 obsc (m, 1 H, 12α-H), 1.97 (dt, *J* = 3.76 Hz, *J* = 13.65 Hz, 1 H, 12β-H), 2.11 (m, 1 H, 7β-H), 2.16 and 2.17 each (s, 3 H, OAc and NAc), 2.27 (m, 1 H, 11α-H), 2.58 (m, 1 H, 9α-H), 2.84 (m, 2 H, 6-H), 3.77 (s, 3 H, OMe), 4.82 (dd, *J* = 1.14 Hz, *J* = 8.65 Hz, 1 H, 4′-H), 5.36 (br. s, 1 H, 15-H), 5.65 (d, *J* = 1.59 Hz, 1 H, 16-H), 6.62 (d, *J* = 2.73 Hz, 1 H, 4-H), 6.72 (dd, *J* = 2.73 Hz, *J* = 8.64 Hz, 1 H, 2-H), 7.23 (d, *J* = 8.64 Hz, 1 H, 1-H), 7.35 (d, *J* = 8.65 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (C-18), 20.3 (*C*H$_3$CON), 21.3 (*C*H$_3$CO$_2$), 26.1 (C-7), 26.5 (C-11), 31.0 (C-6), 38.3 (C-9), 39.3 (C-12), 42.7 (C-8), 48.1 and 49.0 (C-13 and C-14), 55.2 (3-OMe), 86.2 (C-15), 106.2 (C-16), 112.1 (C-2), 112.8 (C-4′), 113.6 (C-4), 123.8 (C-3′), 127.4 (C-1), 131.4 (C-10), 137.9 (C-5), 157.7 (C-3), 160.5 (C-17), 166.6 (CH$_3$*C*ON), 167.8 (CH$_3$*C*O$_2$) ppm. IR ($CHCl_3$): ṽ = 1765 (CO, acetate), 1646 (CO, amide) cm^{-1}. MS (EI): *m*/*z* (%) = 423 [M]$^+$ (20), 381 [M – 42]$^+$ (40). $C_{25}H_{29}NO_5$ (423): calcd. C 70.90, H 6.90, N 3.31; found C 70.90, H 6.91, N 3.34. During the recrystallisation of acetate **7** (58 mg) from aqueous methanol, the presence of hydrolysis product was noted in the mother liquor residue, the further recrystallisation of which yielded ketone **8** (44 mg, 85% yield). $[\alpha]_D^{20}$ = +305.84 (*c* = 0.5). M.p. 212–214 °C (from aqueous methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 18 Me), 1.39 (qd, *J* = 4.08 Hz, *J* = 12.76 Hz, 1 H, 11β-H), 2.05 (m, 1 H, 7β-H), 2.13 (s, 3 H, NAc), 2.32 (dd, ^3J = 6.89 Hz, ^2J = 19.64 Hz, 1 H, 16α-H), 2.41 (m, 1 H, 11α-H), 2.73 (m, 1 H, 9α-H), 2.85 (dd, ^3J = 9.18 Hz, ^2J = 19.64 Hz, 1 H, 16β-H), 2.86 obsc (m, 2 H, 6-H), 3.77 (s, 3 H, OMe), 4.81 (dd, *J* = 1.79 Hz, *J* = 8.93 Hz, 1 H, 4′-H), 5.27 (m, 1 H, 15α-H), 6.62 (d, ^4J = 2.81 Hz, 1 H, 4-H), 6.73 (dd, ^4J = 2.81 Hz, ^3J = 8.67 Hz, 1 H, 2-H), 7.22 (d, ^3J = 8.67 Hz, 1 H, 1-H), 7.41 (d, *J* = 8.93 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (C-18), 20.4 (*C*H$_3$CO), 25.4 (C-7), 26.1 (C-11), 30.9 (C-6), 32.7 (C-12), 35.0 (C-16), 37.6 (C-9), 41.2 (C-8), 46.8 and 53.6 (C-13 and C-14), 55.2 (3-OMe), 77.7 (C-15), 107.6 (C-4′), 112.1 (C-2), 113.7 (C-4), 122.7 (C-3′), 126.9 (C-1), 131.0 (C-10), 137.8 (C-5), 157.8 (C-3), 166.8 (CH$_3$*C*O), 214.5 (C-17) ppm. IR ($CHCl_3$): ṽ = 1738 (CO), 1668 (CO, amide), 1640 (C=C) cm^{-1}. MS (EI): *m*/*z* (%) = 381 [M]$^+$ (70), 339 [M – 42]$^+$ (100). $C_{23}H_{27}NO_4$ (381): calcd. C 72.42, H 7.13, N 3.67; found C 72.33, H 7.17, N 3.71.

