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Intramolecular Hydro-*N*-alkylation of Hydrazones and Oxime Ethers: Synthesis of Novel D-Secoestrone Isoquinuclidines via Domino 1,5-Hydride Shift/Cyclization

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The direct transformation of a benzylic C(sp^3)–H bond into a C–N bond from steroidal hydrazones **10b**, **10f–l** and oxime ethers **28b–d** under the action of a stoichiometric amount of Lewis acid is reported. The mechanism of functionalization to give novel types of isoquinuclidine derivatives **25b**, **25f–l** and **32b–d** is assumed to involve an intramolecular domino 1,5-hydride transfer/cyclization sequence. Azomethine imines **23b**, **23f–l** and oxyiminium ions **29b–d** are proposed as intermediates, which undergo 1,5-hydride shift to give the tertiary carbocation **24b**, **24f–l** or **31b–d**. The nucleophilic addition of the hydrazine or hydroxylamine moiety to the benzylic C-9 carbon led to bridged azaestrone derivatives.

Introduction

Heteroatom-containing polycycles continue to be attractive target molecules for stereoselective syntheses due to the diversity of their biological activity. Especially significant are those among the possible reactions leading to such compounds which can be run as domino processes, in which two or more bond-forming transformations occur, involving functionalities formed in the previous step.[1] Following this conception, a number of complex heterocyclic ring systems have been constructed so far with high efficiency and in a stereocontrolled manner.[2]

One of the widespread synthetic applications of domino reactions is the direct conversion of a C–H into a C–C or C–O bond via a Lewis acid-catalyzed cationic-cationic pathway, although only few examples of this type are to be found in the literature.[3] However, these hydroalkylation and hydro-*O*-alkylation reactions, involving an oxonium ion-induced 1,5-hydride transfer and a subsequent intramolecular ring-closure step, were performed with aldehydes, which are known to possess a high degree of electrophilicity in the presence of a Lewis acid[4] and therefore the ability to induce a through-space hydride shift. In contrast, the similar ionic transformations of a C–H into a C–N bond is rather uncommon, although nitrenium ions derived from *ortho*-substituted aryl oximes have been reported to undergo a formal C(sp^3)–H activated cyclization.[5] In this regard, we previously demonstrated first on a steroid model that arylimines **1** containing an electron-withdrawing group R on the aromatic moiety, possess sufficient electrophilicity in Lewis acid media to be able to induce a 1,5-hydride shift from the benzylic carbon C-9 (Figure 1). The subsequent addition of the amino group to the carbocation center in **3** led to a series of unusual 9,13-bridged steroidal azacycles **4**.[6] Several Lewis and Brønsted acids were then examined, of which $BF_3{\cdot}OEt_2$ was found to be best, as concerns the

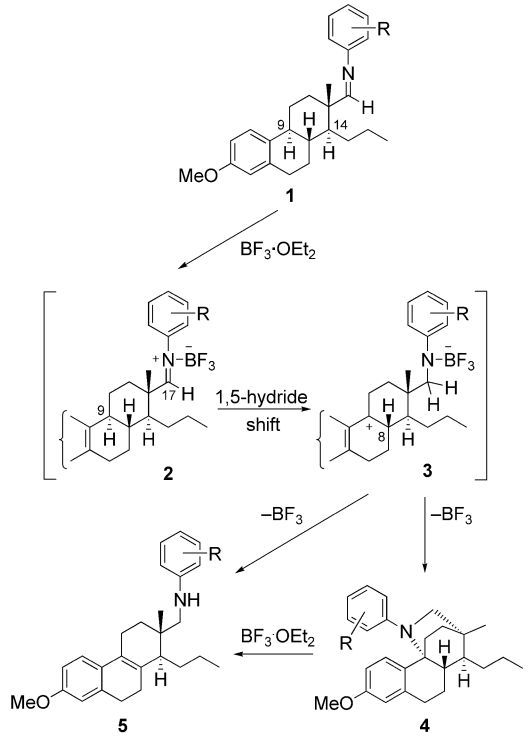

Figure 1. D-Secoestrone isoquinuclidines synthetized earlier in an aryliminium ion-induced cationic-cationic domino reaction.

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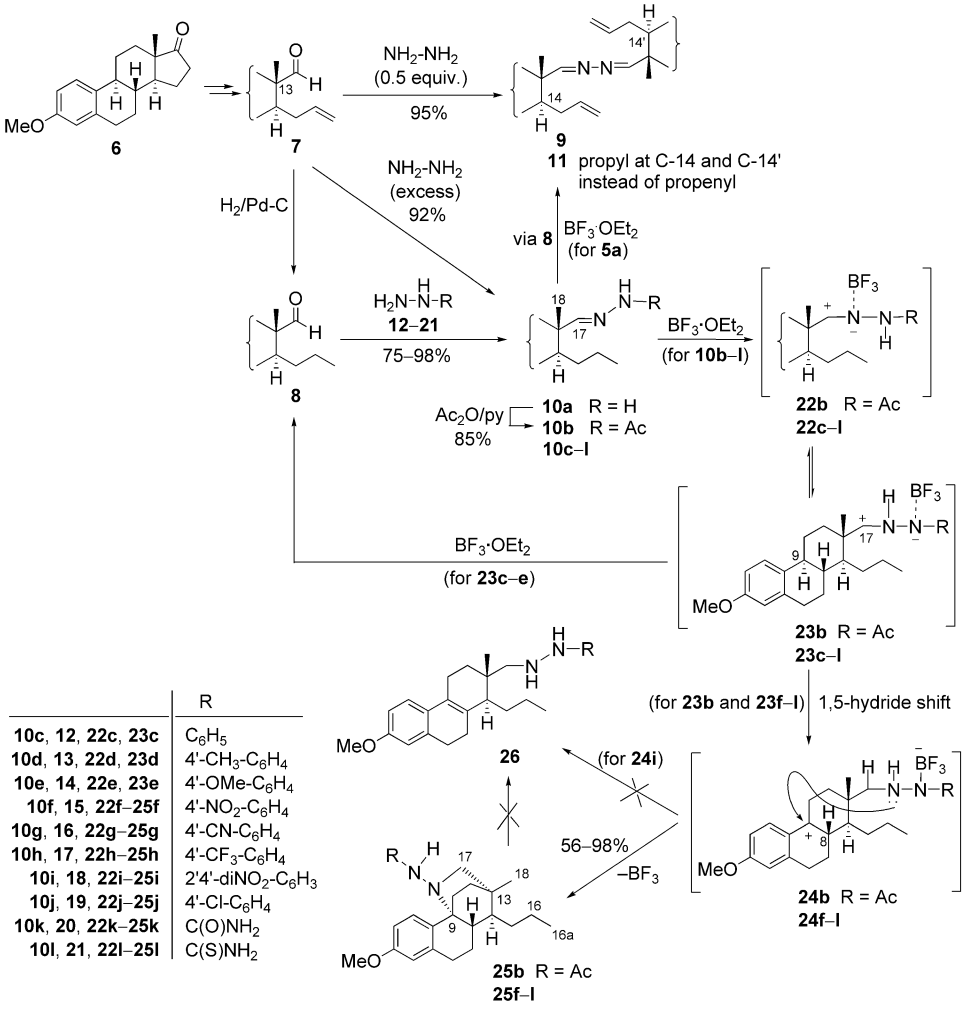
chemoselectivity of the domino process and the yields of the desired products **4**. All other acids favored formation of the unsaturated secondary amine **5** through abstraction of the proton on C-8 in **3**. However, **5** was also obtained on treatment of **4** with an excess of BF_3·OEt_2. In addition, intermediates **3** with an *ortho* R function on the aromatic moiety were observed to undergo elimination to give **5** exclusively, instead of **4**, presumably because of the steric hindrance of intramolecular cyclization by the *ortho* substituent. Although position C-9 in aromatic 19-norsteroids is activated thanks to its benzylic nature, only few intermolecular examples of substitution at this carbon have been reported.[7]

We demonstrate here that steroidal aldehyde hydrazones and aldoxime ethers are also suitable in the presence of BF_3·OEt_2 to induce an intramolecular hydro-*N*-alkylation domino process, whereby a tertiary benzylic C(sp^3)–H bond is transformed directly into a *N*-substituted quaternary center to give novel D-secoestrone derivatives with an isoquinuclidine substructure. Several synthetic molecules containing an isoquinuclidine moiety possess valuable pharmacological activity, such as 5-HT_3 antagonists,[8] epibatidine analogues[9] and expectorants.[10]

Results and Discussion

During our recent interest in taking advantage of the reactions of D-*seco* aldehyde **7**,[11] a precursor of **8**, which is readily accessible from estrone 3-methyl ether **6**,[12] an interesting transformation of **7** with hydrazine hydrate was discovered. When **7** was treated with half an equivalent of hydrazine, aldazine **9** was obtained, which served as a convenient starting material for criss-cross 1,3-dipolar cycloaddition (Scheme 1).[13] However, treatment of **7** with an excess of the same reagent under similar conditions furnished monohydrazone **10a** with simultaneous reduction of the propenyl side-chain, presumably by the diimide generated in situ from hydrazine.[14] As expected, monohydrazone **10a** proved to be quite unstable in the presence of BF_3·OEt_2 in solution, and was easily converted to **8**, which was further transformed to **11** with the releasing hydrazine. Interestingly, acetylhydrazone **10b**, obtained from **10a** by simple acetylation, readily underwent transformation through the use of a stoichiometric amount of BF_3·OEt_2 to give the bridged azaestrone derivative **25b** (Table 1, entry 1) via presumed ionic intermediates **22b**–**24b**. This latter reaction revealed that not only arylimines, but also hydrazones are

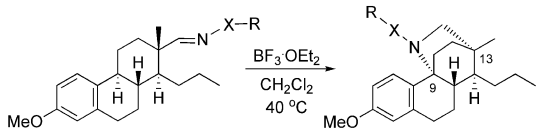


	R
10c, **12**, **22c**, **23c**	C_6H_5
10d, **13**, **22d**, **23d**	4'-CH_3-C_6H_4
10e, **14**, **22e**, **23e**	4'-OMe-C_6H_4
10f, **15**, **22f**–**25f**	4'-NO_2-C_6H_4
10g, **16**, **22g**–**25g**	4'-CN-C_6H_4
10h, **17**, **22h**–**25h**	4'-CF_3-C_6H_4
10i, **18**, **22i**–**25i**	2'4'-diNO_2-C_6H_3
10j, **19**, **22j**–**25j**	4'-Cl-C_6H_4
10k, **20**, **22k**–**25k**	C(O)NH_2
10l, **21**, **22l**–**25l**	C(S)NH_2