1′-Acetoxy-3-methoxy-2′-oxopyrrolidino[4′,5′:14β,15β]estra-1,3,5(10)-trien-17-one (10): (a) $SnCl_4$ (1 M in dichloromethane, 0.3 mmol) was added to a solution of nitro compound **2** (119 mg, 0.3 mmol) in dichloromethane (5 mL) at 0 °C. The colourless mixture was stirred at this temperature until TLC showed the absence of starting material (≈ 1 h). The reaction was quenched by adding deoxygenated 50% acetic acid (2 mL), and the mixture was stirred for 30 min until hydrolysis of the primary product was complete. The resulting mixture was diluted with dichloromethane and water, and the aqueous phase was separated and extracted with dichloromethane. The combined organic phase was washed successively with water, aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Concentration of the mixture and column chromatography of the residue (139 mg) on silica gel with ethyl acetate/toluene (20:80) as the eluent gave product **10** (99 mg, 83% yield). $[\alpha]_D^{20}$ = +64.6 (*c* = 0.65). M.p. 110–111 °C (from benzene) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 18 Me), 2.23 (s, 3 H, OAc), 2.25 (s, 2 H, 3′-H), 2.44 (dd, ^3J = 3.98 Hz, ^2J = 19.8 Hz, 1 H, 16β-H), 2.74 (m, 1 H, 9α-H), 2.86 (td, *J* = 3.7 Hz, *J* = 17.0 Hz, 1 H, 6β-H), 2.96 (m, 1 H, 6α-H), 3.03 (dd, ^3J = 8.9 Hz, ^2J = 19.8 Hz, 1 H, 16α-H), 3.79 (s, 3 H, OMe), 4.49 (dd, *J* = 3.9 Hz, *J* = 8.9 Hz, 1 H, 15α-H), 6.64 (d, ^4J = 2.7 Hz, 1 H, 4-H), 6.75 (dd, ^4J = 2.7 Hz, ^3J = 8.7 Hz, 1 H, 2-H), 7.21 (d, ^3J = 8.7 Hz, 1 H, 1-H) ppm. ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 0.77 (s, 3 H, 18 Me), 1.57 (s, 3 H, OAc), 1.72 (d, ^2J = 17.5 Hz, 1 H, 3′-H), 1.83 obsc (d, ^2J = 17.5 Hz, 1 H, 3′-H), 2.19 (dd, ^3J = 4.1 Hz, ^2J = 19.6 Hz, 1 H, 16β-H), 2.42 (dd, ^3J = 8.7 Hz, ^2J = 19.6 Hz, 1 H, 16α-H), 2.52 (m, 1 H, 6-H), 2.67 (m, 1 H, 6-H), 3.40 (s, 3 H, OMe), 3.82 (dd, *J* = 4.1 Hz, *J* = 8.7 Hz, 1 H, 15α-H), 6.6 (d, ^4J = 2.7 Hz, 1 H, 4-H), 6.86 (dd, ^4J = 2.7 Hz, ^3J = 8.8 Hz, 1 H, 2-H), 7.02 (d, ^3J = 8.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (C-18), 18.1 (*C*H$_3$CO), 23.6 (C-7), 26.4 (C-11), 30.8 (C-6), 33.0 (C-12), 37.4 (C-3′), 38.2 (C-9), 38.8 (C-16), 43.4 (C-8), 48.7 (C-14), 53.6 (C-13), 55.2 (3-OMe), 56.4 (C-15), 112.3 (C-2), 113.4 (C-4), 126.9 (C-1), 130.3 (C-10), 137.4 (C-5), 157.8 (C-3), 167.2 (CH$_3$*C*O) 168.5 (C-2′), 215.4 (C-17) ppm. IR ($CHCl_3$): ṽ = 1800 (Ac), 1739 (CO), 1721 (NC=O) cm^{-1}. MS (EI): *m*/*z* (%) = 397 [M]$^+$ (80), 355 [M – 42]$^+$ (70), 338 [M – 59]$^+$ (20). $C_{23}H_{27}NO_5$ (397): calcd. C 69.50, H 6.85, N 3.52; found C 68.84, H 7.02, N 2.93. HR-MS: *m*/*z* = 397.1869 [M]$^+$, calcd. for $C_{23}H_{27}NO_5$: 397.1889.

(b) $TiCl_4$ (1 M in dichloromethane, 0.4 mmol) was added to a solution of nitro compound **2** (159 mg, 0.4 mmol) in dichloromethane (10 mL) at –70 °C. The orange mixture was warmed to 0 °C and stirred at this temperature until TLC showed the absence of starting material (≈ 1 h). The reaction was quenched by the addition of HCl (1.3 M, 2 mL), warmed to room temperature and stirred for 16 h until hydrolysis of the primary product was complete. The resulting mixture was diluted with dichloromethane, and the aqueous phase was separated and extracted with dichloromethane. The combined organic phase was washed with water and brine and dried ($MgSO_4$). Concentration of the mixture and column chromatography of the residue (195 mg) on silica gel with ethyl acetate/toluene (20:80) as the eluent gave product **10** (103 mg, 65% yield).