Scheme 1. BF_3·OEt_2-promoted hydro-*N*-alkylation of hydrazones.

able to induce a 1,5-hydride shift from a benzylic carbon under Lewis acid conditions, and further motivated us to investigate the mechanism of the process. Accordingly, starting from aldehyde **8** with phenylhydrazine **12** and its substituted derivatives **13**–**19**, a series of phenylhydrazones **10c**–**j** were prepared in good to excellent yields. In view of the chemical shift of the 17-CH proton in **10c**–**j** of about 7.00 ppm, formation of the corresponding (*E*) isomers during the condensation reactions is assumed. However, phenylhydrazones **10c**–**e** proved to be quite unstable on treatment with $BF_3{\cdot}OEt_2$ and were easily converted into the starting material **8**. In contrast, phenylhydrazones **10f**–**j**, containing one or two electron-withdrawing groups on the aromatic ring, underwent facile 1,5-hydride shift/cyclization to afford isoquinuclidine derivatives **25f**–**j** (Table 1, entries 2–6). Since the reaction of 2′,4′-phenylhydrazone **10i** also led to exclusively **25i**, instead of the unsaturated hydrazine derivative **26i**, the *ortho* substituent on the phenyl ring seems to have no influence on the intramolecular cylization of carbocation **24i**. The absence of steric hindrance in this case is not surprising, as an –NH– linker is located between the C=N bond and the aromatic moiety. Moreover, on treatment of **25** with an excess of $BF_3{\cdot}OEt_2$, the bridged six-membered ring remained stable, and conversion to **26** was not observed. Similarly to phenylhydrazones **10c**–**j**, the semicarbazone **10k** and thiosemicarbazone **10l** of **8** with **20** and **21** were also prepared and subjected to Lewis acid treatment. In this way, the corresponding azacycles **25k** and **25l** were obtained in lower yields than those from phenylhydrazones **10f**–**i** (Table 1, entries 7 and 8).

Table 1. Stereoselective synthesis of 9,13-bridged steroidal azacycles.



10 X = NH
28 X = O

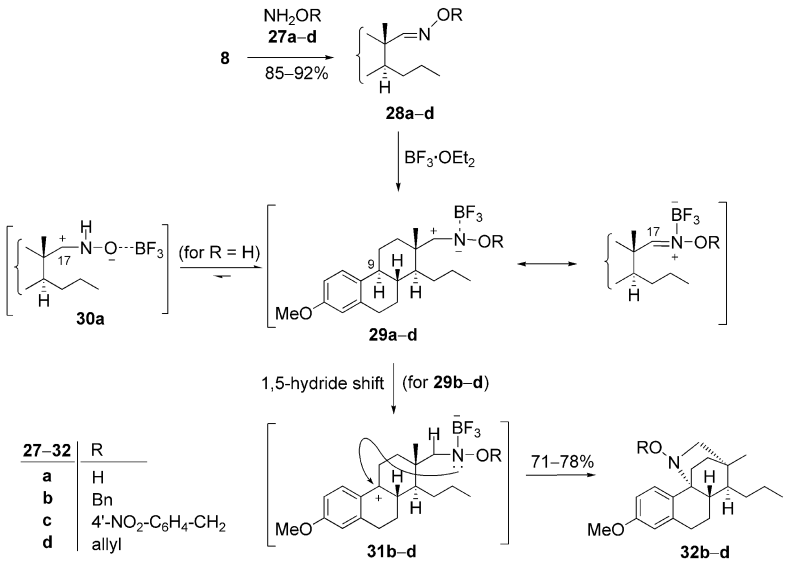
25 X = NH
32 X = O

Entry	Substrate	R	*t* [h]	Product	Yield[a]
(1)	**10b**	Ac	4	**25b**	78
(2)	**10f**	4′-NO_2-C_6H_4	4	**25f**	98
(3)	**10g**	4′-CN-C_6H_4	4	**25g**	92
(4)	**10h**	4′-CF_3-C_6H_4	4	**25h**	89
(5)	**10i**	2′,4′-NO_2-C_6H_3	4	**25i**	93
(6)	**10j**	4′-Cl-C_6H_4	6	**25j**	56
(7)	**10k**	C(O)NH_2	8	**25k**	66
(8)	**10l**	C(S)NH_2	8	**25l**	63
(9)	**28b**	Bn	6	**32b**	71
(10)	**28c**	4′-NO_2-C_6H_4-CH_2	4	**32c**	78
(11)	**28d**	allyl	8	**32d**	72

[a] Determined after purification by column chromatography.

The following mechanism is proposed for the described transformation. Reaction of monosubstituted hydrazones **10b**–**l** with $BF_3{\cdot}OEt_2$ results in ionic intermediates **22b**–**l**, which can undergo tautomerization to give the quasi-azomethine imine 1,3-dipolar intermediates **23b**–**l**.[15] Coordination to the Lewis acid of phenylhydrazones containing an electron-donating group (CH_3 or OMe) on the aromatic ring, as in **10d** or **10e**, is presumed to be somewhat more favorable than that of phenylhydrazones with an electron-withdrawing group (NO_2, CN, CF_3) in **10f**–**i** or of acetylhydrazone **10b**.[16] Nevertheless, complexation and the following *N*,*N*′-proton shift are assumed to occur under the given reaction conditions to afford intermediates **23b**–**l**. Earlier, monosubstituted hydrazones as in situ azomethine imine precursors were reported to undergo 1,3-dipolar cycloaddition reactions with unsaturated dipolarophiles under thermal and Lewis acid conditions to give *N*-containing five-membered heterocycles.[16,17] The overall electrophilicity scale established by Pérez et al.[18] for a series of dipoles and dipolarophiles commonly used in 1,3-dipolar cycloaddition reactions indicates that azomethine imine 1,3-dipoles may be regarded as marginal electrophiles and hence will more probably behave as electron donor species. However, the electrophilicity of such dipoles may be drastically changed by suitable substitution, i.e. the presence of a strong electron-withdrawing group on the dipole and/or coordination of a dipole with a Lewis acid, results in a large increase in the overall electrophilicity of these systems. Accordingly, azomethine imines **23b** and **23f**–**i** seem to possess sufficient electrophilic character to promote hydride transfer from the activated benzylic carbon C-9 to give carbocations **24b** and **24f**–**i**, respectively, which are stabilized by intramolecular addition of the hydrazine moiety to afford **25b** and **25f**–**i**. Dipolar intermediates **23d** and **23e**, on the other hand, rather acquire increased nucleophilicity due to the electron-donating groups on the phenyl ring and they are therefore unsuitable for hydride abstraction. These dipoles are rather converted into the starting aldehyde **8**, such as **23c**, where the unsubstituted aromatic ring can not change the extant reactivity of the dipole. The domino 1,5-hydride shift/cyclization of **23j**–**l** can also furnish the corresponding products **25j**–**l**, but with lower conversion during a longer reaction time. This can easily be explained by the decreased electron-withdrawing effect of the substituents R in **23j**–**l**, due to positive mesomeric effects and thus the smaller increase in the overall electrophilicity of the related azomethine imine dipoles.

Since hydrazones proved to be suitable precursors for this domino process, our attention next focused on an investigation as to whether the oxime and oxime ethers of aldehyde **8** can undergo similar transformation. First, the aldoxime **28a** of **8** with hydroxylamine hydrochloride was prepared in basic 2-propanol under reflux (Scheme 2), and proved to be quite stable on treatment with a stoichiometric amount of $BF_3{\cdot}OEt_2$. Although the isomerization of intermediate **29a** to nitrone 1,3-dipole **30a** through an *O*,*N*-hydrogen shift is conceivable,[19] the nitrone structure is presumed to be the less stable tautomer in the equilibrium.[20] The oxyiminium ion **29a**, however, did not seem to have enough electrophilic force to induce a hydride shift. Interestingly, when the oxime ethers **28b**–**d** of **8** were subjected to similar Lewis acid treatment, formation of the corresponding 9,13-bridged products **32b**–**d** was observed (Table 1, entries 9–11). These results indicate that *O*-substituted oxyiminium ions and



Scheme 2. BF_3·OEt_2-promoted hydro-*N*-alkylation of oxime ethers.

azomethine imines have similar electrophilicity to that of aryliminium ions and are able to cleave a hydride from the activated benzylic position. Therefore, the reactivity scale of Mayr and Ofial[21] may be completed additionally with these two types of ionic intermediates.

The structures of the newly synthetized steroid azacycles **25b**,**f**–**l** and **32b**–**d** were determined by NMR spectroscopy. In the ^{1}H NMR spectra of compounds **25b**,**f**–**l** and **32b**–**d**, a triplet is observed for 16a-H_3 at δ = 0.94–0.99 ppm with J = 6.9–7.0 Hz. In all cases, the corresponding proton resonated at higher fields (ca. 0.85 ppm) in the starting phenylhydrazones **10b**,**f**–**l** and oxime ethers **28b**–**d**. The ^{13}C NMR spectra of **25b**,**f**–**l** and **32b**–**d** obtained by a J-MOD pulse sequence, contain the expected signals; the peaks for C-9 and C-17 appear at relatively high chemical shifts, at around δ = 57.5 ppm for C-9 and δ = 68.5 ppm for C-17.

Conclusions

In conclusion, a new type of domino reaction leading to steroidal isoquinuclidines has been described. The intramolecular hydride ion abstraction induced by azomethine imines and oxyiminium ions, generated in situ from hydrazones and oxime ethers in Lewis acid media, is a rather unusual process and to the best of our knowledge has not been reported previously. Besides their simplicity, the transformations display high chemo- and regioselectivity.

Experimental Section

General Methods: All solvents were distilled and dried prior to use. Reagents and materials were obtained from commercial suppliers and were used without purification. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254F) layers (0.25 mm thickness). The spots were detected by spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid. The R_f values were determined for spots observed in UV light (λ = 254 and 365 nm). Flash chromatography: silica gel 60, 40–63 μm. Melting points were determined on a Kofler block and are uncorrected. EI mass spectra were obtained with a Varian MAT 311A spectrometer with ionization energy 70 eV. ^{1}H NMR spectra were obtained in $CDCl_3$ or in [D_6]DMSO solution at 400 MHz (Bruker DRX 400) or 500 MHz (Bruker DRX 500), and the ^{13}C NMR spectra at 100 or 125 MHz with the same instruments. Chemical shifts are reported relative to TMS; J values are given in Hz. ^{13}C NMR spectra are ^{1}H-decoupled. For determination of the multiplicities, the J-MOD pulse sequence was used. Elemental analyses were carried out with a Perkin–Elmer model 2400 CHN analyzer.

16,17-*seco*-3-Methoxyestra-1,3,5(10)trien-17-al Hydrazone (10a): To a solution of **7** (298 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), hydrazine hydrate (98%, 1 mL, 20 mmol) and 1 drop of acetic acid were added. The mixture was stirred overnight at room temperature and the solvent was then evaporated in vacuo. The residue was dissolved in MeOH (5 mL) and diluted with water. The crude product **10a** (289 mg, 92%) was filtered off as a white precipitate, washed with water and dried; m.p. 68–70 °C; R_f = 0.79 (MeOH/CH_2Cl_2 = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H, 16a-H_3), 1.05 (s, 3 H, 18-H_3), 1.14–1.62 (m, 10 H), 2.08 (m, 1 H), 2.31 (m, 2 H), 2.86 (m, 2 H, 6-H_2), 3.78 (s, 3 H, 3-OMe), 6.63 (d, J = 2.3 Hz, 1 H, 4-H), 6.72 (dd, J = 8.6, J = 2.3 Hz, 1 H, 2-H), 6.94 (s, 1 H, 17-H), 7.21 (d, J = 8.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 15.8 (C-18), 24.4 (CH_2), 26.2 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.1 (CH_2), 37.6 (CH_2), 41.2 (C-8), 41.8 (C-13), 43.4 (C-9), 48.0 (C-14), 55.1 (3-OMe), 111.7 (C-2), 113.4 (C-4), 126.5 (C-1), 132.5 (C-10), 137.8 (C-5), 155.5 (C-17), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 314 (100) [M^+], 271 (100), 174 (23), 112 (30). $C_{20}H_{30}N_2O$ (314.46): calcd. for C 76.39, H 9.62; found C 76.52, H 9.47.

16,17-*seco*-3-Methoxyestra-1,3,5(10)trien-17-al Hydrazone Acetate (10b): Compound **10a** (250 mg, 0.80 mmol) was dissolved in a mixture of pyridine (5 mL) and acetic anhydride (5 mL) and the solution was stirred at room temperature for 2 h. The mixture was then poured onto a mixture of sulfuric acid (5 mL) and ice (10 g). The crude product **10b** (242 mg, 85%) was filtered off as a white precipitate, washed with water and dried; m.p. 158–161 °C; R_f = 0.39 (MeOH/CH_2Cl_2 = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.5 Hz, 3 H, 16a-H_3), 1.08 (s, 3 H, 18-H_3), 1.14–1.70 (m, 10

H), 2.08 (m, 1 H), 2.31 (m, 2 H), 2.28 (s, 3 H, Ac-H_3), 2.86 (m, 2 H, 6-H_2), 3.78 (s, 3 H, 3-OMe), 6.63 (d, J = 2.3 Hz, 1 H, 4-H), 6.72 (dd, J = 8.6, J = 2.3 Hz, 1 H, 2-H), 7.00 (s, 1 H, 17-H), 7.21 (d, J = 8.6 Hz, 1 H, 1-H), 9.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 15.6 (C-18), 20.3 (Ac-CH_3), 24.4 (CH_2), 26.1 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.3 (CH_2), 37.4 (CH_2), 41.2 (C-8), 42.4 (C-13), 43.3 (C-9), 47.6 (C-14), 55.2 (3-OMe), 111.7 (C-2), 113.5 (C-4), 126.5 (C-1), 132.2 (C-10), 137.8 (C-5), 155.6 (C-17), 157.5 (C-3), 173.6 (Ac-CO) ppm. MS (70 eV, EI): m/z (%) = 356 (82) [M^+], 313 (100), 174 (69), 126 (40), 112 (58). $C_{22}H_{32}N_2O_2$ (356.50): calcd. for C 74.12, H 9.05; found C 73.96, H 9.32.

General Procedure for the Synthesis of Hydrazones 10c–l

Method A: Compound **8** (300 mg, 1.00 mmol) and (substituted) hydrazine hydrochloride derivative (1.00 mmol) were suspended in MeOH (5 mL), a solution of anhydrous NaOAc (150 mg, 1.80 mmol) in MeOH (5 mL) was added, and the mixture was stirred for a given time at room temperature. The resulting precipitate was filtered off, washed with a small amount of MeOH and allowed to stand at room temperature until completely dry.

Method B: A solution of compound **8** (300 mg, 1.00 mmol) and substituted hydrazine derivative (1.00 mmol) in MeOH (5 mL) was stirred in the presence of 2 drops of AcOH for a given time at room temperature. The resulting precipitate was filtered off, washed with a small amount of MeOH and dried.

16,17-*seco*-3-Methoxyestra-1,3,5(10)trien-17-al Phenylhydrazone (10c): Phenylhydrazine hydrochloride **12** (145 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time: 1 h. The crude product **10c** (336 mg, 86%) was obtained as a white precipitate; m.p. 148–150 °C; R_f = 0.58 (hexane/CH_2Cl_2 = 40:60). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.7 Hz, 3 H, 16a-H_3), 1.13 (s, 3 H, 18-H_3), 1.18–1.53 (m, 8 H), 1.66 (m, 2 H), 2.09 (m, 1 H), 2.32 (m, 2 H), 2.86 (m, 2 H, 6-H_2), 3.78 (s, 3 H, 3-OMe), 6.63 (d, J = 2.4 Hz, 1 H, 4-H), 6.72 (dd, J = 8.6, J = 2.4 Hz, 1 H, 2-H), 6.81 (m, 1 H, 4′-H), 6.89 (br. s, 1 H, NH), 7.00 (d, J = 7.8 Hz, 2 H, 2′-H and 6′-H), 7.14 (s, 1 H, 17-H), 7.22 (m, 2 H, 3′-H and 5′-H), 7.25 (d, J = 8.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 16.1 (C-18), 24.6 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 30.6 (CH_2), 32.3 (CH_2), 38.1 (CH_2), 41.4 (C-8), 42.1 (C-13), 43.4 (C-9), 48.2 (C-14), 55.2 (3-OMe), 111.7 (C-2), 112.5 (2 C, C-2′ and C-6′), 113.5 (C-4), 119.3 (C-4′), 126.5 (C-1), 129.2 (2 C, C-3′ and C-5′), 132.5 (C-10), 137.9 (C-5), 145.7 (C-1′), 149.9 (C-17), 157.5 (C-3) ppm. $C_{26}H_{34}N_2O$ (390.56): calcd. for C 79.96, H 8.77; found C 80.14, H 8.54.

16,17-*seco*-3-Methoxyestra-1,3,5(10)trien-17-al 4′-Tolylhydrazone (10d): 4-Tolylhydrazine hydrochloride **13** (159 mg) was used for the synthesis as described in the Geneal Procedure, Method A. Reaction time: 2 h. The crude product **10d** (327 mg, 81%) was obtained as a white precipitate; m.p. 143–146 °C; R_f = 0.75 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, J = 6.6 Hz, 3 H, 16a-H_3), 1.12 (s, 3 H, 18-H_3), 1.17–1.55 (m, 8 H), 1.65 (m, 2 H), 2.08 (m, 1 H), 2.26 (s, 3 H, 4′-CH_3), 2.31 (m, 2 H), 2.86 (m, 2 H, 6-H_2), 3.77 (s, 3 H, 3-OMe), 6.63 (d, J = 2.1 Hz, 1 H, 4-H), 6.71 (dd, J = 8.5, J = 2.1 Hz, 1 H, 2-H), 6.86 (s, 1 H, NH), 6.91 (d, J = 8.2 Hz, 2 H, 2′-H and 6′-H), 7.03 (m, 3 H, 3′-H, 5′-H and 17-H), 7.21 (d, J = 8.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 16.1 (C-18), 20.5 (4′-CH_3), 24.6 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 30.6 (CH_2), 32.2 (CH_2), 38.1 (CH_2), 41.4 (C-8), 42.1 (C-13), 43.4 (C-9), 48.2 (C-14), 55.2 (3-OMe), 111.7 (C-2), 112.7 (2 C, C-2′ and C-6′), 113.5 (C-4), 126.5 (C-1), 128.5 (C-4′), 129.6 (2 C, C-3′ and C-5′), 132.6 (C-10), 137.9 (C-5), 143.6 (C-1′), 149.5 (C-17), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 404 (90) [M^+], 298 (100). $C_{27}H_{36}N_2O$ (404.59): calcd. for C 80.15, H 8.97; found C 80.29, H 9.05.

16,17-*seco*-3-Methoxyestra-1,3,5(10)trien-17-al 4′-Methoxyphenylhydrazone (10e): 4-Methoxyphenylhydrazine hydrochloride **14** (175 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time: 1 h. The crude product **10e** (328 mg, 78%) was obtained as a white precipitate; m.p. 108–110 °C; R_f = 0.75 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 6.6 Hz, 3 H, 16a-H_3), 1.13 (s, 3 H, 18-H_3), 1.16–1.52 (m, 8 H), 1.65 (m, 2 H), 2.08 (m, 1 H), 2.30 (m, 2 H), 2.87 (m, 2 H, 6-H_2), 3.77 (s, 3 H) and 3.78 (s, 3 H): 3-OMe and 4′-OMe, 6.63 (d, J = 2.2 Hz, 1 H, 4-H), 6.72 (dd, J = 8.5, J = 2.2 Hz, 1 H, 2-H), 6.84 (d, J = 8.8 Hz, 2 H, 2′-H and 6′-H), 6.89 (s, 1 H, NH), 6.97 (m, 3 H, 3′-H, 5′-H and 17-H), 7.22 (d, J = 8.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 16.1 (C-18), 24.6 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 30.6 (CH_2), 32.2 (CH_2), 38.1 (CH_2), 41.4 (C-8), 42.1 (C-13), 43.4 (C-9), 48.2 (C-14), 55.2 (3-OMe), 55.8 (4′-OMe), 111.7 (C-2), 113.5 (C-4), 113.9 (2 C, C-3′ and C-5′), 114.7 (2 C, C-2′ and C-6′), 126.5 (C-1), 132.3 (C-10), 137.9 (C-5), 140.0 (C-1′), 149.6 (C-17), 153.4 (C-4′), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 420 (94) [M^+], 298 (100), 122 (29). $C_{27}H_{36}N_2O_2$ (420.59): calcd. for C 77.10, H 8.63; found C 76.93, H 8.84.