(c) A solution of nitro compound **2** (240 mg, 0.6 mmol) in acetic anhydride (9 mL) was deoxygenated by bubbling nitrogen through the solution for 20 min, and then fused sodium acetate (118 mg, 1.2 mmol) was added. The resulting solution was refluxed for 40 min and cooled. HCl (1 M, 2 mL) was added, and stirring was continued. After 15 min, the reaction mixture was diluted with ethyl acetate (40 mL) and water (40 mL), and solid sodium carbonate (9.68 g, 92 mmol) was added portionwise. After acetic anhydride had been destroyed, the organic phase was separated, washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified on a silica gel column with ethyl acetate/toluene (15:85) as the eluent to give product **10** (160 mg, 67% yield) as a foam.

1′-Hydroxy-3-methoxy-2′-oxopyrrolidino[4′,5′:14β,15β]estra-1,3,5(10)-trien-17-one (11): Compound **10** (305 mg, 0.77 mmol) was dissolved in aqueous methanol (10:1, 11 mL), and methanolic KOH (2 M, 0.96 mL) was added. The solution was stirred at ambient temperature for 30 min, and then solid NH_4Cl was added, followed by water (15 mL) and $CHCl_3$ (15 mL). The aqueous phase was separated and extracted with $CHCl_3$ (×2). The combined organic phase was washed with water and brine and dried ($MgSO_4$). Concentration of the mixture and column chromatography of the residue (308 mg) on silica gel with ethyl acetate as the eluent gave product **11** (237 mg, 87% yield). $[\alpha]_D^{20}$ = +25.9 (*c* = 0.69). M.p. 240–

242 °C (from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 18 Me), 1.41 (qd, J = 3.8 Hz, J = 12.4 Hz, 1 H, 11β-H), 1.79 (m, 1 H, 7β-H), 2.14 (d, ^2J = 17.4 Hz, 1 H, 3′-H), 2.25 (d, ^2J = 17.4 Hz, 1 H, 3′-H), 2.38 (m, 1 H, 11α-H), 2.46 (dd, ^3J = 3.4 Hz, ^2J = 19.9 Hz, 1 H, 16β-H), 2.67 (m, 1 H, 9α-H), 2.86 (m, 2 H, 6-H), 3.09 (dd, ^3J = 9.1 Hz, ^2J = 19.9 Hz, 1 H, 16α-H), 3.77 (s, 3 H, OMe), 4.36 (dd, J = 3.4 Hz, J = 9.1 Hz, 1 H, 15α-H), 6.61 (d, ^4J = 2.6 Hz, 1 H, 4-H), 6.73 (dd, ^4J = 2.6 Hz, ^3J = 8.7 Hz, 1 H, 2-H), 7.2 (d, ^3J = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-18), 23.2 (C-7), 26.4 (C-11), 30.8 (C-6), 33.4 (C-12), 38.1 (C-9), 38.6 (C-3′), 39.2 (C-16), 43.7 (C-8), 48.1 (C-14), 53.4 (C-13), 55.2 (3-OMe), 58.0 (C-15), 112.4 (C-2), 113.5 (C-4), 127.1 (C-1), 130.3 (C-10), 137.0 (C-5), 157.8 (C-3), 168.6 (C-2′), 216.0 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3092 br (NOH), 1738 (CO), 1682 (C=N) cm^{-1}. MS (EI): m/z (%) = 355 (100) $[M]^+$, 339 $[M - 16]^+$ (40). $C_{21}H_{25}NO_4$ (355): calcd. C 70.96, H 7.09, N 3.94; found C 70.88, H 7.10, N 3.99.

14β-(Cyanomethyl)-3-methoxyestra-1,3,5(10),15-tetraen-17-one (9): (a) A mixture of nitro compound **2** (119 mg, 0.3 mmol), $NaHCO_3$ (176 mg, 2.1 mmol) and triphenylphosphane (157 mg, 0.6 mmol) in aqueous ethanol (22 mL, 10:1) was deoxygenated by bubbling nitrogen through the mixture for 20 min and then refluxed for 2 h. The colourless solution was cooled, diluted with dichloromethane (20 mL) and filtered. The precipitate was washed with dichloromethane and the combined filtrate was evaporated, diluted again with dichloromethane, washed with water and brine and dried ($MgSO_4$). The concentrated solid residue (273 mg) was chromatographed on silica gel. Elution with toluene afforded unreacted triphenylphosphane. Elution with ethyl acetate/toluene (10:90) gave product **9** (91 mg, 94% yield). $[\alpha]_D^{20}$ = +241.59 (c = 1.00). M.p. 142–144 °C (from aqueous methanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (s, 3 H, 18 Me), 2.56 (d, ^2J = 17.2 Hz, 1 H, CHCN), 2.86 obsc (m, 2 H, 6-H), 2.87 (d, ^2J = 17.2 Hz, 1 H, CHCN), 3.76 (s, 3 H, OMe), 6.36 (d, ^3J = 5.9 Hz, 1 H, 16-H), 6.58 (d, ^4J = 2.7 Hz, 1 H, 4-H), 6.71 (dd, ^4J = 2.7 Hz, ^3J = 8.7 Hz, 1 H, 2-H), 7.05 (d, ^3J = 8.7 Hz, 1 H, 1-H), 7.25 (d, ^3J = 5.9 Hz, 1 H, 15-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (C-18), 22.5 (C-2′), 24.6 (C-7), 27.4 (C-11), 28.9 (C-12), 30.5 (C-6), 33.8 (C-9), 42.4 (C-8), 51.7 and 52.6 (C-13 and C-14), 55.2 (3-OMe), 112.6 (C-2), 113.0 (C-4), 117.1 (C-1′), 128.1 (C-1), 132.0 (C-10), 133.5 (C-16), 136.5 (C-5), 157.5 (C-3), 160.6 (C-15), 211.4 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2251 (CN), 1709 (CO) cm^{-1}. MS (EI): m/z (%) = 321 $[M]^+$ (80). $C_{21}H_{23}NO_2$ (321): calcd. C 78.47, H 7.21, N 4.36; found C 78.29, H 7.26, N 4.10.