16,17-*seco*-3-Methoxyestra-1,3,5(10)trien-17-al (4′-Nitrophenyl)hydrazone (10f): 4-Nitrophenylhydrazine hydrochloride **15** (190 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time: 2 h. The crude product **10f** (418 mg, 96%) was obtained as an orange precipitate; m.p. 213–215 °C; R_f = 0.49 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.5 Hz, 3 H, 16a-H_3), 1.16 (s, 3 H, 18-H_3), 1.20–1.55 (m, 8 H), 1.68 (m, 2 H), 2.09 (m, 1 H), 2.32 (m, 2 H), 2.88 (m, 2 H, 6-H_2), 3.79 (s, 3 H, 3-OMe), 6.64 (d, J = 2.5 Hz, 1 H, 4-H), 6.73 (dd, J = 8.6, J = 2.5 Hz, 1 H, 2-H), 7.00 (d, J = 9.1 Hz, 2 H, 2′-H and 6′-H), 7.03 (s, 1 H, 17-H), 7.22 (d, J = 8.6 Hz, 1 H, 1-H), 7.75 (br. s, 1 H, NH), 8.15 (d, J = 9.1 Hz, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 15.9 (C-18), 24.5 (CH_2), 26.2 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.3 (CH_2), 37.8 (CH_2), 41.3 (C-8), 42.6 (C-13), 43.4 (C-9), 48.0 (C-14), 55.2 (3-OMe), 111.2 (2 C, C-2′ and C-6′), 111.8 (C-2), 113.5 (C-4), 126.2 (2 C, C-3′ and C-5′), 126.5 (C-1), 132.2 (C-10), 137.8 (C-5), 139.7 (C-4′), 150.3 (C-1′), 153.8 (C-17), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 435 (50) [M^+], 298 (100). $C_{26}H_{33}N_3O_3$ (435.56): calcd. for C 71.70, H 7.64; found C 71.85, H 7.54.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al (4′-Cyanophenyl)hydrazone (10g): 4-Cyanophenylhydrazine hydrochloride **16** (170 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time: 2 h. The crude product **10g** (407 mg, 98%) was obtained as a white precipitate; m.p. 184–186 °C; R_f = 0.42 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.5 Hz, 3 H, 16a-H_3), 1.15 (s, 3 H, 18-H_3), 1.20–1.55 (m, 8 H), 1.68 (m, 2 H), 2.10 (m, 1 H), 2.33 (m, 2 H), 2.88 (m, 2 H, 6-H_2), 3.79 (s, 3 H, 3-OMe), 6.65 (d, J = 2.4 Hz, 1 H, 4-H), 6.74 (dd, J = 8.6, J = 2.4 Hz, 1 H, 2-H), 6.98 (s, 1 H, 17-H), 7.02 (d, J = 8.6 Hz, 2 H, 2′-H and 6′-H), 7.22 (d, J = 8.6 Hz, 1 H, 1-H), 7.49 (d, J = 8.6 Hz, 2 H, 3′-H and 5′-H), 7.58 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 15.9 (C-18), 24.5 (CH_2), 26.2 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.3 (CH_2), 37.9 (CH_2), 41.3 (C-8), 42.4 (C-13), 43.4 (C-9), 48.0 (C-14), 55.2 (3-OMe), 100.9 (C-4′), 111.8 (C-2), 112.2 (2 C, C-2′ and C-6′), 113.5 (C-4), 120.2 (4′-CN), 126.5 (C-1), 132.3 (C-10), 133.6 (2 C, C-3′ and C-5′), 137.8 (C-5), 148.6 (C-1′), 152.6 (C-17), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 415 (42) [M^+], 298 (100), 257

(35). $C_{27}H_{33}N_3O$ (415.57): calcd. for C 78.03, H 8.00; found C 77.86, H 8.12.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al 4′-(Trifluoromethyl)-phenylhydrazone (10h): 4-(Trifluoromethyl)phenylhydrazine **17** (176 mg) was used for the synthesis as described in the General Procedure, Method B. Reaction time: 4 h. The crude product **10h** (357 mg, 78%) was obtained as a white precipitate; m.p. 118–120 °C; R_f = 0.46 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.7 Hz, 3 H, 16a-H_3), 1.16 (s, 3 H, 18-H_3), 1.20–1.56 (m, 8 H), 1.68 (m, 2 H), 2.11 (m, 1 H), 2.33 (m, 2 H), 2.88 (m, 2 H, 6-H_2), 3.80 (s, 3 H, 3-OMe), 6.66 (d, J = 2.6 Hz, 1 H, 4-H), 6.75 (dd, J = 8.6, J = 2.6 Hz, 1 H, 2-H), 6.94 (s, 1 H, 17-H), 7.05 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 7.23 (d, J = 8.6 Hz, 1 H, 1-H), 7.37 (br. s, 1 H, NH), 7.48 (d, J = 8.5 Hz, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 16.0 (C-18), 24.6 (CH_2), 26.3 (CH_2), 27.4 (CH_2), 30.6 (CH_2), 32.3 (CH_2), 38.0 (CH_2), 41.4 (C-8), 42.3 (C-13), 43.4 (C-9), 48.1 (C-14), 55.2 (3-OMe), 111.7 (C-2), 111.8 (2 C, C-2′ and C-6′), 113.5 (C-4), 115.0 (C-4′), 120.7 (4′-CF_3), 126.5 (3 C, C-1, C-3′ and C-5′), 132.4 (C-10), 137.9 (C-5), 148.0 (C-1′), 151.4 (C-17), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 458 (6) [M^+], 165 (100). $C_{27}H_{33}F_3N_2O$ (458.56): calcd. for C 70.72, H 7.25; found C 70.94, H 7.12.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al (2′,4′-Dinitrophenyl)hydrazone (10i): 2,4-Dinitrophenylhydrazine **18** (198 mgl) was used for the synthesis as described in the General Procedure, Method B. Reaction time: 4 h. The crude product **10i** (456 mg, 95%) was obtained as an orange precipitate; m.p. 234–236 °C; R_f = 0.59 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.4 Hz, 3 H, 16a-H_3), 1.21 (s, 3 H, 18-H_3), 1.27–1.57 (m, 8 H), 1.73 (m, 2 H), 2.11 (m, 1 H), 2.36 (m, 2 H), 2.89 (m, 2 H, 6-H_2), 3.79 (s, 3 H, 3-OMe), 6.64 (d, J = 2.5 Hz, 1 H, 4-H), 6.73 (dd, J = 8.5, J = 2.5 Hz, 1 H, 2-H), 7.22 (d, J = 8.5 Hz, 1 H, 1-H), 7.39 (s, 1 H, 17-H), 7.95 (d, J = 9.6 Hz, 1 H, 6′-H), 8.31 (dd, J = 9.6, J = 2.2 Hz, 1 H, 5′-H), 9.12 (dd, J = 2.2 Hz, 1 H, 3′-H), 11.0 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 15.7 (C-18), 24.4 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 30.4 (CH_2), 32.5 (CH_2), 37.5 (CH_2), 41.2 (C-8), 43.3 (C-9), 43.4 (C-13), 47.7 (C-14), 55.2 (3-OMe), 111.8 (C-2), 113.5 (C-4), 116.6 (C-6′), 123.5 (C-3′), 126.4 (C-1), 128.9 (C-2′), 129.9 (C-5′), 132.0 (C-10), 137.7 (2 C, C-5 and C-4′), 145.3 (C-1′), 157.6 (C-3), 160.7 (C-17) ppm. MS (70 eV, EI): m/z (%) = 480 (29) [M^+], 298 (100). $C_{26}H_{32}N_4O_5$ (480.56): calcd. for C 64.98, H 6.71; found C 65.14, H 6.93.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al (4′-Chlorophenyl)-hydrazone (10j): 4-Chlorophenylhydrazine hydrochloride **19** (180 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time: 4 h. The crude product **10j** (319 mg, 75%) was obtained as a white precipitate; m.p. 145–147 °C; R_f = 0.44 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.7 Hz, 3 H, 16a-H_3), 1.14 (s, 3 H, 18-H_3), 1.16–1.52 (m, 8 H), 1.65 (m, 2 H), 2.08 (m, 1 H), 2.31 (m, 2 H), 2.87 (m, 2 H, 6-H_2), 3.80 (s, 3 H, 3-OMe), 6.65 (d, J = 2.5 Hz, 1 H, 4-H), 6.74 (dd, J = 8.6, J = 2.5 Hz, 1 H, 2-H), 6.91 (s, 1 H, 17-H), 6.95 (d, J = 8.8 Hz, 2 H, 2′-H and 6′-H), 7.15 (br. s, 1 H, NH), 7.19 (d, J = 8.8 Hz, 2 H, 3′-H and 5′-H), 7.23 (d, J = 8.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 16.0 (C-18), 24.6 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 30.6 (CH_2), 32.3 (CH_2), 38.0 (CH_2), 41.4 (C-8), 42.2 (C-13), 43.4 (C-9), 48.1 (C-14), 55.2 (3-OMe), 111.7 (C-2), 113.5 (C-4), 113.6 (2 C, C-2′ and C-6′), 123.8 (C-4′), 126.5 (C-1), 129.0 (2 C, C-3′ and C-5′), 132.4 (C-10), 137.9 (C-5), 144.3 (C-1′), 150.5 (C-17), 157.5 (C-3) ppm. MS (70 eV, EI): m/z (%) = 426 (12), 424 (38) [M^+], 298 (100). $C_{26}H_{33}ClN_2O$ (425.01): calcd. for C 73.48, H 7.83; found C 73.61, H 7.72.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al Semicarbazone (10k): Semicarbazide hydrochloride **20** (112 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time 8 h, under reflux. The crude product **10k** (293 mg, 82%) was obtained as a white precipitate; m.p. 163–166 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 0.87 (t, J = 6.6 Hz, 3 H, 16a-H_3), 1.10 (s, 3 H, 18-H_3), 1.19–1.42 (m, 8 H), 1.55–1.71 (m, 2 H), 2.08 (m, 1 H), 2.34 (m, 2 H), 2.86 (m, 2 H, 6-H_2), 3.77 (s, 3 H, 3-OMe), 6.17 (m, 2 H, NH_2), 6.68 (d, J = 2.1 Hz, 1 H, 4-H), 6.76 (dd, J = 8.5, J = 2.1 Hz, 1 H, 2-H), 7.13 (s, 1 H, 17-H), 7.26 (d, J = 8.5 Hz, 1 H, 1-H), 9.75 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 14.3 (C-16a), 15.3 (C-18), 23.8 (CH_2), 25.7 (CH_2), 26.7 (CH_2), 29.8 (CH_2), 31.4 (CH_2), 37.0 (CH_2), 40.7 (C-8), 41.3 (C-13), 42.6 (C-9), 47.2 (C-14), 54.7 (3-OMe), 111.6 (C-2), 113.0 (C-4), 126.2 (C-1), 131.8 (C-10), 137.2 (C-5), 151.5 (C-17), 156.7 and 156.9 (C-3 and C=O) ppm. $C_{21}H_{31}N_3O_2$ (357.49): calcd. for C 70.55, H 8.74; found C 70.36, H 8.83.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al Thiosemicarbazone (10l): Thiosemicarbazide **21** (91 mg) was used for the synthesis as described in the General Procedure, Method A. Reaction time 6 h, under reflux. The crude product **10l** (276 mg, 74%) was obtained as a white precipitate; m.p. 126–128 °C; R_f = 0.18 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.7 Hz, 3 H, 16a-H_3), 1.06 (s, 3 H, 18-H_3), 1.19–1.50 (m, 8 H), 1.57–1.72 (m, 2 H), 2.07 (m, 1 H), 2.32 (m, 2 H), 2.86 (m, 2 H, 6-H_2), 3.78 (s, 3 H, 3-OMe), 6.52 (br. s, 1 H, one proton of NH_2), 6.63 (d, J = 2.5 Hz, 1 H, 4-H), 6.72 (dd, J = 8.6, J = 2.5 Hz, 1 H, 2-H), 7.08 (br. s, 1 H, the other proton of NH_2), 7.18 (d, J = 8.6 Hz, 1 H, 1-H), 7.21 (s, 1 H, 17-H), 9.91 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 15.4 (C-18), 24.4 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 30.4 (CH_2), 32.3 (CH_2), 37.2 (CH_2), 41.1 (C-8), 42.7 (C-13), 43.2 (C-9), 47.6 (C-14), 55.2 (3-OMe), 111.8 (C-2), 113.4 (C-4), 126.4 (C-1), 132.0 (C-10), 137.7 (C-5), 156.9 (C-17), 157.5 (C-3), 178.1 (C = S) ppm. MS (70 eV, EI): m/z (%) = 373 (54) [M^+], 297 (77), 174 (78), 126 (58), 102 (100). $C_{21}H_{31}N_3OS$ (373.56): calcd. for C 67.52, H 8.36; found C 67.41, H 8.18.