(b) A solution of LDA [from 2.5 M BuLi (0.23 mL) and diisopropylamine (0.11 mL) in THF (1 mL)] was added to oxazine **3** (99 mg, 0.26 mmol) in THF (4 mL) at –80 °C by cannula, and the resulting solution was stirred for 0.5 h and then warmed to –20 °C and kept at this temperature for 3 h. The solution was cooled again to –80 °C, acetic acid (0.1 mL) was added, and the solution was warmed to ambient temperature. After 30 min, ethyl acetate (20 mL) and water (20 mL) were added. The aqueous phase was separated and extracted with ethyl acetate. The organic phases were combined, washed with saturated $NaHCO_3$, water and brine and dried ($MgSO_4$). Concentration of the mixture and column chromatography of the residue on silica gel with ethyl acetate/toluene (10:90) as the eluent gave a product (38 mg, 45% yield), followed by oxazine **4** (21 mg, 24% yield).

(c) A solution of nitro compound **2** (16 mg, 0.04 mmol), fused sodium acetate (7 mg, 0.08 mmol) and triphenylphosphane (21 mg, 0.08 mmol) was refluxed for 50 min in acetic anhydride (1 mL) and then cooled. The reaction mixture was diluted with ethyl acetate (2 mL) and water (2 mL), and solid potassium carbonate (2 g) was added. After acetic anhydride had been destroyed, the organic phase was separated, washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified on a silica gel column with ethyl acetate/toluene (15:85) as the eluent to give product **9** (10 mg, 75% yield).

14β-[5-(Hydroxymethyl)isoxazol-3-ylmethyl]-3-methoxyestra-1,3,5(10),15-tetraen-17-one (12): $NaHCO_3$ (210 mg, 2.5 mmol) and propargyl alcohol (0.3 mL, 5 mmol) were added to a suspension of nitro compound **2** (199 mg, 0.5 mmol) in absolute ethanol (20 mL). The mixture was refluxed for 6 h, cooled and diluted with dichloromethane (40 mL). The precipitate was filtered off, washed with dichloromethane and the filtrates were concentrated. The residue was again dissolved in dichloromethane (20 mL), and the solution was washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting oil (247 mg) was chromatographed on silica gel with ethyl acetate/toluene (40:60) as the eluent to give product **12** (100 mg, 50% yield) as a foam. $[\alpha]_D^{20}$ = +130.5 (c = 1.2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (s, 3 H, 18 Me), 2.76 (m, 2 H, 6-H), 3.07 and 3.16 each (d, J = 15.44 Hz, 1 H, 14β-CH_2), 3.74 (s, 3 H, OMe), 4.75 (br. s, 2 H, CH_2OH), 6.15 (s, 1 H, 4′-H), 6.28 (d, J = 6.01 Hz, 1 H, 16-H), 6.54 (d, J = 2.66 Hz, 1 H, 4-H), 6.68 (dd, J = 2.66 Hz, J = 8.54 Hz, 1 H, 2-H), 7.02 (d, J = 8.54 Hz, 1 H, 1-H), 7.41 (d, J = 6.01 Hz, 1 H, 15-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9 (C-18), 24.9 (C-7), 27.6 (C-11), 28.4, 29.8, 30.9 (C-6), 33.2 (C-9), 42.8 (C-8), 52.4 and 54.6 (C-13 and C-14), 55.2 (3-OMe), 56.6 (CH_2OH), 103.3 (C-4′), 112.4 (C-2), 112.9 (C-4), 128.3 (C-1), 132.0 (C-16), 133.0 (C-10), 136.8 (C-5), 157.2 (C-3), 160.6 (C-3′), 164.5 (C-15), 171.4 (C-5′), 213.5 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3601 (OH), 1701 (CO) cm^{-1}. MS (EI): m/z (%) = 393 $[M]^+$ (40), 363 $[M - 30]^+$ (10), 281 $[M - 112]^+$ (50). $C_{24}H_{27}NO_4$ (393): calcd. C 73.26, H 6.92, N 3.56; found C 73,19, H 6.98, N 3.45. HR-MS: m/z = 393.1927 $[M]^+$, calcd. for $C_{24}H_{27}NO_4$: 393.1940.

14β-[5-(Acetoxymethyl)isoxazol-3-ylmethyl]-3-methoxyestra-1,3,5(10),15-tetraen-17-one (13): Compound **12** (168 mg, 0.43 mmol) was dissolved in pyridine (1 mL), and acetic anhydride (51 mg, 0.5 mmol) was added. After 5 h, the solution was poured into ice water and extracted with dichloromethane. The organic phase was washed with saturated $NaHCO_3$, 1 M HCl, water and brine, dried ($MgSO_4$) and concentrated. The resulting oil (227 mg) was purified on a short silica gel column with ethyl acetate/toluene (20:80) as the eluent to give product **13** (174 mg, 93% yield) as an oil. $[\alpha]_D^{20}$ = +110.9 (c = 1.2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (s, 3 H, 18 Me), 2.12 (s, 3 H, OAc), 2.76 (m, 2 H, 6-H), 3.07 and 3.17 each (d, J = 15.47 Hz, 1 H, 14β-CH_2), 3.74 (s, 3 H, OMe), 5.15 (s, 2 H, CH_2OAc), 6.20 (s, 1 H, 4′-H), 6.29 (d, J = 5.95 Hz, 1 H, 16-H), 6.54 (d, J = 2.67 Hz, 1 H, 4-H), 6.68 (dd, J = 2.67 Hz, J = 8.80 Hz, 1 H, 2-H), 7.02 (d, J = 8.80 Hz, 1 H, 1-H), 7.40 (d, J = 5.95 Hz, 1 H, 15-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6 (C-18), 23.1 (CH_3CO), 24.9 (C-7), 27.6 (C-11), 28.1 (t), 29.7 (t), 30.6 (C-6), 33.1 (C-9), 42.1 (C-8), 52.3 and 54.5 (C-13 and C-14), 55.2 (3-OMe), 56.3 (CH_2OH), 105.4 (C-4′), 112.4 (C-2), 112.9 (C-4), 128.3 (C-1), 132.1 (C-16), 133.0 (C-10), 136.8 (C-5), 157.3 (C-3), 160.7 (C-3′), 164.2 (C-15), 166.6 (CH$_3$CO), 170.1 (C-5′), 213.2 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1744 (CO, ester), 1703 (CO) cm^{-1}. MS (EI): m/z (%) = 435 $[M]^+$ (40), 362 $[M - 73]^+$ (10), 280 $[M - 155]^+$ (50). $C_{26}H_{29}NO_5$ (435): calcd. C 71.70, H 6.71, N 3.22; found C 71,22, H 6.75, N 3.10. HR-MS: m/z = 435.2039 $[M]^+$, calcd. for $C_{26}H_{29}NO_5$: 435.2045.

3-Methoxy-16α-nitro-14,17-ethanoestra-1,3,5(10)-trien-17β-yl Acetate (14): Nitro steroid **2** (300 mg, 0.76 mmol) was dissolved in a

mixture of ethanol (120 mL) and THF (30 mL). Palladium on charcoal (10%, 70 mg) was added, and the solution was stirred under 1 atm of hydrogen for 24 h. The catalyst was filtered off, washed with dichloromethane, and the combined filtrates were evaporated to give a product (305 mg). Recrystallisation from ethanol gave nitro steroid **14** (252 mg, 83% yield). $[\alpha]_D^{20}$ = +55.8 (*c* = 0.96). M.p. 169–170 °C (from ethanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, 18 Me), 2.09 (s, 3 H, OAc), 2.68 (m, 1 H, 9α-H), 2.86 (m, 2 H, 6-H), 3.78 (s, 3 H, OMe), 5.30 (ddd, *J* = 1.84 Hz, *J* = 3.9 Hz, *J* = 10.6 Hz, 1 H, 16β-H), 6.62 (d, *J* = 2.69 Hz, 1 H, 4-H), 6.73 (dd, *J* = 2.69 Hz, *J* = 8.54 Hz, 1 H, 2-H), 7.2 (d, *J* = 8.54 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2 (C-18), 21.5 (CH_3CO), 23.0 (t), 23.8 (C-7), 25.8 (t), 26.3 (t), 28.2 (t), 29.8 (t), 37.0 (C-8), 38.3 (t), 39.8 (C-9), 45.6 and 51.6 (C-13 and C-14), 55.2 (3-OMe), 89.1 (C-16), 92.0 (C-17), 111.7 (C-2), 113.8 (C-4), 126.4 (C-1), 132.2 (C-10), 137.5 (C-5), 157.3 (C-3), 169.9 (CH_3CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1744 (OAc), 1552 and 1367 (NO_2) cm^{-1}. MS (EI): *m*/*z* (%) = 399 (100) $[M]^+$, 311 $[M - 88]^+$ (20). $C_{23}H_{29}NO_5$ (399): calcd. C 69.15, H 7.32, N 3.51; found C 69.39, H 7.46, N 3.61.