Bis[16,17-*seco*-3-methoxyestra-1,3,5(10)-trien-17-al] Bishydrazone (11): Compound **10a** (280 mg, 0.89 mmol) was dissolved in CH_2Cl_2 (10 mL) and $BF_3{\cdot}OEt_2$ (a 48% solution in diethyl ether, 0.26 mL, 0.89 mmol) was added dropwise under a nitrogen atmosphere. The mixture was stirred for 4 h at 0 °C, then quenched by the addition of $NaHCO_3$ (1 M, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (CH_2Cl_2) and recrystallized from CH_2Cl_2/hexane to give **11** (494 mg, 93%) as white crystals; m.p. 171–172 °C; R_f = 0.34 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.5 Hz, 6 H, 16a-H_3 and 16a′-H_3), 1.14 (s, 6 H, 18-H_3 and 18′-H_3), 1.18–1.55 (m, 16 H), 1.71 (m, 4 H), 2.11 (m, 2 H), 2.34 (m, 4 H), 2.87 (m, 4 H, 6-H_2 and 6′-H_2), 3.79 (s, 6 H, 3-OMe and 3′-OMe), 6.64 (d, J = 2.3 Hz, 2 H, 4-H and 4′-H), 6.74 (dd, J = 8.6, J = 2.3 Hz, 2 H, 2-H and 2′-H), 7.23 (d, J = 8.6 Hz, 2 H, 1-H and 1′-H), 7.61 (s, 2 H, 17-H and 17′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (2 C, C-16a and C-16a′), 15.6 (2 C, C-18 and C-18′), 24.3 (2 CH_2), 26.0 (2 CH_2), 27.3 (2 CH_2), 30.5 (2 CH_2), 32.3 (2 CH_2), 37.1 (2 CH_2), 41.1 (2 C, C-8 and C-8′), 42.4 (2 C, C-13 and C-13′), 43.3 (2 C, C-9 and C-9′), 47.5 (2 C, C-14 and C-14′), 55.2 (2 C, 3-OMe and 3′-OMe), 111.7 (2 C, C-2 and C-2′), 113.5 (2 C, C-4 and C-4′), 126.5 (2 C, C-1 and C-1′), 132.4 (2 C, C-10 and C-10′), 137.8 (2 C, C-5 and C-5′), 157.5 (2 C, C-3 and C-3′), 171.0 (2 C, C-17 and C-17′) ppm. MS (70 eV, EI): m/z (%) = 596 (100) [M^+], 112 (14). $C_{40}H_{56}N_2O_2$ (596.88): calcd. for C 80.49, H 9.46; found C 80.69, H 9.33.

General Procedure for the Synthesis of Isoquinuclidines 25b and 25f-l: Without purification by column chromatography, the crude hydrazone **10b** or **10f**–**l** was dissolved in CH_2Cl_2 (10 mL), and $BF_3{\cdot}OEt_2$ (a 48% solution in diethyl ether, 1 equiv.) was added slowly at room temperature under a nitrogen atmosphere. The mixture was then refluxed for a given time (see, Table 1). The reaction was next quenched by the addition of ice-cold $NaHCO_3$ (1 M, 10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo.

Cyclization of 10b to 25b: Compound **10b** (200 mg, 0.56 mmol) and $BF_3{\cdot}OEt_2$ (0.16 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (EtOAc/CH_2Cl_2 = 50:50) and recrystallized from CH_2Cl_2/hexane to give **25b** (156 mg) as white crystals; m.p. 78–80 °C; R_f = 0.50 (EtOAc/CH_2Cl_2 = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, 18-H_3), 0.95 (t, J = 6.9 Hz, 3 H, 16a-H_3), 1.04–1.22 (overlapping m, 2 H), 1.31 (m, 2 H), 1.36 (s, 3 H, Ac-H_3), 1.41 (m, 1 H), 1.54 (m, 3 H), 1.70–1.85 (overlapping m, 2 H), 2.23 (m, 1 H), 2.53 (d, J = 10.2 Hz, 1 H, 17-$H_{2,ax}$), 2.62 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 3.25 (d, J = 10.2 Hz, 1 H, 17-$H_{2,eq}$), 3.74 (s, 3 H, 3-OMe), 6.57 (d, J = 2.6 Hz, 1 H, 4-H), 6.68 (dd, J = 8.7, J = 2.6 Hz, 1 H, 2-H), 6.92 (br. s, 1 H, NH), 7.15 (d, J = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (C-16a), 19.2 (Ac-CH_3), 21.2 (CH_2), 23.0 (C-18), 25.0 (CH_2), 27.4 (CH_2), 27.9 (CH_2), 30.4 (CH_2), 32.2 (C-13), 34.2 (CH_2), 46.9 and 47.5 (C-8 and C-14), 55.0 (3-OMe), 57.5 (C-9), 68.6 (C-17), 110.8 (C-2), 113.6 (C-4), 128.9 (C-10), 130.2 (C-1), 139.1 (C-5), 158.5 (C-3), 175.7 (Ac-CO) ppm. MS (70 eV, EI): m/z (%) = 356 (46) [M^+], 313 (100), 174 (25), 87 (22). $C_{22}H_{32}N_2O_2$ (356.50): calcd. for C 74.12, H 9.05; found C 74.27, H 8.92.

Cyclization of 10f to 25f: Compound **10f** (418 mg, 0.96 mmol) and $BF_3{\cdot}OEt_2$ (0.29 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (CH_2Cl_2) and recrystallized from diisopropyl ether/hexane to give **25f** (410 mg) as orange crystals; m.p. 202–204 °C; R_f = 0.54 (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, 18-H_3), 0.97 (t, J = 6.9 Hz, 3 H, 16a-H_3), 1.17–1.62 (overlapping m, 9 H), 1.84 (m, 2 H, 7-H_2), 2.57 (m, 1 H, 17-$H_{2,ax}$), 2.66 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 3.34 (m, 1 H, 17-$H_{2,eq}$), 3.62 (s, 3 H, 3-OMe), 5.47 (s, 1 H, NH), 6.45 (overlapping m, 4 H, 2-H, 4-H, 2′-H and 6′-H), 7.11 (d, J = 8.8 Hz, 1 H, 1-H), 7.82 (d, J = 9.0 Hz, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7 (C-16a), 21.4 (CH_2), 23.1 (C-18), 25.0 (CH_2), 28.1 (2 C, C-7 and C-12), 30.3 (C-6), 32.9 (C-13), 34.1 (CH_2), 47.1 and 47.5 (C-8 and C-14), 55.0 (3-OMe), 57.6 (C-9), 68.6 (C-17), 109.9 (2 C, C-2′ and C-6′), 111.2 (C-2), 113.0 (C-4), 125.7 (2 C, C-3′ and C-5′), 128.7 (C-10), 129.6 (C-1), 138.0 (C-4′), 139.1 (C-5), 154.8 (C-1′), 158.3 (C-3) ppm. MS (70 eV, EI): m/z (%) = 435 (24) [M^+], 298 (100). $C_{26}H_{33}N_3O_3$ (435.56): calcd. for C 71.70, H 7.64; found C 71.92, H 7.46.

Cyclization of 10g to 25g: Compound **10g** (208 mg, 0.50 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (hexane/diisopropyl ether = 80:20) and recrystallized from hexane/diisopropyl ether to give **25g** (191 mg) as white crystals; m.p. 178–180 °C; R_f = 0.60 (hexane/diisopropyl ether = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, 18-H_3), 0.97 (t, J = 6.9 Hz, 3 H, 16a-H_3), 1.13–1.25 (overlapping m, 2 H), 1.32–1.62 (overlapping m, 7 H), 1.84 (m, 2 H, 7-H_2), 2.62 (m, 1 H, 17-$H_{2,ax}$), 2.65 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 3.27 (m, 1 H, 17-$H_{2,eq}$), 3.65 (s, 3 H, 3-OMe), 5.24 (s, 1 H, NH), 6.47 (overlapping m, 4 H, 2-H, 4-H, 2′-H and 6′-H), 7.16 (overlapping m, 3 H, 1-H, 3′-H and 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (C-16a), 21.4 (CH_2), 23.2 (C-18), 27.8 (CH_2), 28.2 (2 C, 2 × CH_2), 30.3 (C-6), 32.8 (C-13), 34.2 (CH_2), 47.2 and 47.5 (C-8 and C-14), 55.0 (3-OMe), 57.3 (C-9), 68.9 (C-17), 98.7 (C-4′), 111.0 (C-2), 111.2 (2 C, C-2′ and C-6′), 112.9 (C-4), 120.6 (4′-CN), 129.1 (C-10), 129.6 (C-1), 132.9 (2 C, C-3′ and C-5′), 139.0 (C-5), 152.9 (C-1′), 158.2 (C-3) ppm. MS (70 eV, EI): m/z (%) = 415 (44) [M^+], 298 (100). $C_{27}H_{33}N_3O$ (415.57): calcd. for C 78.03, H 8.00; found C 78.32, H 8.22.

Cyclization of 10h to 25h: Compound **10h** (229 mg, 0.50 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (hexane/diisopropyl ether = 90:10) to give **25h** (204 mg) as a colorless oil. R_f = 0.44 (hexane/diisopropyl ether = 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, 18-H_3), 0.97 (t, J = 6.9 Hz, 3 H, 16a-H_3), 1.12–1.61 (overlapping m, 9 H), 1.82 (m, 2 H, 7-H_2), 2.63 (m, 1 H, 17-$H_{2,ax}$), 2.65 (m, 1 H), 2.87 (m, 2 H, 6-H_2), 3.25 (m, 1 H, 17-$H_{2,eq}$), 3.65 (s, 3 H, 3-OMe), 4.96 (s, 1 H, NH), 6.45 (d, J = 2.5 Hz, 1 H, 4-H), 6.48 (dd, J = 8.6, J = 2.5 Hz, 1 H, 2-H), 6.56 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 7.16 (d, J = 8.5 Hz, 2 H, 3′-H and 5′-H), 7.19 (d, J = 8.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (C-16a), 21.5 (CH_2), 23.2 (C-18), 27.8 (CH_2), 28.3 (2 C, 2 × CH_2), 30.4 (C-6), 32.9 (C-13), 34.2 (CH_2), 47.3 and 47.7 (C-8 and C-14), 55.0 (3-OMe), 57.2 (C-9), 69.2 (C-17), 111.1 (C-2), 111.3 (2 C, C-2′ and C-6′), 112.9 (C-4), 116.5 (C-4′) 118.6 (4′-CF_3), 125.8 (2 C, C-3′ and C-5′), 129.6 (C-10), 129.8 (C-1), 139.0 (C-5), 152.2 (C-1′), 158.1 (C-3) ppm. MS (70 eV, EI): m/z (%) = 458 (35) [M^+], 298 (80), 173 (100), 147 (98). $C_{27}H_{33}F_3N_2O$ (458.56): calcd. for C 70.72, H 7.25; found C 70.65, H 7.33.

Cyclization of 10i to 25i: Compound **10i** (240 mg, 0.50 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (hexane/diisopropyl ether = 80:20) and recrystallized from MeOH/H_2O to give **25i** (223 mg) as orange crystals; m.p. 59–61 °C; R_f = 0.50 (hexane/CH_2Cl_2 = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 18-H_3), 0.99 (t, J = 7.0 Hz, 3 H, 16a-H_3), 1.21–1.63 (overlapping m, 8 H), 1.89 (m, 2 H), 2.33 (m, 1 H), 2.72 (d, J = 11.2 Hz, 1 H, 17-$H_{2,ax}$), 2.77 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 3.38 (d, J = 11.2 Hz, 1 H, 17-$H_{2,eq}$), 3.65 (s, 3 H, 3-OMe), 6.34 (d, J = 8.6 Hz, 1 H, 2-H), 6.41 (s, 1 H, 4-H), 7.01 (d, J = 8.6 Hz, 1 H, 1-H), 7.19 (d, J = 9.5 Hz, 1 H, 6′-H), 7.84 (dd, J = 9.5, J = 2.1 Hz, 1 H, 5′-H), 8.85 (d, J = 2.1 Hz, 1 H, 3′-H), 9.34 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (C-16a), 21.4 (CH_2), 23.0 (C-18), 25.2 (CH_2), 27.6 (CH_2), 27.9 (CH_2), 30.1 (C-6), 32.4 (C-13), 34.1 (CH_2), 46.7 and 47.4 (C-8 and C-14), 55.0 (3-OMe), 58.3 (C-9), 67.9 (C-17), 111.0 (C-2), 113.4 (C-4), 115.8 (C-6′), 123.3 (C-3′), 127.6 (C-10), 129.0 (2 C, C-1 and C-5′), 136.0 (C-2′), 139.2 (2 C, C-5 and C-4′), 149.9 (C-1′), 158.6 (C-3) ppm. MS (70 eV, EI): m/z (%) = 480 (13) [M^+], 298 (100). $C_{26}H_{32}N_4O_5$ (480.56): calcd. for C 64.98, H 6.71; found C 65.15, H 6.54.

Cyclization of 10j to 25j: Compound **10j** (212 mg, 0.50 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (hexane/diisopropyl ether = 70:30) to give **25j** (119 mg) as a colorless oil. R_f = 0.83 (hexane/diisopropyl ether = 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (s, 3 H, 18-H_3), 0.97 (t, J = 7.0 Hz, 3 H, 16a-H_3), 1.17–1.62 (overlapping m, 9 H), 1.81 (m, 2 H, 7-H_2), 2.63 (m, 1 H, 17-$H_{2,ax}$), 2.65 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 3.25 (dd, J = 10.9, J = 2.9 Hz, 1 H, 17-$H_{2,eq}$), 3.65 (s, 3

H, 3-OMe), 4.67 (br. s, 1 H, NH), 6.51 (overlapping m, 4 H, 2-H, 4-H, 2′-H and 6′-H), 6.89 (d, J = 8.8 Hz, 2 H, 3′-H and 5′-H), 7.22 (d, J = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (C-16a), 21.5 (CH_2), 23.3 (C-18), 27.8 (2× CH_2), 28.3 (CH_2), 30.4 (C-6), 33.0 (C-13), 34.2 (CH_2), 47.4 and 47.7 (C-8 and C-14), 55.1 (3-OMe), 57.0 (C-9), 69.5 (C-17), 111.0 (C-2), 112.8 (C-4), 113.5 (2 C, C-2′ and C-6′), 122.1 (C-4′), 128.2 (2 C, C-3′ and C-5′), 129.8 (C-1), 130.1 (C-10), 138.9 (C-5), 148.3 (C-1′), 158.0 (C-3) ppm. MS (70 eV, EI): m/z (%) = 426 (6) [M^+], 424 (15), 174 (100), 147 (70). $C_{26}H_{33}ClN_2O$ (425.01): calcd. for C 73.48, H 7.83; found C 73.21, H 7.95.

Cyclization of 10k to 25k: Compound **10k** (178 mg, 0.50 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (EtOAc) to give **25k** (118 mg) as white crystals; m.p. 220–222 °C; R_f = 0.13 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, 18-H_3), 0.95 (t, J = 6.9 Hz, 3 H, 16a-H_3), 1.13–1.57 (overlapping m, 8 H), 1.79 (m, 2 H), 2.07 (m, 1 H), 2.59 (d, J = 11.2 Hz, 1 H, 17-$H_{2,ax}$), 2.66 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 3.28 (d, J = 11.2 Hz, 1 H, 17-$H_{2,eq}$), 3.74 (s, 3 H, 3-OMe), 6.46 (br. s, 1 H, NH), 6.55 (d, J = 2.5 Hz, 1 H, 4-H), 6.68 (dd, J = 8.7, J = 2.5 Hz, 1 H, 2-H), 7.27 (d, J = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (C-16a), 21.2 (CH_2), 23.0 (C-18), 25.2 (CH_2), 27.7 (CH_2), 27.8 (CH_2), 30.3 (CH_2), 32.2 (C-13), 34.3 (CH_2), 46.7 and 47.7 (C-8 and C-14), 55.0 (3-OMe), 57.1 (C-9), 68.7 (C-17), 111.0 (C-2), 113.5 (C-4), 128.9 (C-10), 130.0 (C-1), 138.4 (C-5), 158.5 (C-3), 160.5 (C=O) ppm. MS (70 eV, EI): m/z (%) = 357 (86) [M^+], 313 (100), 298 (70), 174 (38), 88 (42). $C_{21}H_{31}N_3O_2$ (357.49): calcd. for C 70.55, H 8.74; found C 70.41, H 8.96.

Cyclization of 10l to 25l: Compound **10l** (187 mg, 0.50 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL) were used for the synthesis as described in the General Procedure. The crude product was purified by column chromatography (EtOAc/CH_2Cl_2 = 10:90) and recrystallized from EtOAc/CH_2Cl_2 to give **25l** (118 mg) as white crystals; m.p. 211–213 °C; R_f = 0.51 (EtOAc/CH_2Cl_2 = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, 18-H_3), 0.95 (t, J = 6.9 Hz, 3 H, 16a-H_3), 1.13–1.58 (overlapping m, 8 H), 1.81 (m, 2 H), 2.06 (m, 1 H), 2.69 (d, J = 11.4 Hz, 1 H, 17-$H_{2,ax}$), 2.75 (m, 1 H), 2.87 (m, 2 H, 6-H_2), 3.25 (dd, J = 11.4, J = 2.7 Hz, 1 H, 17-$H_{2,eq}$), 3.74 (s, 3 H, 3-OMe), 5.49 (br. s, 1 H) and 6.30 (br. s, 1 H): NH_2, 6.54 (d, J = 2.5 Hz, 1 H, 4-H), 6.71 (dd, J = 8.7, J = 2.5 Hz, 1 H, 2-H), 7.30 (d, J = 8.7 Hz, 1 H, 1-H), 7.67 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-16a), 21.2 (CH_2), 22.9 (C-18), 25.8 (CH_2), 27.7 (CH_2), 27.9 (CH_2), 30.3 (CH_2), 32.1 (C-13), 34.2 (CH_2), 46.9 and 47.6 (C-8 and C-14), 55.0 (3-OMe), 57.5 (C-9), 67.5 (C-17), 111.3 (C-2), 113.6 (C-4), 128.0 (C-10), 129.7 (C-1), 138.2 (C-5), 158.7 (C-3), 181.2 (C = S) ppm. MS (70 eV, EI): m/z (%) = 373 (37) [M^+], 313 (100), 298 (98), 174 (96). $C_{21}H_{31}N_3OS$ (373.56): calcd. for C 67.52, H 8.36; found C 67.38, H 8.21.