16α-Amino-3-methoxy-14,17-ethanoestra-1,3,5(10)-trien-17β-yl Acetate (15) and 16α-Acetylamino-3-methoxy-14,17-ethanoestra-1,3,5(10)-trien-17β-yl Acetate (16): An excess of ethanol-washed Raney nickel and a solution of nitro compound **2** (119 mg, 0.3 mmol) in ethanol (70 mL) were placed into a high-pressure vessel and stirred under 20 bar of hydrogen at 30 °C. After 4 h, the catalyst was filtered off and washed with ethanol (150 mL) and $CHCl_3$ (150 mL). The filtrates were combined and concentrated to give amine **15** as a colourless oil. [^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, 18 Me), 2.05 (s, 3 H, OAc), 2.68 (m, 1 H, 9α-H), 2.86 (m, 2 H, 6-H), 3.58 (m, 1 H, 16β-H), 3.77 (s, 3 H, OMe), 6.62 (d, *J* = 2.82 Hz, 1 H, 4-H), 6.71 (dd, *J* = 2.82 Hz, *J* = 8.80 Hz, 1 H, 2-H), 7.21 (d, *J* = 8.80 Hz, 1 H, 1-H) ppm], which was dissolved in dichloromethane (5 mL) contained triethylamine (0.1 mL). Acetyl chloride (1 M in dichloromethane, 0.4 mL) was added, and the solution was stirred for 20 min. The reaction mixture was diluted with dichloromethane, washed with aqueous $NaHCO_3$, water and brine and dried ($MgSO_4$). Evaporation of the solvent afforded a poorly soluble crystalline residue (122 mg), which was purified on a silica gel column to give amide **16** (100 mg, 81% yield). $[\alpha]_D^{20}$ = –50.7 (*c* = 0.75). M.p. 280–281 °C (from methanol/$CHCl_3$) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, 18 Me), 1.99 (s, 3 H, NAc), 2.06 (s, 3 H, OAc), 2.86 (m, 2 H, 6-H), 3.77 (s, 3 H, OMe), 4.15 (m, 1 H, 16β-H), 6.61 (d, *J* = 2.14 Hz, 1 H, 4-H), 6.71 (dd, *J* = 2.14 Hz, *J* = 8.80 Hz, 1 H, 2-H), 7.2 (d, *J* = 8.80 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (C-18), 21.5 (CH_3CO), 23.3 (t), 23.6 (t), 25.8 (t), 27.3 (t), 27.4 (t), 30.0 (t), 37.0 (d), 39.9 (d), 43.2 (t), 44.6 and 49.5 (C-13 and C-14), 54.4 (C-16), 55.2 (3-OMe), 91.4 (C-17), 111.8 (C-2), 113.7 (C-4), 126.3 (C-1), 132.7 (C-10), 137.8 (C-5), 157.5 (C-3), 171.0 (CH_3CO_2), 172.7 (CH_3CON) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3389 br (NH), 1732 (CO, acetate), 1658 (CO, amide) cm^{-1}. MS (EI): *m*/*z* (%) = 411 $[M]^+$ (40), 369 $[M - 42]^+$ (15), 282 $[M - 129]^+$ (100). $C_{25}H_{33}NO_4$ (411): calcd. C 72.96, H 8.08, N 3.40; found C 72.63, H 8.09, N 3.40.