Synthesis of 16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al Oxime (28a): Compound **8** (300 mg, 1.00 mmol) and hydroxylamine hydrochloride **27a** (70 mg, 1.00 mmol) were suspended in 2-PrOH (10 mL) and a solution of NaOAc (150 mg, 1.80 mmol) in 2-PrOH (10 mL) was added. The mixture was refluxed for 4 h, and then poured into cold water. The white precipitate was filtered off and dried to give **28a** (290 mg, 92%); m.p. 131–133 °C; R_f = 0.39 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.8 Hz, 3 H, 16a-H_3), 1.08 (s, 3 H, 18-H_3), 1.16–1.53 (overlapping m, 8 H), 1.69 (m, 2 H), 2.09 (m, 1 H), 2.33 (m, 2 H), 2.87 (m, 2 H, 6-H_2), 3.79 (s, 3 H, 3-OMe), 6.64 (d, J = 2.5 Hz, 1 H, 4-H), 6.73 (dd, J = 8.7, J = 2.5 Hz, 1 H, 2-H), 7.21 (d, J = 8.7 Hz, 1 H, 1-H), 7.31 (s, 1 H, 17-H), 8.21 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-16a), 15.4 (C-18), 24.3 (CH_2), 26.0 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.1 (CH_2), 37.4 (CH_2), 41.0 (C-8), 41.3 (C-13), 43.3 (C-9), 47.9 (C-14), 55.2 (3-OMe), 111.7 (C-2), 113.5 (C-4), 126.5 (C-1), 132.2 (C-10), 137.8 (C-5), 157.5 (C-3), 160.4 (C-17) ppm. MS (70 eV, EI): m/z (%) = 315 (8) [M^+], 298 (70), 112 (100). $C_{20}H_{29}NO_2$ (315.45): calcd. for C 76.15, H 9.27; found C 75.93, H 9.35.

General Procedure for the Synthesis of Oxime Ethers 28b-d: Compound **8** (300 mg, 1.00 mmol) and *O*-substituted hydroxylamine hydrochloride **27b**, **27c** or **27d** (1.00 mmol, respectively) were suspended in 2-PrOH (10 mL) and a solution of NaOAc (150 mg, 1.80 mmol) in 2-PrOH (10 mL) was added. The mixture was refluxed for 8 h, poured into cold water and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al Oxime Benzyl Ether (28b): For the synthesis, given in the General Procedure, *O*-benzylhydroxylamine hydrochloride **27b** (160 mg) was used. The crude product was purified by column chromatography (CH_2Cl_2) to give **28b** (357 mg, 88%) as a colorless oil. R_f = 0.43 (EtOAc/CH_2Cl_2 = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 6.8 Hz, 3 H, 16a-H_3), 1.07 (s, 3 H, 18-H_3), 1.16–1.51 (overlapping m, 8 H), 1.64 (m, 2 H), 2.06 (m, 1 H), 2.28 (m, 2 H), 2.87 (m, 2 H, 6-H_2), 3.79 (s, 3 H, 3-OMe), 5.10 (s, 2 H, OCH_2), 6.64 (d, J = 2.4 Hz, 1 H, 4-H), 6.73 (dd, J = 8.6, J = 2.4 Hz, 1 H, 2-H), 7.21 (d, J = 8.6 Hz, 1 H, 1-H), 7.30–7.41 (overlapping m, 6 H, 17-H, 2′-H, 3′-H, 4′-H, 5′-H and 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-16a), 15.5 (C-18), 24.4 (CH_2), 26.0 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.3 (CH_2), 37.6 (CH_2), 41.1 (C-8), 41.4 (C-13), 43.3 (C-9), 47.8 (C-14), 55.2 (3-OMe), 75.5 (OCH_2), 111.7 (C-2), 113.5 (C-4), 126.5 (C-1), 127.7 (C-4′), 128.2 (2 C) and 128.3 (2 C): C-2′, C-3′, C-5′ and C-6′, 132.3 (C-10), 137.8 (C-5), 138.0 (C-1′), 157.5 (C-3), 159.6 (C-17) ppm. MS (70 eV, EI): m/z (%) = 405 (9) [M^+], 314 (49), 298 (88), 112 (100), 91 (38). $C_{27}H_{35}NO_2$ (405.57): calcd. for C 79.96, H 8.70; found C 79.84, H 8.94.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al Oxime 4′-Nitrobenzyl Ether (28c): For the synthesis, given in the General Procedure, *O*-(4-nitrobenzyl)hydroxylamine hydrochloride **27c** (204 mg) was used. The crude product was purified by column chromatography (CH_2Cl_2/hexane = 50:50) and recrystallized from CH_2Cl_2/hexane to give **28c** (385 mg, 85%) as white crystals; m.p. 116–118 °C; R_f = 0.63 (CH_2Cl_2/hexane = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 6.8 Hz, 3 H, 16a-H_3), 1.03 (s, 3 H, 18-H_3), 1.13–1.50 (overlapping m, 8 H), 1.63 (m, 2 H), 2.06 (m, 1 H), 2.31 (m, 2 H), 2.85 (m, 2 H, 6-H_2), 3.78 (s, 3 H, 3-OMe), 5.17 (s, 2 H, OCH_2), 6.63 (d, J = 2.4 Hz, 1 H, 4-H), 6.71 (dd, J = 8.6, J = 2.4 Hz, 1 H, 2-H), 7.20 (d, J = 8.6 Hz, 1 H, 1-H), 7.35 (s, 1 H, 17-H), 7.52 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 8.22 (d, J = 8.5 Hz, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-16a), 15.4 (C-18), 24.4 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 30.5 (CH_2), 32.3 (CH_2), 37.5 (CH_2), 41.0 (C-8), 41.5 (C-13), 43.2 (C-9), 47.6 (C-14), 55.2 (3-OMe), 73.9 (OCH_2), 111.7 (C-2), 113.4 (C-4), 123.5 (2 C, C-3′ and C-5′), 126.5 (C-1), 128.2 (2 C, C-2′ and C-6′), 132.1 (C-10), 137.8 (C-5), 146.0 (2 C, C-1′ and C-4′), 157.5 (C-3), 160.5 (C-17) ppm. MS (70 eV, EI): m/z (%) = 450 (2) [M^+], 314 (22), 298 (90), 112 (100). $C_{27}H_{34}N_2O_4$ (450.57): calcd. for C 71.97, H 7.61; found C 72.08, H 7.55.

16,17-*seco*-3-Methoxyestra-1,3,5(10)-trien-17-al Oxime Allyl Ether (28d): For the synthesis, given in the General Procedure, *O*-allylhydroxylamine hydrochloride **27d** (110 mg) was used. The crude product was purified by column chromatography (CH_2Cl_2/hexane = 50:50) to give **28d** (316 mg, 89%) as a colorless oil. R_f = 0.57 (EtOAc/CH_2Cl_2 = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89

(t, J = 6.9 Hz, 3 H, 16a-H_3), 1.07 (s, 3 H, 18-H_3), 1.13–1.50 (overlapping m, 8 H), 1.64 (m, 2 H), 2.07 (m, 1 H), 2.29 (m, 2 H), 2.86 (m, 2 H, 6-H_2), 3.79 (s, 3 H, 3-OMe), 4.55 (d, J = 5.6 Hz, 2 H, 1′-H_2), 5.22 (d, J = 10.5 Hz, 1 H) and 5.31 (d, J = 17.3 Hz, 1 H): 3′-H_2, 6.01 (m, 1 H, 2′-H), 6.64 (d, J = 2.5 Hz, 1 H, 4-H), 6.73 (dd, J = 8.6, J = 2.5 Hz, 1 H, 2-H), 7.21 (d, J = 8.6 Hz, 1 H, 1-H), 7.30 (s, 1 H, 17-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-16a), 15.5 (C-18), 24.5 (CH_2), 26.0 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 32.3 (CH_2), 37.7 (CH_2), 41.1 (C-8), 41.3 (C-13), 43.3 (C-9), 47.8 (C-14), 55.2 (3-OMe), 74.3 (C-1′), 111.7 (C-2), 113.5 (C-4), 117.3 (C-3′), 126.5 (C-1), 132.3 (C-10), 134.4 (C-2′), 137.8 (C-5), 157.5 (C-3), 159.4 (C-17) ppm. $C_{23}H_{33}NO_2$ (355.51): calcd. for C 77.70, H 9.36; found C 77.93, H 9.48.

General Procedure for the Synthesis of Isoquinuclidines 32b-d: Oxime ether **28b**, **28c** or **28d** (0.50 mmol) was dissolved in CH_2Cl_2 (10 mL), and BF_3·OEt_2 (a 48% solution in diethyl ether, 0.16 mL, 1 equiv.) was added slowly at room temperature under a nitrogen atmosphere. The mixture was then refluxed for a given time (see, Table 1). The reaction was next quenched by the addition of ice-cold $NaHCO_3$ (1 M, 10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo.

Cyclization of 28b to 32b: Compound **28b** (203 mg) was used for the synthesis, as described in the General Procedure. The crude product was purified by column chromatography (diisopropyl ether/hexane = 50:50) to give **32b** (144 mg) as a colorless oil. R_f = 0.25 (diisopropyl ether/hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 18-H_3), 0.95 (t, J = 7.0 Hz, 3 H, 16a-H_3), 1.01 (m, 1 H), 1.14 (m, 1 H), 1.26–1.53 (overlapping m, 6 H), 1.68 (m, 2 H), 2.18 (m, 1 H), 2.71 (m, 1 H), 2.86 (m, 2 H, 6-H_2), 2.98 (m, 1 H), 3.08 (dd, J = 11.8, J = 2.9 Hz, 1 H, one proton of OCH_2), 3.81 (s, 3 H, 3-OMe), 3.95 (m, 1 H), 3.99 (m, 1 H, the other proton of OCH_2), 6.64 (d, J = 2.6 Hz, 1 H, 4-H), 6.73 (dd, J = 8.7, J = 2.7 Hz, 1 H, 2-H), 7.09 and 7.24 (m, 2 H; m, 3 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 7.50 (d, J = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (C-16a), 21.6 (CH_2), 23.1 (C-18), 27.2 (2 C, 2 × CH_2), 27.7 (CH_2), 30.8 (C-6), 34.2 (2 C, CH_2 and C-13), 46.7 and 47.1 (C-8 and C-14), 55.1 (3-OMe), 57.9 (C-9), 68.1 (C-17), 75.8 (OCH_2), 111.2 (C-2), 112.8 (C-4), 127.2 (2 C, C-2′ and C-6′), 127.9 (3 C, C-3′, C-4′ and C-5′), 128.9 (C-1), 138.4 (2 C, C-1′ and C-10), 139.3 (C-5), 158.1 (C-3) ppm. MS (70 eV, EI): m/z (%) = 405 (6) [M^+], 314 (100), 241 (16). $C_{27}H_{35}NO_2$ (405.57): calcd. for C 79.96, H 8.70; found C 79.78, H 8.61.