16α-Amino-3-methoxy-14,17-ethenoestra-1,3,5(10)-trien-17β-yl Acetate (17) and 16α-Acetylamino-3-methoxy-14,17-ethenoestra-1,3,5(10)-trien-17β-yl Acetate (18): Nitro compound **2** (120 mg, 0.3 mmol) was dissolved in deoxygenated acetic acid (20 mL) at 100 °C, and zinc (130 mg) was added, followed by water (0.02 mL). The mixture was kept at reflux for 20 min and cooled. Zinc was filtered off and washed with dichloromethane. The combined filtrates were concentrated, the residue was dissolved in dichloromethane, and the resulting solution was washed with water, a mixture of $NaHCO_3$ and brine (1:1) and brine and dried ($MgSO_4$). The solvent was evaporated, and the residue (150 mg) was separated on a silica gel column with ethyl acetate as the eluent to give amine **17** (39 mg, 36% yield) as an unstable oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (s, 3 H, 18 Me), 2.13 (s, 3 H, OAc), 2.50 (m, 3 H, NH_2 and 9α-H), 2.86 (m, 2 H, 6-H), 3.70 (m, 1 H, 16β-H), 3.77 (s, 3 H, OMe), 6.26 and 6.33 each (d, *J* = 6.14 Hz, 1 H, 17^1 and 17^2-H), 6.61 (d, *J* = 2.67 Hz, 1 H, 4-H), 6.73 (dd, *J* = 2.67 Hz, *J* = 8.54 Hz, 1 H, 2-H), 7.2 (d, *J* = 8.54 Hz, 1 H, 1-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1727 (CO) cm^{-1}. MS (EI): *m*/*z* (%) = 324 $[M - 43]^+$ (20). Amine **17** was dissolved in benzene (5 mL), and triethylamine (0.1 mL) was added, followed by acetyl chloride (31 mg, 0.4 mmol) in benzene (0.6 mL). After 20 min, the solution was diluted with ethyl acetate, washed with water, saturated $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent gave a residue (133 mg), which was purified on a silica gel column to give amide **18** (41 mg, 94% yield). $[\alpha]_D^{20}$ = +84.13 (*c* = 0.27). M.p. 260–261 °C (from ethyl methyl ketone). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, 18 Me), 1.91 (s, 3 H, NAc), 2.10 (s, 3 H, OAc), 2.46 (m, 1 H, 9α-H), 2.86 (m, 2 H, 6-H), 3.77 (s, 3 H, OMe), 4.62 (m, 1 H, 16β-H), 6.2 (br. d, *J* = 6.67 Hz, 1 H, NH), 6.31 and 6.52 each (d, *J* = 6.2 Hz, 1 H, 17^1 and 17^2-H), 6.62 (d, *J* = 2.69 Hz, 1 H, 4-H), 6.73 (dd, *J* = 2.69 Hz, *J* = 8.74 Hz, 1 H, 2-H), 7.2 (d, *J* = 8.74 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.6 (C-18), 21.6 (CH_3CO_2), 23.5 (t), 23.7 (CH_3CON), 26.7 (t), 28.5 (t), 30.1 (t), 39.0 (d), 40.0 (d), 54.5 (s), 54.8 (s), 55.2 (3-OMe), 60.7 (C-16), 95.9 (C-17), 111.8 (C-2), 113.7 (C-4), 126.9 (C-1), 129.2 and 137.1 (C-17^1 and C-17^2), 132.1 (C-10), 137.8 (C-5), 157.5 (C-3), 170.2 (CH_3CO_2), 171.9 (CH_3CON) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3433 (NH), 1732 (CO, acetate), 1656 (CO, amide) cm^{-1}. MS (EI): *m*/*z* (%) = 324 $[M - 85]^+$ (20), 282 $[M - 127]^+$ (100). $C_{25}H_{31}NO_4$ (409): calcd. C 73.32, H 7.63, N 3.42; found C 73.00, H 7.76, N 3.41.

14β-(Cyanomethyl)-3-methoxyestra-1,3,5(10)-trien-17-one (19): A mixture of nitro compound **14** (88 mg, 0.22 mmol), $NaHCO_3$ (84 mg, 1 mmol) and triphenylphosphane (87 mg, 0.33 mmol) in aqueous ethanol (16.5 mL, 10:1) was refluxed for 40 min. The colourless solution was cooled and concentrated by ca. 90%. The residue was extracted with ethyl acetate, and the organic phase was washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave a solid residue (168 mg), which was chromatographed on silica gel. Elution with toluene afforded unreacted triphenylphosphane (33 mg, 0.12 mmol). Elution with ethyl acetate/toluene (10:90) gave product **19** (68 mg, 96% yield). $[\alpha]_D^{20}$ = +76.1 (*c* = 1.0). M.p. 172–174 °C (from MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (s, 3 H, 18 Me), 2.70 obsc (m, 1 H, 9α-H), 2.94 (m, 2 H, 6-H), 3.79 (s, 3 H, OMe), 6.65 (d, *J* = 2.67 Hz, 1 H, 4-H), 6.74 (dd, *J* = 2.67 Hz, *J* = 8.54 Hz, 1 H, 2-H), 7.21 (d, *J* = 8.54 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.0 (C-18), 23.3 (CH_2CN), 25.2 (t), 25.7 (t), 26.0 (t), 30.2 (t), 32.0 (t), 32.9 (t), 37.6 (C-9), 42.0 (C-8), 47.2 and 53.0 (C-13 and C-14), 55.2 (3-OMe), 112.1 (C-2), 113.5 (C-4), 118.0 (CN), 126.6 (C-1), 131.0 (C-10), 137.3 (C-5), 157.8 (C-3), 219.3 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2244 (CN), 1733 (CO) cm^{-1}. MS (EI): *m*/*z* (%) = 323 (100) $[M]^+$, 295 $[M - 28]^+$ (40). $C_{21}H_{25}NO_2$ (323): calcd. C 77.99, H 7.79, N 4.33; found C 77.93, H 7.83, N 4.29.