Cyclization of 28c to 32c: Compound **28c** (225 mg) was used for the synthesis, as described in the General Procedure. The crude product was purified by column chromatography (diisopropyl ether/hexane = 20:80) and recrystallized from hexane to give **32c** (176 mg) as white crystals; m.p. 64–66 °C; R_f = 0.87 (diisopropyl ether/hexane = 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 18-H_3), 0.93 (t, J = 7.0 Hz, 3 H, 16a-H_3), 0.99 (m, 1 H), 1.16 (m, 1 H), 1.27–1.55 (overlapping m, 6 H), 1.67 (m, 2 H), 2.07 (m, 1 H), 2.69 (m, 1 H), 2.83 (m, 2 H, 6-H_2), 2.97 (m, 1 H), 3.05 (dd, J = 11.6, J = 2.6 Hz, 1 H, one proton of OCH_2), 3.79 (s, 3 H, 3-OMe), 3.99 (m, 1 H, the other proton of OCH_2), 4.04 (m, 1 H), 6.58 (d, J = 2.3 Hz, 1 H, 4-H), 6.66 (dd, J = 8.7, J = 2.3 Hz, 1 H, 2-H), 7.19 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 7.42 (d, J = 8.7 Hz, 1 H, 1-H), 8.06 (d, J = 8.5 Hz, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (C-16a), 21.6 (CH_2), 23.1 (C-18), 27.1 (2 C, 2 × CH_2), 27.6 (CH_2), 30.7 (C-6), 34.1 (2 C, CH_2 and C-13), 46.6 and 47.0 (C-8 and C-14), 55.1 (3-OMe), 58.0 (C-9), 68.0 (C-17), 74.3 (OCH_2), 111.3 (C-2), 112.8 (C-4), 123.1 (3 C, C-1, C-3′ and C-5′), 129.2 (2 C, C-2′ and C-6′), 136.9 (C-10), 139.3 (C-5), 146.1 and 147.1 (C-1′ and C-4′), 158.2 (C-3) ppm. MS (70 eV, EI): m/z (%) = 450 (2) [M^+], 241 (15), 165 (14), 314 (100). $C_{27}H_{34}N_2O_4$ (450.57): calcd. for C 71.97, H 7.61; found C 71.86, H 7.85.

Cyclization of 28d to 32d: Compound **28d** (178 mg) was used for the synthesis, as described in the General Procedure. The crude product was purified by column chromatography (diisopropyl ether/hexane = 10:90) to give **32d** (128 mg) as a colorless oil. R_f = 0.48 (hexane/diisopropyl ether = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, 18-H_3), 0.94 (t, J = 7.0 Hz, 3 H, 16a-H_3), 1.02–1.57 (overlapping m, 8 H), 1.67 (m, 2 H), 2.16 (m, 1 H), 2.71 (m, 1 H), 2.82 (m, 2 H, 6-H_2), 2.99 (m, 1 H), 3.20 (d, J = 12.1 Hz, 1 H, one proton of 1′-H_2), 3.38 (m, 1 H), 3.51 (dd, J = 12.1, J = 6.1 Hz, 1 H, the other proton of 1′-H_2), 3.78 (s, 3 H, 3-OMe), 4.98 (m, 2 H, 3′-H_2), 5.64 (m, 1 H, 2′-H), 6.59 (d, J = 2.6 Hz, 1 H, 4-H), 6.68 (dd, J = 8.7, J = 2.6 Hz, 1 H, 2-H), 7.44 (d, J = 8.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (C-16a), 21.6 (CH_2), 23.1 (C-18), 27.1 (2 C, 2 × CH_2), 27.7 (CH_2), 30.8 (C-6), 34.2 (2 C, CH_2 and C-13), 46.8 and 47.1 (C-8 and C-14), 55.1 (3-OMe), 57.8 (C-9), 68.3 (C-17), 74.7 (C-1′), 111.0 (C-2), 112.7 (C-4), 116.5 (C-3′), 130.3 (C-1), 131.3 (C-10), 135.2 (C-2′), 139.2 (C-5), 158.1 (C-3) ppm. MS (70 eV, EI): m/z (%) = 355 (3) [M^+], 314 (100), 241 (18), 165 (36). $C_{23}H_{33}NO_2$ (355.51): calcd. for C 77.70, H 9.36; found C 77.83, H 9.21.

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[1] a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[2] a) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967–1983; b) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341–5378; c) L. F. Tietze, N. Rackelmann, in: *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**, pp. 121–168.
[3] a) S. J. Pastine, D. Sames, *Org. Lett.* **2005**, *7*, 5429–5431; b) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180–12181; c) M. R. Attwood, P. S. Gilbert, M. L. Lewis, K. Mills, P. Quayle, S. P. Thompson, S. Wang, *Tetrahedron Lett.* **2006**, *47*, 3607–3611.
[4] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77.
[5] a) P. T. Lansbury, N. R. Mancuso, *J. Am. Chem. Soc.* **1966**, *88*, 1205–1212; b) G. Neef, G. Michl, *Tetrahedron Lett.* **1991**, *32*, 5071–5072; c) C. G. Savarin, C. Grisé, J. A. Murry, R. A. Reamer, D. L. Hughes, *Org. Lett.* **2007**, *9*, 981–983.
[6] a) J. Wölfling, É. Frank, Gy. Schneider, L. F. Tietze, *Angew. Chem.* **1999**, *111*, 151–152; *Angew. Chem. Int. Ed.* **1999**, *38*, 200–201; b) J. Wölfling, É. Frank, Gy. Schneider, L. F. Tietze, *Eur. J. Org. Chem.* **2004**, 90–100.
[7] a) A. Guy, J. Doussot, M. Lemaire, *Synthesis* **1991**, 460–462; b) S. Schwarz, M. Schumacher, S. Ring, A. Nanninga, G. Weber, I. Thieme, B. Undeutsch, W. Elger, *Steroids* **1999**, *64*, 460–471; c) P. Bovicelli, P. Lupattelli, E. Mincione, T. Prencipe, R. Curci, *J. Org. Chem.* **1992**, *57*, 2182–2184; d) R. Tedesco, J. A. Katzenellenbogen, E. Napolitano, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2919–2924.
[8] I. Iriepa, F. J. Villasante, E. Gálvez, L. Labeaga, A. Innerarity, A. Orjales, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 189–192.
[9] G. R. Krow, O. H. Cheung, Z. Hu, Q. Huang, J. Hutchinson, N. Liu, K. T. Nguyen, S. Ulrich, J. Yuan, Y. Xiao, D. M. Wypij, F. Zuo, P. J. Carroll, *Tetrahedron* **1999**, *55*, 7747–7756.

[10] M. Yokota, E. Takizawa, Y. Ohkura, C. Fukai, T. Tomiyama, *Eur. J. Med. Chem.* **1997**, *32*, 377–384.
[11] a) L. F. Tietze, Gy. Schneider, J. Wölfling, A. Fecher, T. Nöbel, S. Petersen, I. Schuberth, C. Wulff, *Chem. Eur. J.* **2000**, *6*, 3755–3760; b) L. F. Tietze, Gy. Schneider, J. Wölfling, T. Nöbel, C. Wulff, I. Schuberth, A. Rübeling, *Angew. Chem.* **1998**, *110*, 2644–2646; *Angew. Chem. Int. Ed.* **1998**, *37*, 2469–2470; c) É. Frank, E. Mernyák, J. Wölfling, Gy. Schneider, *Synlett* **2002**, 419–422; d) É. Frank, E. Mernyák, J. Wölfling, Gy. Schneider, *Synlett* **2002**, 1803–1806; e) J. Wölfling, É. Frank, E. Mernyák, G. Bunkóczi, J. A. C. Seijo, Gy. Schneider, *Tetrahedron* **2002**, *58*, 6851–6861.
[12] a) Gy. Schneider, S. Bottka, L. Hackler, J. Wölfling, P. Sohár, *Liebigs Ann. Chem.* **1989**, 263–267; b) L. F. Tietze, J. Wölfling, Gy. Schneider, *Chem. Ber.* **1991**, *124*, 591–594.
[13] É. Frank, J. Wölfling, B. Aukszi, V. König, T. R. Schneider, Gy. Schneider, *Tetrahedron* **2002**, *58*, 6843–6849.
[14] G. A. Potter, S. E. Barrie, M. Jarman, M. G. Rowlands, *J. Med. Chem.* **1995**, *38*, 2463–2471.
[15] a) T. Shimizu, Y. Hayashi, M. Miki, K. Teramura, *J. Org. Chem.* **1987**, *52*, 2277–2285; b) C. Gergely, J. B. Morgan, L. E. Overman, *J. Org. Chem.* **2006**, *71*, 9144–9152.
[16] É. Frank, Z. Mucsi, I. Zupkó, B. Réthy, G. Falkay, Gy. Schneider, J. Wölfling, *J. Am. Chem. Soc.* **2009**, *131*, 3894–3904.
[17] a) R. Grashey, in: *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**, vol. 1, pp. 741–743; b) R. Grigg, J. Kemp, N. Thompson, *Tetrahedron Lett.* **1978**, *31*, 2827–2830; c) V. V. Khau, M. J. Martinelli, *Tetrahedron Lett.* **1996**, *37*, 4323–4326; d) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani, J. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 13678–13679; e) Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 11279–11282; f) É. Frank, Zs. Kardos, J. Wölfling, Gy. Schneider, *Synlett* **2007**, 1311–1313.
[18] P. Pérez, L. R. Domingo, M. J. Aurell, R. Contreras, *Tetrahedron* **2003**, *59*, 3117–3125.
[19] M. J. Uddin, M. Kikuchi, K. Takedatsu, K.-I. Arai, T. Fujimoto, J. Motoyishiya, A. Kakehi, R. Iriye, H. Shirai, I. Yamamoto, *Synthesis* **2000**, *3*, 365–374.
[20] M. Noguchi, H. Okada, S. Nishimura, Y. Yamagata, S. Takamura, M. Tanaka, A. Kakehi, H. Yamamoto, *J. Chem. Soc. Perkin Trans. 1* **1999**, 185–191.
[21] H. Mayr, A. R. Ofial, *Tetrahedron Lett.* **1997**, *38*, 3503–3506.

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