14β-[5-(Hydroxymethyl)isoxazol-3-ylmethyl]-3-methoxyestra-1,3,5(10)-trien-17-one (20): $NaHCO_3$ (84 mg, 1 mmol) and propargyl alcohol (0.1 mL, 1.71 mmol) were added to a solution of nitro compound **14** (89 mg, 0.22 mmol) in absolute ethanol (10 mL). The mixture was refluxed for 3 h, propargyl alcohol (0.05 mL) was added, and refluxing was continued for a further 3 h. The solution was cooled, and HCl (2.7 M, 0.6 mL) was added. The solution was stirred for 1 h and then diluted with water (2 mL), evaporated to about 25% of the original volume without heating and extracted

with dichloromethane. The organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting oil (89 mg) was chromatographed on silica gel with ethyl acetate/toluene (20:80) as the eluent to give starting material (4 mg) and an unidentified product (9 mg), followed by isoxazole **20** (43 mg, 49% yield) as an oil. $[\alpha]_D^{20}$ = +49.6 (*c* = 0.7). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (s, 3 H, 18 Me), 2.63 (m, 1 H, 9α-H), 2.57 and 2.94 each (d, *J* = 14.5 Hz, 1 H, 14β-CH_2), 2.87 (m, 2 H, 6-H), 3.77 (s, 3 H, OMe), 4.69 (s, 2 H, CH_2OH), 6.09 (s, 1 H, 4′-H), 6.65 (d, *J* = 2.72 Hz, 1 H, 4-H), 6.73 (dd, *J* = 2.72 Hz, *J* = 8.8 Hz, 1 H, 2-H), 7.2 (d, *J* = 8.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.6 (C-18), 23.9 (t), 24.1 (t), 25.0 (t), 30.2 (t), 32.9 (t), 33.1 (t), 33.5 (t), 38.3 (C-9), 42.6 (C-8), 48.6 and 52.8 (C-13 and C-14), 55.2 (3-OMe), 56.3 (CH_2OH), 103.5 (C-4′), 111.7 (C-2), 113.5 (C-4), 126.2 (C-1), 132.2 (C-10), 137.7 (C-5), 157.7 (C-3), 160.8 (C-3′), 171.6 (C-5′), 222.3 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3603 (OH), 1727 (CO), 1605 cm^{-1}. MS (EI): *m*/*z* (%) = 395 [M]$^+$ (30), 364 [M – 31]$^+$ (20), 283 [M – 112]$^+$ (30). $C_{24}H_{29}NO_4$ (395): calcd. C 72.89, H 7.39, N 3.54; found C 72,79, H 7.43, N 3.41.

3-Methoxy-14β-(2-nitroethyl)estra-1,3,5(10),15-tetraen-17-one (21): Methanolic KOH (2 M, 0.5 mL) was added to nitro compound **2** (99 mg, 0.25 mmol) in methanol (8 mL) at ambient temperature. The solution was stirred for 9 h, and dry ice was added. The solvent was evaporated without heating, and the solid residue was dissolved in ethyl acetate (15 mL) and washed with 0.5% HCl, water and brine and dried ($MgSO_4$). The concentrated crystalline residue (102 mg) was chromatographed on a short column with silica gel. Elution with toluene/ethyl acetate (95:5) afforded product **21** (78 mg, 88% yield). $[\alpha]_D^{20}$ = +188.9 (*c* = 0.95). M.p. 156–157 °C (from acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 18 Me), 1.36 (qd, *J* = 2.41 Hz, *J* = 6.43 Hz, 1 H, 11β-H), 1.91 (m, 1 H, 12β-H), 2.20 (m, 1 H, 7β-H), 2.30 (m, 2 H, 9α-H and 11α-H), 2.49 (m, 2 H, CH_2CH_2NO$_2$), 2.86 (m, 2 H, 6-H), 3.75 (s, 3 H, OMe), 4.34 (m, 2 H, CH$_2$CH_2NO$_2$), 6.27 (d, *J* = 6.03 Hz, 1 H, 16-H), 6.58 (d, *J* = 2.81 Hz, 1 H, 4-H), 6.70 (dd, *J* = 2.81 Hz, *J* = 8.64 Hz, 1 H, 2-H), 7.05 (d, *J* = 8.64 Hz, 1 H, 1-H), 7.33 (d, *J* = 6.03 Hz, 1 H, 15-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (C-18), 24.7 (C-7), 27.4 (C-11), 30.7 (C-6), 31.1 (CH_2CH$_2$NO$_2$), 31.4 (C-12), 35.4 (C-9), 42.9 (C-8), 51.7 and 53.6 (C-13 and C-14), 55.2 (3-OMe), 72.3 (CH_2NO$_2$), 112.5 (C-2), 113.1 (C-4), 127.9 (C-1), 132.1 (C-10), 132.6 (C-16), 136.8 (C-5), 157.5 (C-3), 162.5 (C-15), 212.3 (C-17) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1705 (CO), 1552 and 1373 (NO_2) cm^{-1}. MS (EI): *m*/*z* (%) = 355 [M]$^+$ (15). $C_{21}H_{25}NO_4$ (355): calcd. C 70.96, H 7.09, N 3.94; found C 71.04, H 7.08, N 3.91.

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